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

REPORT EP0147

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STUDY INFORMATION

Title	Evaluating the occurrence of adverse events among pediatric patients exposed to intravenous lacosamide (VIMPAT) using real world data
Study Number	Final version 1.0
Date of last version of Study Report	Not applicable
European (EU) Post-Authorization Study (PAS) register number (if applicable)	EUPAS32597
Research question and objectives	To estimate the incidence of the selected medical events for 8 System Organ Classes and 3 Standardized Medical Dictionary for Regulatory Activities Queries in pediatric patients after treatment with higher intravenous lacosamide doses, compared to pediatric patients treated with recommended initial/maintenance intravenous lacosamide dose.
Country(-ies) of study	United States
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2 ABSTRACT

Title

Evaluating the occurrence of adverse events among pediatric patients exposed to intravenous lacosamide (VIMPAT) using real world data

Keywords

Adverse event, adverse reaction, pediatric, intravenous lacosamide, incidence

Rationale and background

VIMPAT (lacosamide, LCM) is available as oral solution, oral tablet, and intravenous (iv) solution. It is currently approved in United States (US) for use as oral solution and oral tablet in patients over 4 years of age and as iv solution in patients over 17 years of age as an alternative to oral administration (Food and Drug Administration Agency, FDA, 2017). VIMPAT dosage in adult patients can be started with the recommended initial dosage (as monotherapy 100mg twice daily; as adjunctive therapy 50mg twice daily) followed by a titration regimen (increase by 50mg twice daily every week). Alternatively, it may be initiated with a single loading dose of 200mg. 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

The **primary objective** of this study is to estimate the incidence of the selected medical events of interest, those being the 8 System Organ Classes (SOCs) (ie, 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 Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) (ie, drug reaction with eosinophilia and systemic symptoms syndrome, severe cutaneous adverse reactions, hypersensitivity), in pediatric patients after iv treatment with higher than the recommended LCM doses, compared to pediatric patients treated with recommended initial/maintenance LCM dose:

The secondary objectives of this study are:

1. To estimate the incidence of the selected medical events among the SOCs, in pediatric patients after treatment with higher than the recommended initial 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 selected medical events for 8 SOCs and 3 SMQ terms, compared to pediatric patients treated with recommended initial/maintenance iv LCM dose.

Study design

This was a retrospective cohort study that used electronic healthcare records (EHR) data from the PEDSnet data network. Based on first iv LCM dose and patients age and weight, pediatric patients were classified into initial loading and recommended dose cohorts and followed for a maximum of 37 days.

Setting

PEDSnet (pedsnet.org) is a national clinical research network that collects standardized EHR data for millions of children.

Patients and study size, including dropouts

In the PEDSNet database after applying selection criteria and subsequent chart reviewing, 686 patients aged ≥1 month to <17 years and 28 neonates aged <30 days were eligible for the study.

Variables and data sources

Incidence rates of a wide range of selected medical events under study were estimated by initial iv LCM dose (loading dose vs recommended dose).

The PEDSnet database contains data stored in a structured format. Chart reviews of unstructured data were used to validate eligibility criteria and to collect data on study outcomes.

Results

Of 686 patients aged ≥1 month to <17 years, 68.7% vs 31.3% were administered the iv LCM recommended dose and loading dose as initial doses, respectively. Of 28 patients aged <30 days, 57.1% vs 42.9% were administered the iv LCM recommended dose and loading dose as initial doses, respectively. Over half of patients aged ≥1 month to <17 years and almost all of patients aged <30 days were treated in an intensive care unit (ICU) at the time of iv LCM initiation. Patients in both age groups were refractory to at least four lines of therapy. In patients aged ≥1 month to <17 years and <30 days, 47 and [redacted] deaths were reported in critically ill patients, respectively, but none of them were attributed to LCM.

Crude incidence rates by adverse event diagnostic categories

In patients aged ≥1 month to <17 years, the crude incidence rates per 1000 person-days of overall adverse events (AEs) in the recommended and loading dose cohorts were 64.44 (95% confidence interval, CI: 55.88, 73.95) vs 50.00 (95% CI: 39.82, 61.98), respectively.

In patients aged <30 days, the crude incidence rates per 1000 person-days of overall AEs in the recommended and loading dose cohorts were 36.04 (95% CI: 15.56, 71.01) vs 8.85 (95% CI: 1.07, 31.97), respectively.

Crude incidence rates by specific AE diagnoses

In patients aged ≥1 month to <17 years, the crude incidence rates per 1000 person-days ranged from 0.16 (95% CI: 0.00, 0.89) for atrioventricular (AV) block, bradyarrhythmia, ventricular tachyarrhythmia, Stevens-Johnson syndrome, loss of consciousness, appetite disorder and hypophagia each to 4.91 (95% CI: 3.29, 7.05) for bradycardia in the recommended dose cohort. The crude incidence rates per 1000 person-days ranged from 0.33 (95% CI: 0.01, 1.86) for injection site erythema, dizziness, and pruritis individually to 6.55 (95% CI: 3.88, 10.35) for rash in the loading dose cohort.

In patients aged <30 days, only one AE was reported in the recommended dose cohort, ie, cardiac arrest and the crude incidence rate per 1000 person-days was 12.86 (95% CI: 3.50, 32.93). No AE was reported in the loading dose cohort.

Crude incidence rates by AEs that physicians attributed to LCM

In patients aged ≥1 month to <17 years, the crude incidence rates per 1000 person-days of overall AEs that physicians attributed to LCM in the recommended and loading dose cohorts were 0.98 (95% CI: 0.36, 2.12) vs 1.37 (95% CI: 0.37, 3.51), respectively.

In patients aged <30 days, no AEs were reported that physicians attributed to LCM.

Incidence rate ratios by categories and specific AE diagnoses

In patients aged ≥1 month to <17 years, after adjusting for possible observed confounding variables by Poisson regression with inverse probability treatment weights (IPTW), no statistically significant increased incidence rate ratios (IRR) in AE diagnostic categories and most of the specific AE diagnoses were observed between the recommended and loading dose cohorts. The risk of rash was increased by two-fold in the loading dose cohort compared with the recommended dose cohort (adjusted IRR: 2.11; 95% CI: 1.02, 4.38).

In patients aged <30 days, no IRRs were calculated due to small sample size.

Mortality

In patients aged ≥1 month to <17 years, crude mortality rates per 1000 person-days in the recommended and loading dose cohorts were 4.77 (95% CI: 3.22, 6.80) vs 5.67 (95% CI: 3.30, 9.06), respectively. In patients aged <30 days, crude mortality rates per 1000 person-days in the recommended and loading dose cohorts were 14.75 (95% CI: 4.81, 34.08) vs 7.14 (95% CI: 0.87, 25.56), respectively.

In patients aged ≥1 month to <17 years, after adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant increased IRRs were observed in the loading dose cohort when compared with the recommended dose cohort (adjusted IRR: 1.18; 95% CI: 0.57, 2.42). In patients aged <30 days, no IRRs were calculated due to small sample size.

Discussion

No relevant statistically significant differences were observed between the recommended and loading dose cohorts for the AE diagnostic categories and most of the specific AE diagnoses in patients aged ≥1 month to <17 years. In ≥1 month to <17 years, there was a two-fold increased risk of rash in the loading dose cohort compared with the recommended dose cohort. Overall, the current study findings are in line with the previously established LCM safety profile.

Marketing Authorization Holder(s)

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AED	Antiepileptic drug (s)
AV	Atrioventricular
BZD	Benzodiazepines
CI	Confidence interval
CLB	Clobazam
CLZ	Clonazepam
CZP	Carbamazepine
DCC	Data Coordinating Center
DQA	Data Quality Assessment
DZP	Diazepam
EHR	Electronic Health record (s)
EMA	European Medicines Agency
ETL	Extract, Lransform, Load
FBM	Felbamate
FDA	Food and Drug Administration Agency
FOS	Fosphenytoin
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IPTW	Inverse Probability of Treatment Weights
IQR	Interquartile Range
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
iv	Intravenous
kg	Kilogram
LCM	Lacosamide
LEV	Levetiracetam
LRZ	Lorazepam
LTG	Lamotrigine
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MP	Methylprednisolone
n/a	Not applicable

n/e	Not estimable
NR	Not reported
OMOP	Observational Medical Outcomes Partnership
OHDSI	Observational Health Data Sciences and Informatics
OXC	Oxcarbazepine
PASS	Post-Authorization Safety Study
PB	Phenobarbitone
PCORnet	Patient-Centered Clinical Research Network
PHE	Phenytoin
PMCA	Pediatric Medical Complexity Algorithm
PPN	Perampanel
RWE	Real world evidence
SD	Standard deviation
SE	Status epilepticus
SMQs	Standard Medical Dictionary for Regulatory Activities Queries
SNOMED-CT	Systematized nomenclature of medicine-clinical terms
SOC	System Organ Classes
TPM	Topiramate
TRX	Tranxene
US	United States
VNS	Vagal nerve stimulator
VPA	Valproic acid
ZNS	Zonisamide

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A list of all collaborating institutions and investigators can be obtained upon request.

5 STUDY PROTOCOL AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	10 Feb 2020	Sections 5	Amendment	Protocol was amended to address the comments from FDA on dosing and population criteria

6 MILESTONES

Milestones	Planned dates	Actual dates	Comments
Protocol first approval by IEC/IRB	Not applicable	16 Aug 2019	Not applicable
Amendment approval by IEC/IRB	Not applicable	21 Feb 2020	Not applicable
Start of data collection	Jan 2020	31 Jan 2020	Not applicable
End of data collection	30 Apr 2020	15 Jul 2020	Not applicable
Registration in the EU PAS register	Not applicable	04 Dec 2019	Not applicable
Final report of study results	30 Jun 2020	14 Sep 2020	Not applicable

7 RATIONALE AND BACKGROUND

Epilepsy affects the pediatric population with an estimated prevalence of 6.8 per 1000 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 study program (McGinnis and Kessler, 2016; Osokogu et al, 2016). VIMPAT (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 iv solution. It is currently approved in US for use as oral solution and oral tablet in patients over 4 years of age and as iv solution in patients over 17 years of age as an alternative to oral administration (FDA, 2017) for the treatment of partial onset seizures. VIMPAT was approved in the US in Oct 2008 and first introduced to the market in 2009. Intravenous use of LCM in children over 4 years of age is authorized in the EU; its benefit-risk profile is assessed as favorable by UCB and by the EU Health Authorities. VIMPAT dosage in adult patients can be started with the recommended initial dosage (as monotherapy 100mg twice daily; as adjunctive therapy 50mg twice daily) followed by a titration regimen (increase by 50mg twice daily every week). Alternatively, it may be initiated with a single loading dose of 200mg. 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 LCM in a pediatric population by using available data from electronic healthcare databases.

8 RESEARCH QUESTION AND OBJECTIVES

The **primary objective** of this study is to estimate the incidence of the selected medical events of interest, those being the 8 SOCs and 3 SMQs listed below, in pediatric patients after iv treatment with higher than the recommended LCM doses, compared to pediatric patients treated with recommended initial/maintenance 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 (DRESS)
- Severe cutaneous adverse reactions
- Hypersensitivity

The secondary objectives of this study are:

1. To estimate the incidence of the selected medical events among the SOCs and SMQs as indicated below, in pediatric patients after treatment with higher than the recommended initial iv LCM doses, compared to pediatric patients treated with recommended initial/maintenance iv LCM dose.

- Cardiac disorders
  - AV block
  - AV block complete
  - AV block first degree
  - AV 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 complication
  - Injection 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 selected medical events for 8 SOCs and 3 SMQ terms (listed in the primary objectives), compared to pediatric patients treated with recommended initial/maintenance iv LCM dose.

9 RESEARCH METHODS

9.1 Study design

This was a retrospective cohort study that used EHR data from the PEDSnet data network. The cohort design allowed the identification of pediatric patients treated with higher iv LCM doses than recommended dose (ie, loading dose) or a recommended initial/maintenance iv LCM dose, and the ability to follow them to identify the occurrence of outcomes of interest.

Data was collected in two steps. First, data elements within the PEDSnet database were examined. The PEDSnet database comprised structured data extracted from EHRs and transformed to the OMOP/OHDSI (Observational Medical Outcomes Partnership/Observational Health Data Sciences and Informatics) common data model (https://www.ohdsi.org/data-standardization/the-common-data-model/). Second, data not

available in the PEDSnet database, such as adverse drug events, were collected via chart reviews of the EHRs.

9.2 Setting

PEDSnet (pedsnet.org) is a national clinical research network that collects standardized EHR data for millions of children. The PEDSnet network includes the following health systems participating in this study: Children's Hospital of Philadelphia; Cincinnati Children's Hospital Medical Center; Children's Hospital of Colorado; Nationwide Children's Hospital; Nemours Children's Health System (both the Delaware and Florida health systems); Seattle Children's Hospital; and St. Louis Children's Hospital.

9.3 Data source

The PEDSnet database contains data stored in the OMOP/OHDSI common data model. All data elements are in a structured format. Data domains include demographics, vital status, insurance status, vital signs, encounter and provider characteristics, emergency department and inpatient visits, procedures, prescribed or dispensed medications, anthropometric measurements, diagnoses, location, drug exposure, procedures performed, diagnostic test results, and overall primary care, specialty, and acute care (emergency department and inpatient) utilization at member institutions. The full specifications for the PEDSnet database can be found at the following web site location: https://pedsnet.org/data/common-data-model/.

9.4 Study period

This study used the PEDSnet database (version 3.7) that includes individuals with at least one encounter with a PEDSnet institution from 01 Jan 2009 to 29 Feb 2020.

9.5 Patient selection period

The PEDSnet database includes any person with at least one encounter with a member health system from 01 Jan 2009 and until 29 Feb 2020. For persons meeting these criteria, any available data was included in the PEDSnet database, including data earlier than 2009. The **index date** for the loading iv LCM cohort was defined as the initiation of a new iv LCM treatment episode with an initial (ie, first) dose higher than the recommended iv LCM. The time of drug administration was captured. The **index date** for the recommended initial dosage/maintenance iv LCM cohort was the initiation of a new iv LCM treatment episode/receipt corresponding to a recommended initial dosage or a slow up titration.

9.6 Baseline period

The baseline period for this study was at least 3 months before the first newly initiated qualifying treatment episode of iv LCM; for patients less than 3 months of age at index event, the baseline period was from birth until the index event.

9.7 Follow-up period

The duration of follow-up was for a maximum of 37 days from the index date, defined as index date plus 37 days. This could capture up to 38 days of data about the patient. The episode of care concluded on the end date when any of the following happens:

- Discharge from the acute care hospital setting
- Transfer to another hospital or a post-acute care setting
- Death

- 37 days after the index date have elapsed

9.8 End date

The end date was the last day of the follow-up period. If patients had more than one episode of care, only the first episode of same event was included in the analyses. Patient time was contributed until either the end of follow-up or censor point (in days).

9.9 Patients

The study population consisted of two mutually exclusive cohorts and age groups. The groups were defined by age at the index date: patients aged ≥1month (1 month was defined as 30 days) to <17 years and patients aged <30 days. The age groups were mutually exclusive as patients entered the group were based on their earliest lifetime iv LCM exposure, regardless of subsequent iv LCM treatment episodes at a later date.

Selection criteria for patients aged ≥1month to <17 years:

- All patients in the PEDSnet database
- 1 or more iv LCM administration
- No exposure to either oral or iv LCM 3 months before the index date as determined in the PEDSnet database
- Aged ≥1month to <17 years at the index date
- Patients meeting above criteria were all selected for chart review
- Excluded based on oral or iv LCM administered 3 months before the index date as identified by the chart reviewer

Selection criteria for neonates aged <30 days:

- All patients in the PEDSnet database
- 1 or more iv LCM administration
- Aged <30 days at time of the first iv LCM administration
- No exposure to either oral or iv LCM at any time before the index date
- Patients meeting above criteria were all selected for chart review
- Excluded based on oral or iv LCM administered from birth to the index date as identified by the chart reviewer

9.9.1 Chart review

The study included chart reviews for the patients who met inclusion and exclusion criteria as determined from the PEDSnet database.

The chart reviews were conducted by medical students/fellows, physicians, and nurses at PEDSnet network hospitals to obtain data elements not available in the PEDSnet database. They were also used to validate eligibility criteria and LCM dosing information to ensure the validity of this variable, as it was needed to form the comparator cohorts. Chart reviews also identified AEs and potential adverse drug events attributed in the medical record to LCM. The occurrence of some AEs (eg, signs such as rash) are not consistently present in structured data about conditions and may only be recorded in physician or nurse notes as free text. The structured data also does not contain information attributing an adverse drug event to a particular drug, and this was also obtained from patient charts by the chart reviewer. To avoid the observation bias, the chart reviewers were blinded to full study protocol including title, objectives, and the classification of iv LCM dose.

9.10 Variables

9.10.1 Primary exposure variable

The two age-based groups were contrasted into cohorts based on whether the initial (ie, first) dose of iv LCM was given at the recommended dose or was higher than the recommended dose (ie, a loading dose). The cut-offs were estimated to achieve the same exposure as 200mg/day in adults.
The recommended initial dose of iv LCM was defined as follows:

Table 1: Recommended initial dose of iv LCM definition

Weight and age	Dose
<30kg and age <6 months	<4mg/kg
<30kg and age ≥6 months	<6mg/kg
≥30 to <50kg	<4mg/kg
≥50kg	<200mg

mg=Milligram; kg=Kilogram

Initial (ie, first) doses greater than the above levels were categorized as loading dose and defined as follows:

Table 2: Initial loading dose of iv LCM definition

Weight and age	Dose
<30kg and less than 6 months of age	≥4mg/kg
<30kg and greater than or equal to 6 months of age	≥6mg/kg
≥30 to <50kg	≥4mg/kg
≥50kg	≥200mg

mg=Milligram; kg=Kilogram

The information on primary exposure variables was extracted from PEDSnet database and further verified with the patient charts.

9.10.2 Additional exposure variables

Additional exposure variables of interest included details of LCM administration: indication of iv LCM, additional iv LCM administrations, received oral LCM during the follow up period, received iv LCM in the ICU and receipt of other AEDs included non-benzodiazepine before the index date, non-benzodiazepine given concomitantly, benzodiazepines before the index date, and benzodiazepines given concomitantly. The other AEDs were defined using data from the baseline period.

The information on additional variables was extracted from PEDSnet database and further verified with the patient charts.

9.10.3 Study outcome variables

The study examined the occurrence of a large number of AEs and contrasted their occurrence in the two exposure cohorts, ie, the recommended and loading dose cohorts. The outcomes were defined based on first occurrence of the AE of interest in the patient chart (list provided by UCB using MedDRA dictionary) recorded in medical charts. Only the first event of any

kind experienced by a patient was counted. For example, if a patient had a cardiac and a skin event on different dates, only the first event was counted in the overall incidence rate. These AEs are specified in Section 8. The information on AEs was incomplete in PEDSnet database, hence extracted from patient charts. There was also an 'Other' category to capture additional events that were not specified in the study objectives. These events were recorded in free text and were reviewed and adjudicated by PEDSnet physicians and assigned SNOMED-CT (Systematized nomenclature of medicine-clinical terms) concept names to standardize common diagnoses.

9.10.4 Other variables

Other variables included age, sex, race/ethnicity categories, weight at the index date, observation period before the index date, payer, PEDSnet health system, hospitalization in the 3 months before the index date, ambulatory visit in the 3 months prior to the index date, prior history of AE conditions any time prior to the index date, chronic condition body systems (Pediatric Medical Complexity Algorithm [PMCA]) any time prior to the index date, top 50 conditions any time prior to the index date, duration of the follow-up period, reason for censoring, and calendar year of the index date. Details on chronic condition body systems (PMCA) can be found in the published article (Simon et al, 2014).

The information on other variables was extracted from PEDSnet database and further verified with the patient charts.

9.11 Data sources and measurement

PEDSnet data management maintains an extensive structural data quality assessment (DQA) program, including data checks for missingness, data model compliance, and stability of data. This process has two goals: first, it works to maximize the quality of data available in the traditional sense of the word *quality*, that is, to find and correct errors in the collection or standardization of data. This process begins with >1000 tests done on data from each PEDSnet site in each quarterly data cycle. Secondly, the DQA program also is used to describe the operating characteristics of the data in several dimensions. This is especially relevant because PEDSnet collects data obtained in "real world" clinical settings, providing researchers with a window into clinical care. Also, as a Patient-Centered Clinical Research Network (PCORnet) network partner, PEDSnet must also meet the PCORnet's coordinating center quality assessments, which further assesses data elements for data model conformance, missing data in enrollment, encounters, demographics, vital findings, diagnoses, and procedures tables, and the plausibility of date and vital measures data. For details, please refer to the study protocol.

Chart review data was collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Children's Hospital of Philadelphia. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. The chart review data was entered into a REDCap Chart Review Form (CRF).

9.12 Bias

Unmeasured confounding: For the comparison of the incidence rates of the selected medical events of interest between patients who were treated with a loading dose of iv LCM and those who were treated with the recommended dose of iv LCM, certain observable factors were

identified which might have confounded these rates. The factors included age, gender, comorbidities, and exposure to other medications. Unmeasured confounding would only occur if there was a major confounder which was not measured and was thus involved in the adjusted model. However, the EHRs included demographic information, the medical history of the patients and any medications prescribed by the physicians. Also, there was no reason to expect differences in the recording of the medical history data and prescription of medications in patients who were treated with the loading dose LCM and recommended LCM prior to the index date.

Missing data: Data were obtained from EHRs of member institutions in PEDSnet. Patients are able to seek care outside of PEDSnet, which may lead to missing data. This would not be a problem for the follow-up period which occurred during an inpatient admission when complete data would be captured, however, it might have led to the medical history not fully reported during the baseline period.

Misclassification: Ascertainment of outcomes was made using controlled vocabularies. However, there was a risk of misclassification since there were no validated algorithms for defining these outcomes in EHR data. This risk was minimized through chart reviews which were conducted by trained healthcare personnel. Additionally, sensitivity analyses were conducted to assess the impact of the case definitions on the effect estimates. It is likely that any severe AEs would have been recorded. As noted, available data from the chart review were expected to be completed for patients in an inpatient setting. In particular, it was reasonable to expect nurses' notes to contain detailed information on patient responses and patient reported outcomes. As iv LCM was administered for patients in this study, there is a good reason to expect the recording of immediate AEs to be well documented, including those that might have been less severe such as injection site irritation/pain.

9.13 Study size

In the PEDSnet database, there were 1504 patients with at least one administration of iv LCM. After applying inclusion and exclusion criteria and subsequent chart reviewing, 686 patients aged ≥1month to <17 years and 28 neonates aged <30 days were eligible.

9.14 Data transformation

As noted in Section 9.1, the PEDSnet database comprised structured data extracted from EHRs and transformed to the OMOP/OHDSI common data model. Data from the PEDSnet member sites was received quarterly, and the version of the PEDSnet database used in this study was version 3.7. PEDSnet database data was queried using SQL and R programming languages and stored in their own tables as noted in the data dictionary in Appendix 2.

9.15 Statistical methods

9.15.1 Main summary measures

Means and standard deviations, medians and interquartile range, and minimum and maximum values, were used to describe continuous variables, whereas frequencies and percentages were used to describe categorical variables.

9.15.2 Main statistical methods

Statistical analysis and generation of tables, figures, patient data listings, and statistical output were performed using R software version 3.6.3. Additional R packages used:

- Survey 4.0 – to apply propensity score weights
- Epitools 0.5019 – to calculate incidence rates

- Tableone 0.12.0 – to simplify making most of the tables
- Tidyverse 1.30, including tibble 3.0.3, and tidyr 1.1.1 for data manipulation
- Knitr 1.29, scales 1.1.1 and kableExtra 1.1.0 for printing and formatting tables

Means and standard deviations, medians and interquartile range, minimum and maximum values, were used to describe continuous variables, whereas frequencies and percentages were used to describe categorical variables. The p-values associated with means (standard deviations) used t-tests. The p-values associated with medians (range or IQR) used Mann-Whitney test otherwise. Fisher's exact test was used for all binary/categorical variables across the board for consistency and simplicity rather than going back and forth based on small cell sizes.

Propensity scores were generated as logistic regression using the 'glm' function. The 'ps' score was the logistic regression probability of load_cat being 1. The scores were weighted using the Average Treatment Effect (ATE) weighting, where load_cat=1 scores were weighted by 1/ps and load_cat==0 were weighted by 1/(1-ps).

Unadjusted incidence rates were calculated using Poisson regression with an offset of log(days), where days were either the total follow-up days if the event did not happen or the days to event if it did happen. Propensity score weights were applied using the 'svyglm' function in the 'survey' package for R to implement Poisson regression.

The p-values for the adjusted and unadjusted rates were based on coefficient p-values returned by the glm/svyglm functions.

9.15.2.1 Study population characteristics

For the study population characteristics, means and standard deviations, medians and interquartile range, minimum and maximum values, were used to describe continuous variables, whereas frequencies and percentages were used to describe categorical variables. The study population characteristics included age, gender, race/ethnicity, payer at index date, and PEDSnet health system site.

9.15.2.2 Demographics and other baseline characteristics

For the baseline characteristics, means and standard deviations, medians and interquartile range, minimum and maximum values, were used to describe continuous variables, whereas frequencies and percentages were used to describe categorical variables. The baseline characteristics included demographic characteristics, number of previous and concomitant AEDs, concomitant medications prescribed prior to the index date, prevalence of chronic condition comorbidities, preexisting medical events of interest, and dosage of iv LCM. Analyses were stratified by the exposure variable: recommended vs loading dose of iv LCM.

9.15.2.3 Analysis of outcomes

Only the first occurrence of the event after the index date was counted in analyses. For both iv LCM cohorts, counts and frequency of events were recorded as well as patient-days of observation. A patient was censored if they experienced the event/outcome of interest or the censoring event.

For both dose cohorts, several incidence rates were computed. First, the overall incidence rate of any event of interest was calculated. Second, incidence rates and 95% CIs for each of the following events were 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, investigations for long PR interval, DRESS, 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.

For each incidence rate calculation, the numerator was the total number of patients experiencing the outcome during the follow-up period and the denominator was the patient-days of observation for that event. Patient-days of observation were counted either from the index date to the date of the event if the event happened, or from the index date to the date of last follow-up if it did not happen. Only the first occurrence of the particular event for a patient was counted, and patient-days were counted up to the first event only. Unadjusted rate ratios were also computed with their 95% CI for each outcome. Since the sample size was small for patients aged <30 days, the rate ratios were not computed for this age group.

9.15.2.4 Regression analyses

Regression analyses were used to control for differences in the demographic and clinical characteristics between the two cohorts. Adjusted incidence rates and rate ratios were computed using Poisson regression. It is important to note incidence rates per time at risk were based on a constancy assumption. That is, the rates per unit of time assumed that the event occurred with a constant rate over time. Events that were 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. Person-time of observation was not presented in Tables in case of 0 events.

9.15.2.5 Propensity score

For the patients aged ≥1 month to <17 years, a propensity score was estimated using a logistic regression model in which membership in one of the two dose cohorts (loading [scored as 1] vs recommended [scored as 0]) was regressed on baseline characteristics. Specific covariates for inclusion in the propensity score model were selected based on their potential association with the AE outcomes. Covariates that were included:

- Age at index date, categorized at <1, 1-4, 5-11, 12-17 years
- Sex (Male/Female)
- Race/Ethnicity (Hispanic, Black/African-American, White, Asian/Pacific Islander, Other)
- PEDSnet health system (A-H)
- Duration of observation before index date (categorized as none, <1y, 1y, 2y, 3y, 4+y)
- Weight at index date
- Payer at index visit (Commercial, Public, Other)
- Count of the number of unique AEDs given any time before the index date
- Pre-existing health conditions: binary variables for each PMCA chronic condition body system class
- Calendar year of index date

Each patient's propensity score was the probability that they were in the loading dose cohort.

9.15.2.6 Evaluation of propensity score balance

The propensity score was assessed for balance between the two dose cohorts. First, the propensity score distributions were plotted in a box plot and a density plot (x-axis is score and y-axis is density) for the comparator cohorts. To evaluate adequate overlap of the

propensity scores, the density distribution of the propensity scores was visually inspected with the assumption that the distributions between the two cohorts would be similar. Second, the full cohort was split into quintiles based on the propensity score and the proportion of patients in each of the comparator cohorts by quintile was computed. For each quintile the mean (standard deviation) of the propensity score for the two cohorts was computed and a two-sample t-test was computed with equal variances to examine differences between the cohorts.

A second approach was used to assess the balance of the covariates computed standardized differences (ie, differences in means or proportions divided by the pooled standard error) were examined for all variables in both analyses. Although there is no commonly accepted threshold for a meaningful difference between cohorts, a cut-point of 0.35 was used in this study. Additionally, continuous variables were compared using graphical methods including boxplots and density plots.

Some imbalance of propensity scores between the two was probable. If the score was imbalanced, all variables were evaluated for correlation and less clinically important variables were dropped which might be correlated with another covariate. After these changes were made, the balancing evaluation was implemented.

9.15.2.7 Inverse probability of treatment weighting

The IPTW was computed using the propensity scores in order to compute from a regression analysis the average treatment effect. Thus, the weights for the loading dose cohort (the "treated" group) were 1/propensity score, and the weights for the recommended dose cohort were 1/(1-propensity score).

Given IPTW is often hampered by extreme propensity scores, resulting in biased estimates and excessive variance, the distribution of the stabilized weights was evaluated using graphical displays (eg, boxplots) and descriptive statistics. The characteristics of the patients with outlier weights were examined and, if necessary, the model was re-specified and the weights re-estimated. Given the sample size, retention of all patients was helpful. Thus, extreme weights were found they were replaced with the 95th percentile of weights in the respective group. In addition, the usual standard errors generated by the weighted model would tend to be mis-specified, which in turn would produce mis-specified CIs. This issue was circumvented via the use of robust standard errors (sandwich) and trimming excess weights were dropped.

9.15.2.8 Poisson regression models

The IPTW-weighted Poisson regression model with robust variance estimators (regressed on exposure status in the sample weighted by the IPTW) were used to estimate adjusted incidence rate ratios and 95% CIs of each AE outcome. The advantages of IPTW weighting includes retention of all study patients and estimation of an average exposure effect in the whole population of eligible patients as IRR. As this study was reliant on a relatively small population of patients, and where comparison was undertaken between cohorts, retaining all patients allows for greater power to investigate significant differences between cohorts. The IPTW-weighted model was generated using the 'svyglm' function in the 'survey' package for R, which incorporates both IPTW weights as sampling weights and a robust variance estimator. Since these weights may not be integers, quasibinomial and quasipoisson error families were used for generalized linear models. Patient-days of observation were included as an offset.

9.15.3 Missing values

All REDCap questions were designed as required fields. No blank values were allowed on any eCRFs marked as 'Complete'.

9.15.4 Sensitivity analyses

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

- The maximum follow-up time was shortened from the index date plus 37 days down to the index date plus 7 days from the index date, such that any AEs that happen outside that shortened window were included in the incidence rates.
- Exclude patients with pre-existing medical events as determined by the PMCA chronic conditions. However, this still included patients with pre-existing PMCA neurologic conditions.
- For a given AE, any patients with history of with the same category of AE diagnosis were excluded.

9.15.5 Amendments to the statistical analysis plan

The relevant content changes to data presented and analyses planned in the protocol include:

- Loading dose: In the original protocol, the loading dose was defined as "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." This definition was simplified to define dose cohorts by the initial dose at the recommended or loading doses previously mentioned, and not require a lower subsequent dose 12 hours later, as this was more complicated to determine programmatically and patients with higher initial doses might continue to receive the higher dose and not necessarily receive lower doses.
- Follow up period: The follow-up period was modified such that all patients would be followed up for a maximum of 37 days following the index date or until censored. This included patients who received only a single dose of iv LCM, regardless of whether or not they subsequently received oral LCM. This was done because it was challenging to account for patients who switched back and forth between iv and oral, and for patients who might have longer than expected gaps between LCM dosing.
- Censoring: Censoring after the index date would only occur for any of the following 4 events: discharge from the acute care hospital setting, transfer to another hospital or a post-acute care setting (eg, transfer to rehab), death, or 37 days had after the index date. Stopping LCM in favor of an alternative or adjunctive AED was not included as a censoring event as patients who stopped LCM could still potentially have AEs attributable to LCM following cessation of LCM.
- Seizure history details: information about the number of seizures or electroencephalogram results were not part of the PEDSnet structured data and were removed from chart review data collection or use in propensity scoring.
- Separate analysis for status epilepticus: the protocol mentions a request to describe patients with an indication of status epilepticus separately and also as part of the entire study age group. However, this was not done given the small numbers and thus not included in the scientific specifications.

- Sensitivity Analyses: the following protocol-defined sensitivity analyses was not conducted due to the fact that PEDSnet could not relate medications or procedures that occurred after the AE was identified by chart reviewer as treatments/procedures for the AE. There was still the possibility that the treatment/procedure was intended for another reason or condition, unless it was truly pathognomonic for the AE in question. This was beyond the ability of the database to provide this answer-most EHR source systems do not have structured metadata that associate the treatment/procedure with a specific diagnosis/finding. To have identified this relationship, the chart reviewer would have to identify specific treatments/procedures done in response to the AE occurrence.
  - Shorten the baseline period to 6 weeks: this could not be done because the chart reviewers were originally looking at a 3 months baseline period and excluded 82 patients based on receiving LCM at some point during that 3 months period. Chart reviewers were asked to supply the earliest date of LCM during that period. If the time to 6 weeks was shortened, it might have accidentally included patients who were receiving LCM in the 6 weeks before the index date, but there would have no way to be sure without repeating chart reviews on all of those patients.
  - Outcome definitions will include a code for an outcome-related medication/procedure within the period following the diagnosis record (to be defined): it could not be made sure that the outcome-related medication/procedure was specific to the diagnosis of interest.

9.16 Quality control

9.16.1 Identifying inconsistencies between chart review input and PEDSnet structured data

Patients with iv LCM administration were identified electronically using the PEDSnet database and information in CRFs was entered manually using the patient EHR chart data.

9.16.2 Baseline LCM exposure

If the chart reviewer indicated that the patient received any oral or iv LCM inpatient administration at their institution within 3 months prior to the PEDSnet-identified index date, they were prompted to contact the data coordinating center (DCC) for further instruction. In these cases, the DCC asked for the REDCap record_id of the patient and queried the PEDSnet database for any LCM drug exposures in the 3 months prior to the patient's index date. If the DCC could not find a database record of LCM exposure in the 3 months prior to the index date, it could be due to the patient refilling a prescription that was ordered more than 3 months prior but filled by the patient and the pharmacy dispense data was not in the database. Based on the chart reviewer's confirmation of LCM received in the 3 months prior, the patient was excluded from further chart review.

9.16.3 Index or observation period end date discrepancies

The chart reviewer was provided with and asked to confirm the index date and observation end period as determined using PEDSnet database. A custom REDCap report identified instances where chart reviewers indicated that either the index date or observation period end date in the manual chart review did not match the dates extracted from the PEDSnet data. The DCC ran the report on a weekly basis and reviewed the cases of discordance. For each of the date discrepancies, the chart reviewer was prompted to input the actual index or observation period end date as observed in the EHR. For each of these cases, the DCC queried the PEDSnet database to identify if the patient had any drug exposure (ie, prescription,

administration, etc) on the date provided by the chart reviewer. If the DCC determined that the patient did receive an inpatient iv LCM administration on the date provided by the chart reviewer and that the patient met all inclusion criteria on that index date, the DCC provided the chart reviewer with an updated index date and observation period end period date based on the chart reviewer's finding. The chart reviewer then continued with the chart review using the updated dates.

9.16.4 Validation

For some data elements, the chart reviewer was prompted to input the findings from the manual chart review without prior knowledge of the values in the PEDSnet data. These variables were included as validation of the structured data. The DCC compared the manually entered and database elements to determine any discordance but did not alter the pathway of the chart reviewer based upon discrepancies. These date elements included: date of birth, sex, weight nearest to the patient's first inpatient iv LCM administration, date of that weight measurement and the dose, in milligrams, of the first inpatient iv LCM administration.

9.16.5 Demographic discrepancies

If the birth date or sex variables entered by the chart reviewer did not match those available in the PEDSnet database, the DCC contacted the chart reviewer to confirm that the correct value was entered into the CRF. If the chart reviewer confirmed a discrepancy between the EHR and PEDSnet database, the DCC reached out to the Extract, Transform, Load (ETL) analyst at the institution to investigate the potential mapping error.

9.16.6 Weight or dose discrepancies

If the chart reviewer identified a patient weight closer to the index date than identified by the DCC, the DCC queried the PEDSnet database to determine whether a weight is available in the measurement table that was not detected by the closest-weight algorithm. If so, the weight was be updated in the DCC data and chart review proceeded. If the DCC did not find a weight closer to the index date than the chart reviewer does, the DCC reached out to the chart reviewer to prompt them to look for a weight on the date provided. If any discrepancies existed between the dose amounts from the two data sources, the DCC reached out to the institution's ETL analyst to investigate the potential mapping error. The ability of PEDSnet to interact with informaticians at member institutions to resolve identified data-related problems is a major strength of the study setting.

9.16.7 AEs

The CRF contained all specified AEs outlined by UCB. There was also an 'Other' category to capture additional events that were not specifically requested. These events were recorded in free text, and were reviewed by Dr. [redacted] (PEDSnet Clinical Informatician and Study Co-Investigator) and assigned SNOMED-CT concept names to standardize common diagnoses. The assignments were reviewed by Dr. [redacted] (PEDSnet Principal Investigator) and the final adjudication was used to label these 'Other' events.

Dates of AEs were also reviewed and if dates either appeared outside the follow-up period (eg, before the index date or after the end of the follow-up period), the chart reviewer was asked to re-confirm the dates. In some cases where the year appeared to be entered incorrectly, likely from incorrect data entry, the chart reviewer also re-confirmed the year. All such adjudications and changes were tracked and maintained for audit review.

9.16.8 Chart review procedures

All chart reviewers were required to attend a live webinar training before beginning chart review. Prior to the training, a detailed Chart Review Training Manual was created and circulated to the site chart reviewers. During the training the PEDSnet study team reviewed the Chart Review Training Manual in detail, and gave instructions on where to find the required information in the EpicCare health record system the medical record system used by almost all PEDSnet sites.

As part of the training, the PEDSnet study team also trained the chart reviewers on UCB's Safety Reporting Obligations version 4.0. After the training, each chart reviewer submitted a completed Safety Reporting Obligations Vendor Training Assessment Quiz; each quiz was reviewed and graded to ensure every chart reviewer met the minimum 80% accuracy score.

Once the chart reviewers completed the mandatory training and assessment, they completed an initial pre-test of three charts per site. The PEDSnet study team held one-on-one phone calls with each chart reviewer at the completion of their pilot test to review the results and discuss any remaining questions raised by the chart reviewers before they continued on with the full set of charts at each site. As the chart reviewers worked on the chart reviews at each site, the PEDSnet data team was actively reviewing the results and flagging any areas that needed additional clarification or review.

The chart review form data was exported from the REDCap tool and stored in the study database. Attachment in the Appendix 2 contains the CRF with variables, field types, and value sets for the data collected.

10 RESULTS

10.1 Participants

10.1.1 Patients aged ≥1 month to <17 years

Table 3 summarizes the number of patients aged ≥1 month to <17 years that were available in the PEDSnet database. The original data file consisted of 6,528,164 patients in PEDSnet database. Of the 6,528,164 patients, 1504 patients had 1 or more iv LCM administration. After using selection criteria, ie, no exposure to either oral or iv LCM before the index date determined by the PEDSnet database, 769 patients were eligible for chart reviews. From the chart reviews, 83 out of 769 patients did not meet the selection criteria and 686 patients were eligible for the study. Reasons for exclusion of those 83 patients was one patient received oral and not iv LCM, and the other 82 patients had notes indicating that the patients were taking LCM in the 3 months prior to the index date.

Table 3: Patients aged ≥1 month to <17 years: iv LCM attrition

Step	Selection criterion	Number of patients remaining (% Total)	Number of patients excluded (% Prior step)
1	Total number of patients in PEDSnet database	6,528,164 (100.00)	0 (0.00)
2	1 or more iv LCM administration	1,504 (0.02)	6,526,660 (99.98)
3	iv LCM administration at ≥1 month and <17 years of age	1,248 (0.02)	256 (17.02)

Step	Selection criterion	Number of patients remaining (% Total)	Number of patients excluded (% Prior step)
4	No exposure to either oral or iv LCM before index date (determined by PEDSnet database analysis)	769 (0.01)	479 (38.38)
5	Patients remaining after chart review identified patients that actually did not meet all inclusion/exclusion criteria	686 (0.01)	83 (10.79)

iv=Intravenous; LCM=Lacosamide

10.1.2 Patients aged <30 days

Table 4 summarizes the number of neonate patients that were available in PEDSnet database. The original data file consisted of 6,528,164 patients in the PEDSnet database. Of the 6,528,164 patients, 1504 patients had 1 or more iv LCM administration. After using selection criteria, ie, no exposure to either oral or iv LCM before the index date determined by the PEDSnet database and confirmed by chart reviews, 28 patients were eligible for the study.

Table 4: Patients aged <30 days old: iv LCM attrition

Step	Selection criterion	Number of patients remaining (% Total)	Number of patients excluded (% Prior step)
1	Total number of patients (in database)	6,528,164 (100.00)	0 (0.00)
2	Patients with 1 or more intravenous LCM administration	1,504 (0.02)	6,526,660 (99.98)
3	Patients with iv LCM administration at <30 days of age	28 (0.00)	1,476 (98.14)
4	No exposure to either oral or iv LCM before index date (determined by PEDSnet database analysis)	28 (0.00)	0 (0.00)
5	Patients remaining after chart review identified patients that actually did not meet all inclusion/exclusion criteria	28 (0.00)	0 (0.00)

iv=Intravenous; LCM=Lacosamide

10.2 Descriptive data

10.2.1 Classification of patients by age and weight

10.2.1.1 Patients aged ≥1 month to <17 years

For classification of patients in the recommended and loading dose cohorts, the age was classified into the following categories; 30 days to <6 months, 6 months to <1 year, 1 year to <4 years, 4 to <12 years and 12 to <17 years. Each age category was further subclassified into weight groups. The assigned weight group was based on the weight measurement at or closest to the index dose of LCM. The majority of patients weighed between 4 to 10kg in age category of 30 days to <6 months (88.7%) and 6 months to <1 year (89.7%), between 10 to 20kg in age category of 1 to <4 years (80.7%) and between 20 to 30kg in age category of 4 to

<12 years (48.3%) and ≥50kg (52.4%) in age category of 12 to <17 years. There was overlapping of weight categories among age categories (Table 5).

Table 5: Patients aged ≥1 month and <17 years exposed to iv LCM grouped by age and weight

Age/weight category	Number of patients (%)
Total number of patients	686 (100)
30 days to <6 months	
<4kg	[redacted]
4 to 10kg	63 (88.7)
6 months to <1 year	
4 to 10kg	35 (89.7)
10 to 20kg	[redacted]
1 year to <4 years	
<4kg	[redacted]
4 to 10kg	26 (17.9)
10 to 20kg	117 (80.7)
20 to 30kg	[redacted]
4 to <12 years	
10 to 20kg	58 (21.7)
20 to 30kg	129 (48.3)
30 to 50kg	68 (25.5)
≥50kg	12 (4.5)
12 to <17 years	
10 to 20kg	[redacted]
20 to 30kg	18 (11.0)
30 to 50kg	59 (36.0)
≥50kg	86 (52.4)

kg=Kilogram

10.2.1.2 Patients aged <30 days

For classification of patients aged <30 days in the recommended and loading dose cohorts, the age group was classified into two weight categories; <4kg and 4 to 10kg. The weight category was based on the measurement at or close to the index dose of LCM. The ratio of <4kg to 4-10kg was almost 2:1. The majority of patients weighed <4kg (67.9%) (Table 6).

Table 6: Patients aged <30 days exposed to iv LCM grouped by weight

Age/weight category	Number of patients (% total)
Total number of patients	28 (100)
<4kg	19 (67.9)
4 to 10kg	[redacted]

kg=Kilogram

10.2.2 Distribution of age groups by initial dose cohort

10.2.2.1 Patients aged ≥1 month to <17 years

By the initial dosing of iv LCM, two cohorts were formed namely; the recommended dose and the loading dose. The recommended and loading doses were calculated by using the data on age and weight. Of 686 patients, 68.7% were administered the recommended dose vs 31.3% were administered the loading dose as initial doses. Among the recommended dose cohort, the highest proportion of patients (70.3%) weighed less than 30kg and were aged ≥6 months. Among the loading dose cohort, the highest proportion of patients (48.8%) weighed ≥30kg (Table 7).

Table 7: Distribution of patients aged ≥1 month to <17 years by initial dose cohort formed by examining the index LCM administration dosage

Weight-based sub-cohort	Recommended dose cohort, n (%) (N=471)	Loading dose cohort, n (%) (N=215)
<30kg and <6 months	20 (4.2)	51 (23.7)
<30kg and ≥6 months	331 (70.3)	59 (27.5)
≥30 to <50kg	67 (14.2)	60 (27.9)
≥50kg	53 (11.3)	45 (20.9)

kg=Kilogram
Note: The recommended dose cohort met the following age, weight, and initial dose criteria:
Up to 4mg/kg for patients less than 30kg and less than 6 months of age
Up to 6mg/kg for patients less than 30kg and greater than or equal to 6 months of age
Up to 4mg/kg for patients between 30 and 50kg
Up to 200mg for patients greater than 50kg

The loading dose cohort exceeded the dosage level for patients' respective age and weight category.
≥4mg/kg for patients less than 30kg and less than 6 months of age
≥ 6mg/kg for patients less than 30kg and greater than or equal to 6 months of age
≥ 4mg/kg for patients between 30 and 50kg
≥ 200mg for patients greater than 50kg

10.2.2.2 Patients aged <30 days

By the initial dosing of iv LCM, two cohorts were formed in patients <30 days old; namely, the recommended dose and loading dose cohorts. The recommended and loading doses were calculated by using the data on age and weight. Out of 28 patients, 57.1% were administered an iv LCM recommended dose vs 42.9% were given loading dose as initial doses. Weight was classified into two categories: <4kg and 4 to 10kg. The ratio of <4kg to 4-10kg was almost 2:1 in both categories (Table 8).

Table 8: Distribution of patients aged <30 days by initial dose cohort formed by examining the index LCM administration dosage

Weight-based sub-cohort	Recommended dose cohort, n (%) (N=16)	Loading dose cohort, n (%) (N=12)
<4kg	11 (68.8)	[redacted]
4 to 10kg	[redacted]	[redacted]

Note: The recommended dose cohort for newborns was up to 4mg/kg. Loading doses were equal or exceed that level.

10.2.3 Demographic characteristics

10.2.3.1 Patients aged ≥1 month to <17 years

The demographic characteristics between both cohorts were different except age at index date, gender and total duration of observation before the index date. The difference in age distribution, patients with encounter before index date, race/ethnicity, payer and distribution of patients across the PEDSnet health system between both cohorts was statistically significant (Table 9).

10.2.3.1.1 Age

The mean age of patients at index date was 6.9 years in the recommended dose cohort vs 7.6 years in the loading dose cohort.

The patients in both dose cohorts were divided into the following age groups: 30 days to <6 months, 6 months to <1 year, 1 year to <4 years, 4 to <12 years and 12 to <17 years. The majority of patients received iv LCM in 4 to <12 years age group in the recommended dose cohort (45.4%) and 12 to <17 years age group in the loading dose cohort (33.4%). The difference in age distribution between both cohorts was statistically significant (p<0.001). The minority of patients were observed in age category of 30 days to <6 months in the recommended dose (4.2%) and 6 months to <1 year in the loading dose cohorts (0.5%).

10.2.3.1.2 Duration of observation before the index date

In the recommended dose and loading dose cohorts, 87.9% vs 81.4%, respectively, had an encounter before the index date (p=0.032). Mean total duration of observation before the index date was almost the same in both dose cohorts, ie, 1569.1 days in the recommended dose cohort and 1567.6 days in the loading dose cohort.

10.2.3.1.3 Gender

In both the dose cohorts, the genders were distributed similarly, ie, (males were 56.1% in the recommended dose cohort vs 55.3% in the loading dose cohort).

10.2.3.1.4 Ethnicity

In both the dose cohorts, the highest proportion of patients were White, ie, 54.8% in the recommended dose cohort vs 63.3% in the loading dose cohort and none or minority were of American Indian or Alaska natives, ie, 0% in the recommended dose cohort vs 1.3% in the loading dose cohort. The distribution of ethnicity was different between the cohorts and the difference was statistically significant (p=0.009).

10.2.3.1.5 Payer

The highest proportion of patients were public payers in both the cohorts (recommended dose 56.5% vs loading dose 47.0%). In the recommended dose cohort, 31.0% were private or commercial and in the loading dose cohort, 33.5% of patients were self-paid/others. The difference in distribution of the patients by payer type was significantly different between both the cohorts (p<0.001).

10.2.3.1.6 PEDSnet health system

In the recommended dose cohort, sites A and C contributed approximately half of the total patients, while in the loading dose cohort, sites A and B contributed 61.8% of total patients.

The difference in distribution of the patients across the PEDSnet health system was statistically significant between both the cohorts (p<0.001).

Table 9: Demographic characteristics by initial dose cohort in patients aged ≥1 month to <17 years

Characteristic	Recommended dose cohort, n (%) (N=471)	Loading dose cohort, n (%) (N=215)	p-value
Age at index date, years, mean (SD)	[redacted])	[redacted]	0.515
Age, n (%)			
30 days to <6 months	20 (4.2)	51 (23.7)	<0.001
6 months to <1 year	38 (8.1)	[redacted]	
1 year to <4 years	107 (22.7)	38 (17.7)	
4 to <12 years	214 (45.4)	53 (24.7)	
12 to <17 years	92 (19.6)	72 (33.4)	
Duration of observation before index visit			
Patients with encounter before Index Visit, n (%)	414 (87.9)	175 (81.4)	0.032
Total duration, days, mean (SD)	1569.07 (2078.05)	1567.56 (1588.50)	0.993
Gender, n (%)			
Male	264 (56.1)	119 (55.3)	0.929
Female	207 (43.9)	96 (44.7)	
Race/ethnicity, n (%)			
White	258 (54.8)	136 (63.3)	0.009
Black/African-American	62 (13.2)	31 (14.4)	
Asian/Native Hawaiian/Pacific Islander	23 (4.9)	[redacted]	
Hispanic/Latino	74 (15.7)	24 (11.2)	
American Indian or Alaska Native	0 (0.0)	[redacted]	
Multiple/Other/Unknown/Refused	54 (11.4)	15 (7.0)	
Payer (at index visit), n (%)			
Public	266 (56.5)	101 (47.0)	<0.001
Private/Commercial	146 (31.0)	42 (19.5)	
Self-Pay/Other	59 (12.5)	72 (33.5)	
PEDSnet health system, n (%)			
A	103 (21.9)	48 (22.3)	<0.001
B	70 (14.8)	85 (39.5)	
C	132 (28.0)	[redacted]	
D	56 (11.9)	30 (14.0)	
E	64 (13.6)	15 (7.0)	
F	40 (8.5)	20 (9.3)	
G	[redacted]	[redacted]	
H	[redacted]	[redacted]	

SD=Standard deviation
Demographics were taken from the person tables at PEDSnet, except for the age and duration of observation which were based on visit tables.

10.2.3.2 Patients aged <30 days

The demographic characteristics in both the dose cohorts were similar in patients <30 days old except distribution of patients across the PEDSnet health system. This difference in patient contribution by sites in the PEDSnet health system between both the dose cohorts was statistically significant (Table 10).

10.2.3.2.1 Age

The mean age of patients at the index date was 14.2 days in the recommended dose cohort vs 16.2 days in the loading dose cohort.

10.2.3.2.2 Duration of observation before the index visit

In the recommended vs loading dose cohort, 31.2% vs 25.0% had an encounter before the index date.

10.2.3.2.3 Gender

The genders were distributed similarly between the two cohorts, ie, males 43.8% in the recommended dose cohort vs 41.7% in the loading dose cohort.

10.2.3.2.4 Race/ethnicity

In the recommended and loading dose cohorts, the highest proportion of patients were White (68.8% vs 66.7%) and no patients were observed in American Indian or Asian/Native Hawaiian/Pacific Islander origin categories.

10.2.3.2.5 Payer at the index visit

In the recommended dose cohort, half of the patients were public payers. In the loading dose cohort, patients were equally distributed by public, private/commercial and self-pay/others (ie, 33.3% each).

10.2.3.2.6 PEDSnet health system

In the recommended dose cohort, most of the patients were from sites A, D and F, ie, 81.1% and in the loading dose cohort, the highest proportion of patients were from sites A and B, ie, 91.6%. The difference in the distribution of patients among sites between both the dose cohorts was statistically significant (p=0.031).

Table 10: Demographic characteristics by initial dose cohort in patients aged <30 days

Characteristic	Recommended dose cohort, n(%) (N=16)	Loading dose cohort, n(%) (N=12)	p-value
Age at index date, days, mean (SD)	14.19 (8.78)	16.17 (10.65)	0.594
Duration of observation before index visit			
Patients with encounter before Index Visit, n (%)	[redacted]	[redacted]	1.000
Total duration, days, mean (SD)	[redacted]	[redacted]	0.949

Characteristic	Recommended dose cohort, n(%) (N=16)	Loading dose cohort, n(%) (N=12)	p-value
Gender, n (%)			
Male	[redacted]	[redacted]	1.000
Female	[redacted]	[redacted]	
Race/Ethnicity, n (%)			
White	11 (68.8)	[redacted]	
Black/African-American	[redacted]	[redacted]	
Asian/Native Hawaiian/Pacific Islander			0.810
Hispanic/Latino			
American Indian or Alaska Native			
Multiple/Other/Unknown/Refused			
Payer (at index visit), n (%)			
Public	[redacted]	[redacted]	
Private/Commercial			0.639
Self-Pay/Other			
PEDSnet Health System, n (%)			
A	[redacted]	[redacted]	
B			
C			
D			0.031
E			
F			
G			
H			

SD=Standard deviation
Demographics were taken from the person tables at PEDSnet, except for the age and duration of observation which were based on visit tables.

10.2.4 Baseline characteristics

10.2.4.1 Patients aged ≥1 month to <17 years

The baseline characteristics in both the dose cohorts were similar for prior hospitalization in the baseline period, presence of chronic conditions by body system-PMCA, and any prior history of AE conditions. A statistically significant difference was found between both the cohorts for variables such as weight at index date, indication of iv LCM administration and prior ambulatory visit in baseline period and most of the top 50 conditions prior to index date (Table 11).

10.2.4.1.1 Weight at the index date

The weight of patients was divided into the following categories; <4kg, 4 to 10kg, 10 to 20kg, 20 to 30kg, 30 to 50kg and ≥50kg. The highest proportion of patients, 58.4%, were in the 10 to 30kg weight category in the recommended dose cohort while 48.8% were in the 30 to ≥50kg weight category in the loading dose cohort. The difference between both the dose cohorts in the distribution of patients in weight categories was statistically significant (p<0.001) (Table 11).

10.2.4.1.2 Indication for iv LCM administration

The indication for iv LCM administration was classified into the following categories; epilepsy (focal, syndrome), status epilepticus, seizures with fever, seizures without a diagnosis, others. In the recommended and loading dose cohorts, the highest proportion of patients were administered iv LCM for the indication of epilepsy (48.2% vs 42.3%) and status epilepticus (28.5% vs 33.5%). The difference between both the dose cohorts in the distribution of patients in indication categories was statistically significant (p=0.021).

10.2.4.1.3 Prior hospitalization in the baseline period

In the recommended and loading dose cohorts, 36.7% vs 32.6% had prior hospitalization during the baseline period, respectively.

10.2.4.1.4 Prior ambulatory visit in the baseline period

In the recommended and loading dose cohorts, 67.9% vs 56.3% had a prior ambulatory visit during the baseline period, respectively. The difference between both the dose cohorts in the proportion of patients with a prior ambulatory visit was statistically significant (p=0.004).

10.2.4.1.5 Presence of chronic conditions by the body system

Presence of chronic conditions by body systems was identified by using the PMCA algorithm. In the recommended and loading dose cohorts, presence of chronic conditions ranged from 1.3% vs 1.4% for genitourinary body system to 50.3% vs 48.8% for neurologic body system. No statistically significant differences were found between both the cohorts.

10.2.4.1.6 Any prior history of AE conditions

In the recommended dose cohort, the proportion of patients with prior history of AEs ranged from 0 for psychiatric disorders, injury, poisoning and procedural complications, DRESS and hypersensitivity to 15.1% for skin and subcutaneous tissue disorders.

In the loading dose cohort, the proportion of patients with prior history of AEs ranged 0 for injury, poisoning and procedural complications, DRESS and hypersensitivity to 13.5% for general disorders and administration site conditions.

No statistically significant differences were found between both cohorts.

10.2.4.1.7 Top 50 conditions prior to the index date

In the recommended dose cohort, the proportion of top 50 conditions ranged from 8.9% for obstructive sleep apnea syndrome to 46.5% for seizures.

In the loading dose cohort, the proportion of top 50 conditions ranged from 4.7% for pediatric failure to thrive to 27.9% for seizures.

The proportions of patients with conditions prior to the index date in both cohorts were statistically different for the following; seizure, epilepsy, constipation, developmental delay, fever, delay in physiological development, postoperative state, vomiting, acute upper respiratory infection, disorder of brain, feeding problem, and gastroesophageal reflux disease, viral disease, dysphagia, feeding difficulties and mismanagement, incoordination, dehydration, disorder of psychological development, delayed milestone, past history of procedure, gastrostomy, gastrostomy present, history of gastrostomy and pediatric failure to thrive.

Table 11: Baseline clinical characteristics by initial dose cohort in patients aged ≥1 month to ≤17 years

Characteristic	Recommended dose cohort, n (%) (N=471)	Loading dose cohort, n (%) (N=215)	p-value
Weight (at index date)			
<4kg	[redacted]	[redacted]	
4 to 10kg	73 (15.5)	51 (23.7)	
10 to 20kg	144 (30.6)	36 (16.8)	<0.001
20 to 30kg	131 (27.8)	17 (7.9)	
30 to 50kg	67 (14.2)	60 (27.9)	
≥50kg	53 (11.3)	45 (20.9)	
Indication for iv LCM administration			
Epilepsy (focal, syndrome)	227 (48.2)	91 (42.3)	
Status epilepticus	134 (28.5)	72 (33.5)	
Seizures with fever	[redacted]	[redacted]	0.021
Seizures without a diagnosis	89 (18.9)	31 (14.4)	
Other	16 (3.3)	18 (8.4)	
Prior hospitalization in baseline period			
At least one hospitalization in 3 months before index visit	173 (36.7)	70 (32.6)	0.330
Prior ambulatory visit in baseline period			
At least one ambulatory visit in 3 months before index visit	320 (67.9)	121 (56.3)	0.004
Presence of chronic conditions by body system-PMCA			
Cardiovascular	59 (12.5)	29 (13.5)	0.821
Craniofacial	11 (2.3)	[redacted]	0.927
Dermatologic	12 (2.5)	[redacted]	1.000
Endocrinologic	31 (6.6)	16 (7.4)	0.802
Gastrointestinal	62 (13.2)	30 (14.0)	0.872
Genetic	45 (9.6)	18 (8.4)	0.723
Genitourinary	[redacted]	[redacted]	1.000
Hematologic	27 (5.7)	[redacted]	0.690
Immunologic	16 (3.4)	[redacted]	0.770
Malignancy	18 (3.8)	[redacted]	0.763
Mental health	121 (25.7)	43 (20.0)	0.127
Metabolic	43 (9.1)	14 (6.5)	0.316
Musculoskeletal	70 (14.9)	30 (14.0)	0.844

Characteristic	Recommended dose cohort, n (%) (N=471)	Loading dose cohort, n (%) (N=215)	p-value
Neurologic	237 (50.3)	105 (48.8)	0.781
Ophthalmologic	81 (17.2)	28 (13.0)	0.202
Otologic	37 (7.9)	[redacted]	0.168
Any prior history of AE conditions			
Cardiac disorders	57 (12.1)	28 (13.0)	0.830
Skin and subcutaneous tissue disorders	71 (15.1)	24 (11.2)	0.209
Nervous system disorders	35 (7.4)	19 (8.8)	0.630
Metabolism and nutrition disorders	[redacted]	[redacted]	0.948
Psychiatric disorders	0 (0.0)	[redacted]	0.687
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	
General disorders and administration site conditions	63 (13.4)	29 (13.5)	1.000
DRESS	0 (0.0)	0 (0.0)	
Hypersensitivity	0 (0.0)	0 (0.0)	
Top 50 conditions prior to the index date			
Seizure	219 (46.5)	60 (27.9)	<0.001
Epilepsy	169 (35.9)	40 (18.6)	<0.001
Constipation	135 (28.7)	31 (14.4)	<0.001
Developmental delay	131 (27.8)	29 (13.5)	<0.001
Fever	117 (24.8)	23 (10.7)	<0.001
Refractory epilepsy	100 (21.2)	38 (17.7)	0.329
Delay in physiological development	107 (22.7)	29 (13.5)	0.007
Postoperative state	104 (22.1)	28 (13)	0.007
Vomiting	103 (21.9)	25 (11.6)	0.002
Acute upper respiratory infection	98 (20.8)	29 (13.5)	0.029
Disorder of brain	95 (20.2)	25 (11.6)	0.009
Feeding problem	97 (20.6)	22 (10.2)	0.001
Gastroesophageal reflux disease	92 (19.5)	24 (11.2)	0.009
Partial epilepsy with impairment of consciousness	81 (17.2)	33 (15.3)	0.622
Viral disease	95 (20.2)	19 (8.8)	<0.001
Dysphagia	92 (19.5)	21 (9.8)	0.002
Status epilepticus	81 (17.2)	26 (12.1)	0.111

Characteristic	Recommended dose cohort, n (%) (N=471)	Loading dose cohort, n (%) (N=215)	p-value
Seizure disorder	81 (17.2)	25 (11.6)	0.079
Otitis media	75 (15.9)	22 (10.2)	0.062
Epilepsy, not refractory	71 (15.1)	24 (11.2)	0.209
Cough	74 (15.7)	21 (9.8)	0.049
Feeding difficulties and mismanagement	78 (16.6)	16 (7.4)	0.002
Needs influenza immunization	69 (14.6)	24 (11.2)	0.264
Incoordination	73 (15.5)	16 (7.4)	0.005
Dehydration	71 (15.1)	17 (7.9)	0.013
Disorder of psychological development	72 (15.3)	15 (7.0)	0.004
Localization-related(focal)(partial)idiopathic epilepsy and epileptic syndromes with seizures of localized onset	66 (14)	20 (9.3)	0.109
Acute respiratory failure	64 (13.6)	22 (10.2)	0.268
Delayed milestone	69 (14.6)	15 (7.0)	0.007
History of clinical finding in subject	61 (13)	22 (10.2)	0.375
Diarrhea	61 (13)	21 (9.8)	0.287
Tachycardia	59 (12.5)	20 (9.3)	0.272
Past history of procedure	64 (13.6)	12 (5.6)	0.003
Cerebral palsy	58 (12.3)	18 (8.4)	0.163
Gastrostomy	60 (12.7)	15 (7.0)	0.035
Gastrostomy present	62 (13.2)	12 (5.6)	0.005
Hearing loss	56 (11.9)	18 (8.4)	0.213
Generalized convulsive epilepsy	53 (11.3)	20 (9.3)	0.525
Gastroesophageal reflux disease without esophagitis	55 (11.7)	17 (7.9)	0.174
History of gastrostomy	59 (12.5)	13 (6.0)	0.015
Hypoxemia	49 (10.4)	22 (10.2)	1.000
Pediatric failure to thrive	58 (12.3)	[redacted]	0.003
Anemia	54 (11.5)	14 (6.5)	0.061
Localization-related symptomatic epilepsy	48 (10.2)	19 (8.8)	0.678
Intellectual disability	51 (10.8)	13 (6.0)	0.063
Urinary tract infectious disease	47 (10)	16 (7.4)	0.355
Difficulty swallowing	50 (10.6)	13 (6.0)	0.075
Obstructive sleep apnea syndrome	42 (8.9)	18 (8.4)	0.929

Characteristic	Recommended dose cohort, n (%) (N=471)	Loading dose cohort, n (%) (N=215)	p-value
Acidosis	46 (9.8)	14 (6.5)	0.210
Grand mal status	45 (9.6)	15 (7.0)	0.336

AE=Adverse event; DRESS= Drug reaction with eosinophilia and systemic symptoms syndrome; kg=Kilogram; iv=Intravenous; LCM=Lacosamide; PMCA= Pediatric Medical Complexity Algorithm

10.2.4.2 Patients aged <30 days

In both of the dose cohorts, baseline characteristics including weight at the index date, indication for iv LCM administration, prior hospitalization in the baseline period, prior ambulatory visit in the baseline period, presence of chronic conditions by body systems, any prior history of AE conditions and top 50 conditions prior to the index date were similar and no statistically significant differences were found between them (Table 12).

10.2.4.2.1 Weight at the index date

The weight was divided into two categories: <4kg and 4 to 10kg. The ratio of <4kg to 4-10 kg was almost 2:1 in both cohorts.

10.2.4.2.2 Indication for iv LCM administration

In the recommended dose cohort, patients had iv LCM indication for status epilepticus (31.2%), seizure without diagnosis (37.5%), epilepsy (focal, syndrome) (12.5%), and others (18.8%).

In the loading dose cohort, patients had iv LCM indication for status epilepticus (8.3%), seizure without diagnosis (75.0%), and others (16.7%).

10.2.4.2.3 Prior hospitalization in the baseline period

In the recommended and loading dose cohorts, 6.2% vs 0 patients had a prior hospitalization in the baseline period.

10.2.4.2.4 Prior ambulatory visit in the baseline period

In the recommended dose cohort, 12.5% patients had a prior ambulatory visit in the baseline period and in the loading dose cohort, no prior ambulatory visit in the baseline period was observed.

10.2.4.2.5 Presence of chronic conditions by the body system

Using the PMCA algorithm, 6.2% were reported to have chronic (neurologic) conditions in the recommended cohort and none of the patients reported to have any chronic condition in the loading dose cohort.

10.2.4.2.6 Any prior history of AE conditions

None of the patients had any prior history of AE conditions in the recommended dose cohort vs 8.3% patients had a prior history of nervous system AEs in the loading dose cohort.

10.2.4.2.7 Top 50 conditions prior to the index date

In the recommended dose cohort, the proportion of top 50 conditions ranged from 0 for various conditions to 12.5% with fever of the newborn.

In the loading dose cohort, the proportion of top 50 conditions ranged from 0 for several conditions 0 to 16.7% for feeding problem.

Table 12: Baseline clinical characteristics by initial dose cohort in patients aged <30 days old

Characteristic	Recommended dose cohort, n (%) (N=16)	Loading dose cohort, n (%) (N=12)	p-value
Weight (at index Date)			
<4kg	11 (68.8)	[redacted]	1.000
4 to 10kg	[redacted]		
Indication for iv LCM administration			
Epilepsy ([redacted])	[redacted]	0 (0.0)	0.218
Status epilepticus		[redacted]	
Seizures without a diagnosis			
Other			
Prior hospitalization in baseline period			
At least one hospitalization before index visit	[redacted]	0 (0.0)	1.000
Prior ambulatory visit in baseline period			
At least one ambulatory visit before index visit	[redacted]	0 (0.0)	0.492
Presence of chronic conditions by body system PMCA			
Cardiovascular	0 (0.0)	0 (0.0)	1.00
Craniofacial	0 (0.0)	0 (0.0)	
Dermatologic	0 (0.0)	0 (0.0)	
Endocrinologic	0 (0.0)	0 (0.0)	
Gastrointestinal	0 (0.0)	0 (0.0)	
Genetic	0 (0.0)	0 (0.0)	
Genitourinary	0 (0.0)	0 (0.0)	
Hematologic	0 (0.0)	0 (0.0)	
Immunologic	0 (0.0)	0 (0.0)	
Malignancy	0 (0.0)	0 (0.0)	
Mental health	0 (0.0)	0 (0.0)	
Metabolic	0 (0.0)	0 (0.0)	
Musculoskeletal	0 (0.0)	0 (0.0)	
Neurologic	[redacted]	0 (0.0)	
Ophthalmologic	0 (0.0)	0 (0.0)	
Otologic	0 (0.0)	0 (0.0)	

Characteristic	Recommended dose cohort, n (%) (N=16)	Loading dose cohort, n (%) (N=12)	p-value
Renal	0 (0.0)	0 (0.0)	
Respiratory	0 (0.0)	0 (0.0)	
Any prior history of AE conditions			
Cardiac disorders	0 (0.0)	0 (0.0)	
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	
Nervous system disorders	0 (0.0)	[redacted]	
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	
Psychiatric disorders	0 (0.0)	0 (0.0)	0.429
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	
General disorders and administration site conditions	0 (0.0)	0 (0.0)	
DRESS syndrome	0 (0.0)	0 (0.0)	
Hypersensitivity	0 (0.0)	0 (0.0)	
Top 50 conditions prior to the index ate			
Feeding problem	0 (0.0)	[redacted]	0.175
Seizure	[redacted]	[redacted]	1.000
Fever of the newborn	[redacted]	0 (0.0)	0.492
Localization-related(focal)(partial)idiopathic epilepsy and epileptic syndromes with seizures of localized onset	[redacted]	[redacted]	1.000
Convulsions in the newborn	[redacted]	[redacted]	1.000
Pulmonary hypertension	0 (0.0)	[redacted]	0.429
Subdural hemorrhage following injury without open intracranial wound AND with prolonged loss of consciousness (more than 24 hours) without return to pre-existing conscious level	0 (0.0)	[redacted]	0.429
Pericardial effusion	[redacted]	[redacted]	1.000
Respiratory failure			0.429
Swelling, edema symptom			1.000
Baby premature 33 weeks			1.000
Ischemic stroke			0.429
Fetal or neonatal effect of maternal infection			1.000
Prolonged loss of consciousness			0.429
Metabolic disease			0.429
Fever			1.000
Physical child abuse			0.429

Characteristic	Recommended dose cohort, n (%) (N=16)	Loading dose cohort, n (%) (N=12)	p-value
Traumatic intracranial subarachnoid hemorrhage	0 (0.0)	[redacted]	0.429
Failure to thrive in infant	[redacted]	[redacted]	1.000
Disorder of fetus or newborn	[redacted]	[redacted]	0.429
Edema	[redacted]	[redacted]	1.000
Meningitis	[redacted]	[redacted]	0.429
Opioid dependence	[redacted]	[redacted]	0.429
Meconium aspiration syndrome	[redacted]	[redacted]	0.429
Hypoxemia	[redacted]	[redacted]	1.000
Family history of clinical finding	[redacted]	[redacted]	1.000
Opioid withdrawal	[redacted]	[redacted]	0.429
Neonatal tachycardia	[redacted]	[redacted]	1.000
Neonatal respiratory failure	[redacted]	[redacted]	0.429
Cortical hemorrhage	[redacted]	[redacted]	1.000
Hemorrhagic cerebral infarction	[redacted]	[redacted]	0.429
Bacterial meningitis	[redacted]	[redacted]	0.429
Disorder of nervous system	[redacted]	[redacted]	1.000
Cerebral hemisphere hemorrhage	[redacted]	[redacted]	1.000
Bacterial meningoencephalitis	[redacted]	[redacted]	0.429
Intraventricular (nontraumatic) hemorrhage, grade 3, of fetus and newborn	[redacted]	[redacted]	1.000
Obstructive hydrocephalus	[redacted]	[redacted]	0.429
Feeding problems in newborn	[redacted]	[redacted]	0.429
Disturbance of temperature regulation of newborn	[redacted]	[redacted]	1.000
Escherichia coli meningitis	[redacted]	[redacted]	0.429
Posthemorrhagic hydrocephalus	[redacted]	[redacted]	0.429
Vomiting	[redacted]	[redacted]	1.000
Cerebral hemorrhage	[redacted]	[redacted]	1.000
Bacteremia caused by Gram-positive bacteria	[redacted]	[redacted]	0.429
Dialysis finding	[redacted]	[redacted]	0.429
Feeding poor	[redacted]	[redacted]	0.429
Abrasion of head	[redacted]	[redacted]	0.429

Characteristic	Recommended dose cohort, n (%) (N=16)	Loading dose cohort, n (%) (N=12)	p-value
Place of occurrence of accident or poisoning, residential house	[redacted]	[redacted]	0.429
Neonatal aspiration of milk and regurgitated food			0.429
Term birth of newborn			0.429

AE=Adverse event; DRESS= Drug reaction with eosinophilia and systemic symptoms syndrome; kg=Kilogram; iv=Intravenous; LCM=Lacosamide; PMCA= Pediatric Medical Complexity Algorithm

10.2.5 Medication patterns

10.2.5.1 Patients aged ≥1 month to <17 years

There seemed to be no distinction for medication patterns between both the dose cohorts except for count of iv LCM administrations, number of unique non-LCM AEDs and unique non-benzodiazepine AEDs (Table 13).

10.2.5.1.1 Count of iv LCM administrations

The median number of count of iv LCM administrations was 3 (range 1.00-10.00) in the recommended dose cohort and 2 (range 1.00-10.00) in the loading dose cohort. In the recommended and loading dose cohorts, the mean number of LCM administrations was similar, ie, approximately 9 and the majority of patients had ≥4 iv LCM administrations (44.3% vs 45.1%, respectively in the recommended and loading dose cohorts). The difference between the dose cohorts in the count of iv LCM administrations was statistically significant (p<0.001).

10.2.5.1.2 Patients received oral LCM during the follow-up period

In each cohort, 59% patients received oral LCM.

10.2.5.1.3 Patients in ICU at time of initial dose of iv LCM

The initial dose of LCM was administered in ICU in 51.2% of patients in the recommended dose cohort and 58.1% in loading dose cohort.

10.2.5.1.4 Number of unique non-LCM AEDs, any type, any time before the index date

The mean number of any non-LCM AEDs before the index date was 5.57 (range 0-19) in the recommended dose cohort and 4.66 (range 0-17) in the loading dose cohort. The difference between both the dose cohorts was statistically significant (p=0.001).

10.2.5.1.5 Unique non-benzodiazepine AEDs any time before the index date

The mean number of non-benzodiazepine AEDs before the index date was 2.47 (range 0-6) to 1.99 (range 0-6). In the recommended and loading dose cohorts, 91.3% and 84.2% had ≥1 non-benzodiazepine AED before the index date, respectively. The difference between both the dose cohorts was statistically significant (p<0.001).

10.2.5.1.6 Unique benzodiazepine AEDs any time before the index Date

The mean number of benzodiazepine AEDs before the index date was 3.10 (range 0-13) to 2.67 (range 0-11). In the recommended and loading dose cohorts, 92.4% and 88.8% had ≥1 benzodiazepine AED before the index date, respectively.

10.2.5.1.7 Patients on concomitant non-benzodiazepine AEDs

In the recommended and loading dose cohorts, 91.9% and 92.6% had ≥1 concomitant non-benzodiazepine AED before the index date, respectively.

10.2.5.1.8 Patients on concomitant benzodiazepine AEDs

In the recommended and loading dose cohorts, 77.7% and 74.0% had ≥1 concomitant benzodiazepine AED before the index date, respectively.

10.2.5.1.9 Top 10 non-AED medications

In the recommended dose cohort, the proportion of patients ranged from 44.4% with osmotically acting laxatives to 73.9% with anilides-N02BE.

In the loading dose cohort, the proportion of patients ranged from 36.3% with amides-N01BB to 70.7% with anilides-N02BE.

Table 13: Medication patterns in patients aged ≥1 month to <17years

Characteristic	Recommended dose cohort (N=471)	Loading dose cohort (N=215)	p-value
LCM medication administered during episode of care			
Count of iv LCM administrations			
1, n (%)	159 (33.8)	94 (43.7)	<0.001
2, n (%)	70 (14.9)	15 (7.0)	
3, n (%)	33 (7.0)	[redacted]	
4+, n (%)	209 (44.3)	97 (45.1)	
Mean (SD)	8.85 (14.17)	8.87 (16.71)	0.990
Median (IQR)	3 (1.00, 10.00)	2 (1.00, 10.00)	0.234
Minimum	1	1	
Maximum	110	141	
Patients received oral LCM during follow-up period, n (%)	279 (59.2)	127 (59.1)	1.000
Patients in ICU at time of initial dose of iv LCM, n (%)	241 (51.2)	125 (58.1)	0.099
Other anti-epileptic drugs (AEDs)			
Number of unique non-LCM AEDs, any type, any time before index date			
Mean (SD)	5.57 (3.28)	4.66 (3.22)	0.001
Median (IQR)	5 (3.00, 8.00)	4 (2.00, 6.00)	<0.001
Minimum	0	0	

Characteristic	Recommended dose cohort (N=471)	Loading dose cohort (N=215)	p-value
Maximum	19	17	
Unique non-benzodiazepine AEDs any time before index Date			
0 unique non-benzodiazepine AED, n (%)	41 (8.7)	34 (15.8)	
1 unique non-benzodiazepine AED, n (%)	78 (16.6)	53 (24.7)	<0.001
2 unique non-benzodiazepine AEDs, n (%)	130 (27.6)	60 (27.9)	
3+ unique non-benzodiazepine AEDs, n (%)	222 (47.1)	68 (31.6)	
Mean (SD)	2.47 (1.41)	1.99 (1.44)	<0.001
Median (IQR)	2 (1.00, 3.00)	2 (1.00, 3.00)	<0.001
Minimum	0	0	
Maximum	6	6	
Unique benzodiazepine AEDs any time before index Date			
0 unique benzodiazepine, n (%)	36 (7.6)	24 (11.2)	0.190
1 unique benzodiazepine, n (%)	76 (16.1)	43 (20.0)	
2 unique benzodiazepines, n (%)	101 (21.4)	45 (20.9)	
3+ unique benzodiazepines, n (%)	258 (54.9)	103 (47.9)	
Mean (SD)	3.10 (2.11)	2.67 (2.03)	0.013
Median (IQR)	3 (2.00, 4.00)	2 (1.00, 4.00)	0.007
Minimum	0	0	
Maximum	13	11	
Patients on concomitant[1] non-benzodiazepine AEDs, n (%)			
0 concomitant non-benzodiazepine AED	38 (8.1)	16 (7.4)	
1 concomitant non-benzodiazepine AED	134 (28.5)	71 (33.0)	0.653
2 concomitant non-benzodiazepine AEDs	161 (34.2)	66 (30.7)	
3+ concomitant non-benzodiazepine AEDs	138 (29.3)	62 (28.8)	
Patients on concomitant[1] benzodiazepine AEDs, n (%)			
0 concomitant benzodiazepine AED	105 (22.3)	56 (26.0)	
1 concomitant benzodiazepine AED	192 (40.8)	85 (39.5)	0.098
2 concomitant benzodiazepine AEDs	125 (26.5)	63 (29.3)	
3+ concomitant benzodiazepine AEDs	49 (10.4)	11 (5.1)	
Other medications			
Top 10 Non-AED Medications by ATC Drug Class[2] received any time before Index Date, n (%)			
Anilides-N02BE	348 (73.9)	152 (70.7)	0.436
H2-receptor antagonists-A02BA	250 (53.1)	105 (48.8)	0.343

Characteristic	Recommended dose cohort (N=471)	Loading dose cohort (N=215)	p-value
Solutions for parenteral nutrition-B05BA	211 (44.8)	107 (49.8)	0.259
Opioid anesthetics-N01AH	236 (50.1)	80 (37.2)	0.002
Other quaternary ammonium compounds-M03AC	211 (44.8)	101 (47.0)	0.654
Serotonin (5HT3) antagonists-A04AA	216 (45.9)	92 (42.8)	0.505
Other general anesthetics-N01AX	218 (46.3)	81 (37.7)	0.043
Propionic acid derivatives	210 (44.6)	86 (40.0)	0.297
Amides-N01BB	210 (44.6)	78 (36.3)	0.050
Osmotically acting laxatives-A06AD	209 (44.4)	79 (36.7)	0.073

AED=Anti-epileptic drugs; ATC= Anatomical Therapeutic Chemical ; IQR=Interquartile range; iv=Intravenous; LCM=Lacosamide; SD=Standard deviation
[1] Concomitant is defined as administration on the same date as iv LCM.
[2] Top 10 Non-AED Medications by ATC Drug Class were determined from the overall dose cohorts combined, then the number of patients receiving those medications were compared between cohorts. These drug classes were not mutually exclusive as a patient could take medications from multiple drug cohorts.

10.2.5.2 Patients aged <30 days

Overall, no statistically significant difference was found in the medication patterns between the dose cohorts (Table 14).

10.2.5.2.1 Count of iv LCM administrations

The median number of count of iv LCM administrations was 11 (range 1.75-36.50) in the recommended dose cohort and 4 (range 2.50-13.00) in the loading dose cohort. In the recommended dose and loading dose cohorts, mean number of LCM administrations was 19.75 and 11.42 and the highest proportion of patients had ≥4 iv LCM administrations (56.2% vs 50.0%). The proportion of patients with at least 1 LCM administration was same in both the cohorts, ie, 25.0%.

10.2.5.2.2 Patients received oral LCM during the follow-up period

In the recommended and loading dose cohorts, 50.0% and 33.3% patients received oral LCM, respectively.

10.2.5.2.3 Patients in ICU at time of initial dose of iv LCM

The initial dose of LCM was administered in ICU in 93.8% and 100.0% in the recommended and loading dose cohorts, respectively.

10.2.5.2.4 Number of unique non-LCM AEDs, any type, any time before the index date

The mean number of any non-LCM AEDs before the index date was 3.81 (range 2-7) in the recommended dose cohort and 3.58 (range 1-5) in loading dose cohort.

10.2.5.2.5 Unique non-benzodiazepine AEDs any time before the index date

The mean number of non-benzodiazepine AEDs before the index date was 1.25 (range 0-2) in the recommended dose cohort to 1.08 (range 0-2) in the loading dose cohort. In the

recommended and loading dose cohorts, 87.5% and 75.0% had ≥1 benzodiazepine AED before the index date, respectively.

10.2.5.2.6 Unique benzodiazepine AEDs any time before the index date

The mean number of benzodiazepine AEDs before the index date was 2.56 (range 1-5) in the recommended dose cohort to 2.50 (range 0-3) in the loading dose cohort. In the recommended and loading dose cohorts, 100.0% and 91.7% had ≥1 benzodiazepine AED before the index date, respectively.

10.2.5.2.7 Patients on concomitant non-benzodiazepine AEDs

All patients received at least 1 non-benzodiazepine AED concomitantly in both cohorts.

10.2.5.2.8 Patients on concomitant benzodiazepine AEDs

In the recommended and loading dose cohorts, 81.2% and 66.7% received at least 1 or more concomitant benzodiazepine AEDs, respectively.

Table 14: Medication patterns in patients aged <30 days old

Characteristic	Recommended dose cohort (N = 16)	Loading dose cohort (N = 12)	p-value
LCM medication administered during episode of care			
Count of iv LCM administrations 1, n (%) 2, n (%) 3, n (%) 4+, n (%)	[redacted]	[redacted]	0.124
Mean (SD)	19.75 (21.80)	11.42 (19.15)	0.302
Median (IQR)	11 (1.75, 36.50)	4 (2.50, 13.00)	0.497
Minimum	1	1	
Maximum	70	70	
Patients received oral LCM during follow-up period, n (%)	[redacted]		0.459
Patients in ICU at time of initial dose of iv LCM, n (%)	15 (93.8)	12 (100.0)	1.000
Other AEDs			
Number of unique non-LCM AEDs, any type, any time before index date Mean (SD)	3.81 (1.76)	3.58 (1.31)	0.708
Median (IQR)	3.50 (2.00, 5.00)	3.50 (3.00, 5.00)	0.849
Minimum	2	1	
Maximum	7	5	
Unique non-benzodiazepine AEDs any time before index date 0 unique non-benzodiazepine AED, n (%) 1 unique non-benzodiazepine AED, n (%)	[redacted]		0.775

2 unique non-benzodiazepine AEDs, n (%)	[redacted]		
3+ unique non-benzodiazepine AEDs, n (%)			
Mean (SD)	1.25 (0.68)	1.08 (0.79)	0.556
Median (IQR)	1.00 (1.00, 2.00)	1.00 (0.75, 2.00)	0.580
Minimum	0	0	
Maximum	2	2	
Unique benzodiazepine AEDs any time before index date			
0 unique benzodiazepine AED, n (%)	[redacted]		
1 unique benzodiazepine AED, n (%)			0.242
2 unique benzodiazepine AEDs, n (%)			
3+ unique benzodiazepine AEDs, n (%)			
Mean (SD)	2.56 (1.26)	2.50 (1.00)	0.889
Median (IQR)	2.50 (1.75, 3.25)	3 (2.75, 3.00)	0.922
Minimum	1	0	
Maximum	5	3	
Patients on concomitant[1] non-benzodiazepine AEDs, n (%)			
0 concomitant non-benzodiazepine AED	[redacted]	[redacted]	
1 concomitant non-benzodiazepine AED			0.858
2 concomitant non-benzodizapine AEDs			
3+ concomitant non-benzodiazepine AEDs			
Patients on concomitant[1] benzodiazepine AEDs, n (%)			
0 concomitant benzodiazepine AED	[redacted]	[redacted]	
1 concomitant benzodiazepine AED	12 (75.0)		0.807
2 concomitant benzodiazepine AEDs	[redacted]	0 (0.0)	
3+ concomitant benzodiazepine AEDs	0 (0.0)	0 (0.0)	

AED=antiepileptic drugs; ICU=intensive care unit; IQR=interquartile range; iv=intravenous; LCM=lacosamide; SD=standard deviation

[1] Concomitant is defined as administration on the same date as iv LCM.

10.2.6 Duration of follow up period

10.2.6.1 Patients aged ≥1 month to <17 years

No distinction was found between the two dose cohorts; the mean duration of follow up in the recommended and loading dose cohorts was 13 days (range 0-37) and 14 days (range 0-37), respectively. The median duration of follow up in the recommended and loading dose cohorts was 8 days (range 2-23) and 7 days (range 2-27), respectively. The main reason for censoring at follow up in the recommended and loading dose cohorts was discharged home from the acute care hospital setting (77.9% vs 72.6%), 37 days transpired in hospital (13.8% vs 17.2%), death (6.4% vs 7.9%), and transfer to another hospital or a post-acute care setting (1.9% vs 2.3%) (Table 15).

Table 15: Follow-up period characteristics in patients aged ≥1 month to <17 years

Characteristic	Recommended dose cohort (N=471)	Loading dose cohort (N=215)	p-value
Duration of follow-up period (days)			
Mean (SD)	13 (13)	14 (14)	0.591
Median (IQR)	8 (2, 23)	7 (2, 27)	0.941
Minimum	0	0	
Maximum	37	37	
Reason for censoring at follow-up, n (%)			
Death	30 (6.4)	17 (7.9)	
Discharged home from the acute care hospital setting	367 (77.9)	156 (72.6)	0.465
Transferred to another hospital or a post-acute care setting	[redacted]	[redacted]	
37 days transpired in hospital	65 (13.8)	37 (17.2)	

IQR=Interquartile range; SD=Standard deviation

10.2.6.2 Patients aged <30 days

No statistically significant distinction between the two dose cohorts was observed. The mean duration of follow up in the recommended and loading dose cohorts was 21 days (range 1-37) and 23 days (range 3-37), respectively. The median duration of follow up in the recommended and loading dose cohorts was 26 days (range 8-32) and 26 days (range 13-35), respectively. The main reason for censoring in the recommended and loading dose cohorts was discharged home from the acute care setting (37.5% vs 58.3%), deaths (31.2% vs 16.7%), transfer to another hospital or a post-acute care setting (6.3% vs 0%) and 37 days transpired in hospital (25.0% vs 25.0%) (Table 16).

Table 16: Follow-up period characteristics in patients aged <30 days old

Characteristic	Recommended dose cohort (N=16)	Loading dose cohort (N=12)	p-value
Duration of follow-up period			
Mean (SD)	21 (14)	23 (13)	0.679
Median (IQR)	26 (8, 32)	26 (13, 35)	0.779
Minimum	1	3	
Maximum	37	37	
Reason for censoring at follow-up, n (%)			
Death	[redacted]	[redacted]	0.775
Discharged home from the acute care			
Transferred to another hospital or a post-acute care setting			
37 days transpired in hospital			

IQR=Interquartile range; SD=Standard deviation

10.3 Outcome data

10.3.1 Counts of other AEs

10.3.1.1 Patients aged ≥1 month to <17 years

The highest absolute number of events were tachycardia (n=17) under cardiac disorder category in the recommended dose cohort and feeling agitated [redacted] under psychiatric disorders in the loading dose cohort (Table 17).

Table 17: Counts of other AEs in patients aged ≥1 month to <17 years

AE diagnostic categories (SNOMED-CT)	AE	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Cardiac disorders	Disorder of atrioventricular (not morphologically mitral or tricuspid) valve	[redacted]	[redacted]
	Heart failure		
	Hypertensive disorder, systemic arterial		
	Infective endocarditis		
	Left ventricular cardiac dysfunction		
	Left ventricular hypertrophy		
	Low blood pressure	11	
	Prolonged QT interval	[redacted]	
	Shock co-occurrent and due to anaphylaxis		
	Sinus arrest		
	Tachycardia	17	
General disorders and administration site conditions	Abdominal compartment syndrome	[redacted]	[redacted]
	Acute conjunctivitis		
	Acute injury of kidney		
	Anemia		
	Apnea		
	Aspiration pneumonia		
	Bacteremia		
	Bleeding from nose		
	Blood in urine		
	Candidiasis of mouth		
	Corneal ulcer		
	Excessive salivation		
	Exposure keratoconjunctivitis		

AE diagnostic categories (SNOMED-CT)	AE	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
	Febrile neutropenia	[redacted]	[redacted]
	Fever		
	Fracture of femur		
	Functional gait instability		
	Gait disturbances		
	Gastroparesis		
	Hematochezia		
	Hemosiderin pigmentation		
	Hydrocele of testis		
	Hydronephrosis		
	Hypervolemia		
	Hypothermia		
	Hypoxia		
	Increased blood leukocyte number		
	Intestinal obstruction co-occurrent and due to decreased peristalsis		
	Kidney stone		
	On examination - penile discharge		
	Physical deconditioning		
	Pneumatosis coli		
	Pneumonia		
	Pulmonary aspiration		
	Recurrent dislocation of hip		
	Respiratory distress		
	Respiratory failure		
	Respiratory insufficiency		
	Respiratory obstruction		
	Retention of urine		
	Septic shock		
	Shock		
	Stridor		
	Subconjunctival hemorrhage		
	Superior vena cava syndrome		

AE diagnostic categories (SNOMED-CT)	AE	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
	Systemic lupus erythematosus	[redacted]	[redacted]
	Tinnitus		
	Torsion of ovary		
	Tracheitis		
	Urinary tract infectious disease		
	Vascular insufficiency of intestine		
	Venous thrombosis due to central venous access device		
	Ventilator-acquired pneumonia		
	Vocal cord palsy		
Injury, poisoning, and procedural complications	Accidental poisoning by alcohol		
	Acute deep venous thrombosis of right femoral vein		
	Closed fracture of fifth metacarpal		
	Compartment syndrome of lower limb		
	Complication of intravascular line		
	Deep venous thrombosis of left lower extremity		
	Deep venous thrombosis of left upper extremity		
	Dislocation of temporomandibular joint		
	Erythema at injection site		
	Fall from bed		
	Isoflurane poisoning		
	Magnetic resonance imaging of cervical spine abnormal		
	Malignant hyperthermia		
	Thromboembolism of vein		
	Thrombosis of cephalic vein		
	Thrombosis of jugular vein		
	Venous thrombosis due to central venous access device		
Metabolism and nutrition disorders	Abdominal discomfort		
	Constipation		

AE diagnostic categories (SNOMED-CT)	AE	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
	Diabetes insipidus	[redacted]	[redacted]
	Diarrhea		
	Dysphagia		
	Failure to gain weight		
	Feeding difficulties and mismanagement		
	Gastroesophageal reflux disease		
	Gastrostomy hemorrhage		
	Hematochezia		
	Hepatic failure		
	Hyperammonemia		
	Hyperglycemia		
	Hyperkalemia		
	Hypernatremia		
	Hypoglycemia		
	Hypokalemia		
	Hyponatremia		
	Increased aspartate transaminase level		
	Intestinal obstruction co-occurrent and due to decreased peristalsis		
	Lactic acidosis		
	Loose stool		
	Metabolic acidosis		
	Nausea		
	Necrotizing enterocolitis in fetus OR newborn (disorder)		
	Pancreatitis		
	Severe protein-calorie malnutrition		
	Small bowel obstruction		
	Syndrome of inappropriate vasopressin secretion		
	Unable to eat		
	Vitamin D deficiency		
	Volvulus of the small bowel		

AE diagnostic categories (SNOMED-CT)	AE	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
	Vomiting	15	[redacted]
	Weight loss	[redacted]	
Nervous system disorders	Akathisia		
	Anoxic encephalopathy		
	Apraxia		
	Aseptic meningitis		
	Autoimmune encephalitis caused by N-methyl Daspartate receptor antibody		
	Bilateral hearing loss		
	Brain disorder resulting from a period of impaired oxygen delivery to the brain		
	Central fever		
	Cerebral edema		
	Cerebral infarction		
	Cerebrovascular accident		
	Chorea		
	Choreoathetosis		
	Cortical visual impairment		
	Delirium		
	Diplopia		
	Disorder of autonomic nervous system		
	Disorder of brain		
	Dizziness		
	Dyskinesia		
	Dysmetria		
	Dyssomnia		
	Dystonia		
	Encephalitis		
	Esotropia		
	Expressive dysphasia		
	Headache disorder		
	Hemorrhagic cerebral infarction		
	Hypoxic ischemic encephalopathy		

AE diagnostic categories (SNOMED-CT)	AE	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
	Impairment of mental alertness	[redacted]	0
	Incoherent speech		0
	Increased muscle tone		0
	Insomnia		0
	Intracranial hemorrhage		0
	Intracranial hypotension		0
	Left hemiparesis		0
	Lethargy		0
	Low pressure headache		0
	Meningitis		0
	Movement disorder		0
	Muscular hypertonicity		[redacted]
	Nystagmus		
	On examination - fixed, dilated pupils		
	Posterior reversible encephalopathy syndrome		
	Raised intracranial pressure		
	Rasmussen syndrome		
	Slurred speech		
	Spasticity		
	Spinal stenosis in cervical region		
	Spinal subdural hematoma		
	Stupor		
	Subdural hygroma		
	Tremor		
	Weakness of left arm		
	Weakness of left facial muscle		
	Weakness of left leg		
Psychiatric disorder	Adjustment disorder with disturbance of conduct		
	Aggressive behavior		
	Altered mental status		
	Anxiety		

AE diagnostic categories (SNOMED-CT)	AE	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
	Attention deficit hyperactivity disorder	[redacted]	[redacted]
	Catatonia		
	Clouded consciousness		
	Delirium		
	Depressed mood		
	Developmental regression		
	Feeling agitated	12	
	Feeling irritable	[redacted]	
	Hallucinations		
	Impulsive character		
	Mood swings		
	Outbursts of anger		
Skin and subcutaneous tissue disorder	Anasarca		
	Broken skin		
	Cellulitis		
	Dermal mycosis		
	Erythema of skin		
	Fat necrosis of breast		
	Impetigo bullosa		
	Inflammatory disease of mucous membrane		
	Lip ulcer		
	Oral lesion		
	Peeling of skin		
	Petechia		
	Phlegmon		
	Pressure ulcer		
	Skin necrosis		
	Skin nodule		
	Swelling of oral cavity structure		
	Ulcer of anus		
	Ulcer on tongue		
	Wound granuloma		

AE=Adverse event; SNOMED-CT=systematized nomenclature of medicine-clinical terms
Only the first occurrence of AE experienced by a patient was counted.

10.3.1.2 Patients aged <30 days

The highest number of events were vomiting [redacted] under metabolism and nutrition disorder category in the recommended dose cohort and necrotizing enterocolitis in fetus or newborn (disorder) [redacted] under metabolism and nutrition disorder category in loading dose cohort (Table 18).

Table 18: Counts of other AEs in patients aged <30 days

AE diagnostic categories (SNOMED-CT)	AE	Recommended dose cohort (N=16)	Loading dose cohort (N=12)
Cardiac disorders	Low blood pressure	[redacted]	[redacted]
	Pulmonary hypertension		
General disorders and administration site conditions	Aspiration pneumonia		
Metabolism and nutrition disorders	Necrotizing enterocolitis in fetus OR newborn (disorder)		
	Vomiting		
Nervous system disorders	Spinal epidural hematoma		
	Subdural intracranial hematoma		

AE=Adverse event; SNOMED-CT= Systematized nomenclature of medicine-clinical terms
Only the first occurrence of AE experienced by a patient was counted.

10.4 Main results

10.4.1 Crude incidence rates of AEs by diagnostic categories

10.4.1.1 Patients aged ≥1 month to <17 years

The crude incidence rates per 1000 person-days of overall AEs in the recommended and loading dose cohorts were 64.44 (95% CI: 55.88, 73.95) vs 50.00 (95% CI: 39.82, 61.98), respectively.

In the recommended dose cohort, the crude incidence rates per 1000 person-days ranged from 0.48 (95% CI: 0.10, 1.40) for DRESS and hypersensitivity individually to 17.23 (95% CI: 13.74, 21.33) for cardiac disorders. No AEs were observed for ECG indicating long PR and severe cutaneous adverse reactions.

In the loading dose cohort, the crude incidence rates per 1000 person-days ranged from 0.33 (95% CI: 0.01, 1.86) for DRESS to 9.52 (95% CI: 6.10, 14.16) for cardiac disorders. No AEs were observed for ECG indicating long PR, severe cutaneous adverse reactions and hypersensitivity.

In the recommended vs loading dose cohorts, the crude incidence rates per 1000 person-days of most frequently occurring AEs were for categories namely, cardiac disorders (17.23; 95% CI: 13.74, 21.33) vs (9.52; 95% CI: 6.10, 14.16), nervous system disorders (13.21; 95% CI: 10.30, 16.69) vs (8.78; 95% CI: 5.57, 13.18), skin and subcutaneous disorders (8.91; 95% CI:

6.59, 11.78) vs (8.52; 95% CI: 5.40, 12.79), metabolism and nutrition disorders (11.74; 95% CI: 9.02, 15.02) vs (8.90; 95% CI: 5.64, 13.36) and least commonly occurring AEs were DRESS (0.48; 95% CI: 0.10, 1.40) vs (0.33; 95% CI: 0.01, 1.86), hypersensitivity (0.48; 95% CI: 0.10, 1.40) vs (none) (Table 19).

Table 19: Crude incidence rates of AEs diagnostic categories by initial dose cohort in patients aged ≥1 month to <17 years

AE diagnostic categories (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Total number of patients	471 (68.7%)	215 (31.3%)
Overall AE*		
Total number of events	491	163
Unique patients with events	203	83
Patient-days of observation for incidence	3,150	1,660
Total follow-up days for all patients	6,295	3,000
Incident rate per 1000 patient-days (95% CI)	64.44 (55.88, 73.95)	50.00 (39.82, 61.98)
Cardiac disorders		
Total number of events	107	32
Unique patients with events	84	24
Patient-days of observation	4,875	2,522
Incident rate per 1000 patient-days (95% CI)	17.23 (13.74, 21.33)	9.52 (6.10, 14.16)
Skin and subcutaneous tissue disorders		
Total number of events	59	24
Unique patients with events	49	23
Patient-days of observation	5,498	2,699
Incident rate per 1000 patient-days (95% CI)	8.91 (6.59, 11.78)	8.52 (5.40, 12.79)
Nervous system disorders		
Total number of events	89	25
Unique patients with events	70	23
Patient-days of observation	5,300	2,619
Incident rate per 1000 patient-days (95% CI)	13.21 (10.30, 16.69)	8.78 (5.57, 13.18)
Metabolism and nutrition disorders		
Total number of events	82	28
Unique patients with events	63	23
Patient-days of observation	5,368	2,584
Incident rate per 1000 patient-days (95% CI)	11.74 (9.02, 15.02)	8.90 (5.64, 13.36)
Psychiatric disorders		
Total number of events	44	17
Unique patients with events	37	16
Patient days of observation	5,799	2,784
Incident rate per 1000 patient-days (95% CI)	6.38 (4.49, 8.79)	5.75 (3.28, 9.33)

AE diagnostic categories (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Injury, poisoning and procedural complications		
Total number of events	15	[redacted]
Unique patients with events	14	
Patient-days of observation	6,048	2,947
Incident rate per 1000 patient-days (95% CI)	2.31 (1.27, 3.88)	2.04 (0.75, 4.43)
General disorders and administration site conditions		
Total number of events	89	29
Unique patients with events	62	22
Patient days of observation	5,399	2,654
Incident rate per 1000 patient-days (95% CI)	11.48 (8.80, 14.72)	8.29 (5.19, 12.55)
Investigations of ECG indicating long PR		
Total number of events	None	None
Unique patients with events		
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
DRESS		
Total number of events	[redacted]	[redacted]
Unique patients with events	[redacted]	[redacted]
Patient-days of observation	6,265	2,996
Incident rate per 1000 patient-days (95% CI)	0.48 (0.10 - 1.40)	0.33 (0.01, 1.86)
Severe cutaneous adverse reactions		
Total number of events	None	None
Unique patients with events		
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
Hypersensitivity		
Total number of events	[redacted]	None
Unique patients with events	[redacted]	
Patient-days of observation	6,279	
Incident rate per 1000 patient-days (95% CI)	0.48 (0.10, 1.40)	

AE=Adverse event; CI=Confidence interval; DRESS= Drug reaction with eosinophilia and systemic symptoms syndrome; ECG=Electrocardiogram

*: Overall AE were calculated as the first of any event a patient had during the follow-up period. Only the first event of any kind experienced by a patient was counted. For example, if a patient had a cardiac and a skin event on different dates, only the first event was counted in the overall incidence rate.

10.4.1.2 Patients aged <30 days

The crude incidence rates per 1000 person-days of overall AEs in the recommended and loading dose cohorts were 36.04 (95% CI: 15.56, 71.01) and 8.85 (95% CI: 1.07, 31.97), respectively.

In the recommended dose cohort, the crude incidence rates per 1000 person-days ranged from 3.10 (95% CI: 0.08, 17.25) for general disorders and administration site disorders to 18.25 (95% CI: 5.93, 42.59) for cardiac disorders. The crude incidence rates of per 1000 person-days most frequently occurring AE was for categories namely, cardiac disorders 18.25 (95% CI: 5.93, 42.59), nervous system disorders 6.73 (95% CI: 0.82, 24.33) and metabolism and nutrition disorders 6.41(95% CI: 0.78, 23.16). No AEs were observed in skin and subcutaneous tissue disorders, psychiatric disorders, injury, poisoning and procedural complications, investigations of ECG indicating long PR, DRESS, severe cutaneous adverse reactions and hypersensitivity.

In the loading dose cohort, the crude incidence rates per 1000 person-days ranged from 3.91 (95% CI: 0.10, 21.76) for metabolism and nutrition disorders to 4.00 (95% CI: 0.10, 22.29) for hypersensitivity. Most frequently occurring AEs were observed for metabolism and nutrition disorders and hypersensitivity and incidence rate was 3.91 (95% CI: 0.10, 21.76) and 4.00 (95% CI: 0.10, 22.29), respectively. No AEs were observed for cardiac disorders, skin and subcutaneous disorders, nervous system disorders, psychiatric disorders, injury, poisoning and procedural complications, general disorders and administration site conditions, ECG indicating long PR, severe cutaneous adverse reactions, DRESS and hypersensitivity (Table 20).

Table 20: Crude incidence rates of AEs diagnostic categories by initial dose cohort in patients aged <30 days

AE diagnostic categories (MedDRA)	Recommended dose cohort (N=16)	Loading dose cohort (N=12)
Total number of patients	16 (57.1%)	12 (42.9%)
Overall AE*		
Total number of events	11	[redacted]
Unique patients with events	[redacted]	[redacted]
Patient-days of observation for incidence	222	226
Total follow-up days for all patients	339	280
Incident rate per 1000 patient-days (95% CI)	36.04 (15.56, 71.01)	8.85 (1.07, 31.97)
Cardiac disorders		
Total number of events	[redacted]	None
Unique patients with events	[redacted]	
Patient-days of observation	274	
Incident rate per 1000 patient-days (95% CI)	18.25 (5.93, 42.59)	
Skin and subcutaneous tissue disorders		
Total number of events	None	None
Unique patients with events		
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		

AE diagnostic categories (MedDRA)	Recommended dose cohort (N=16)	Loading dose cohort (N=12)
Nervous system disorders		
Total number of events	[redacted]	None
Unique patients with events	[redacted]	
Patient-days of observation	297	
Incident rate per 1000 patient-days (95% CI)	6.73 (0.82, 24.33)	
Metabolism and nutrition disorders		
Total number of events	[redacted]	[redacted]
Unique patients with events	[redacted]	[redacted]
Patient-days of observation	312	256
Incident rate per 1000 patient-days (95% CI)	6.41 (0.78, 23.16)	3.91 (0.10, 21.76)
Psychiatric disorders		
Total number of events	None	None
Unique patients with events		
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
Injury, poisoning and procedural complications		
Total number of events		
Unique patients with events	None	None
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
General disorders and administration site conditions		
Total number of events	[redacted]	None
Unique patients with events	[redacted]	
Patient-days of observation	323	
Incident rate per 1000 patient-days (95% CI)	3.10 (0.08, 17.25)	
Investigations of ECG indicating long PR		
Total number of events	None	None
Unique patients with events		
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
DRESS		
Total number of events		
Unique patients with events	None	None
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
Severe cutaneous adverse reactions		
Total number of events	None	None
Unique patients with events		

AE diagnostic categories (MedDRA)	Recommended dose cohort (N=16)	Loading dose cohort (N=12)
Patient-days of observation Incident rate per 1000 patient-days (95% CI)		
Hypersensitivity Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	[redacted] [redacted] 250 4.00 (0.10, 22.29)

AE=Adverse event; CI=Confidence interval; DRESS= Drug reaction with eosinophilia and systemic symptoms syndrome; ECG=Electrocardiogram
*: Overall AEs were calculated as the first of any event a patient had during the follow-up period. Only the first event of any kind experienced by a patient was counted. For example, if a patient had a cardiac and a skin event on different dates, only the first event was counted in the overall incidence rate.

10.4.2 Crude incidence rates by specific AEs

10.4.2.1 Patients aged ≥1 month to <17 years

In the recommended dose cohort, the crude incidence rates per 1000 person-days ranged from 0.16 (95% CI: 0.00, 0.89) for AV block, bradyarrhythmia, ventricular tachyarrhythmia, Stevens-Johnson syndrome, loss of consciousness, appetite disorder and hypophagia each to 4.91 (95% CI: 3.29, 7.05) for bradycardia. No AEs were observed for AV block complete, AV block 1st degree, AV block 2nd degree, cardiac fibrillation, cardiac flutter, atrial fibrillation, atrial flutter, torsade de pointes, ventricular arrhythmia, ventricular fibrillation, palpitations, toxic epidermal necrolysis, angioedema, paraesthesias, syncope, food aversion, injection site erythema, injection site irritation, and injection site pain.

In the loading dose cohort, the crude incidence rates per 1000 person-days ranged from 0.33 (95% CI: 0.01, 1.86) for injection site erythema, dizziness, and pruritis individually to 6.55 (95% CI: 3.88, 10.35) for rash. No AEs were observed for AV block, AV block complete, AV block 1st degree, arrhythmia, cardiac fibrillation, cardiac flutter, atrial fibrillation, atrial flutter, torsade de pointes, ventricular arrhythmia, ventricular fibrillation, ventricular tachyarrhythmia, palpitations, Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, urticaria, paresthesias, loss of consciousness, syncope, appetite disorder, diet refusal, hypophagia, food aversion, injection site irritation, and injection site pain

In the recommended dose cohort, the crude incidence rates per 1000 person-days of most frequently occurring AEs were bradycardia 4.91 (95% CI: 3.29, 7.05) and rash 4.06 (95% CI: 2.60, 6.04), while in the loading dose cohort was rash 6.55 (95% CI 3.88, 10.35) (Table 21).

Table 21: Crude incidence rates of specific AE diagnoses by initial dose cohort in patients aged ≥1 month to <17 years

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
AV block Patient count of events Patient-days of observation	[redacted] 6,273	None

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	
AV block complete Patient count of events Patient-days of observation Incident rate per 1000 patient-days	None	None
AV block 1st degree Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
AV block 2nd degree Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	[redacted] 2,966 0.34 (0.01, 1.88)
Arrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 6,280 0.32 (0.04, 1.15)	None
Bradyarrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 6,294 0.16 (0.00, 0.89)	[redacted] 2,975 0.34 (0.01, 1.87)
Bradycardia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	29 5,910 4.91 (3.29, 7.05)	[redacted] 2,907 1.72 (0.56, 4.01)
Cardiac fibrillation Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Cardiac flutter Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Tachyarrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	15 6,033 2.49 (1.39, 4.10)	[redacted] 2,908 1.38 (0.37, 3.52)
Atrial fibrillation		

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Atrial flutter Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Cardiac arrest Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	12 6,117 1.96 (1.01, 3.43)	[redacted] 2,936 1.02 (0.21, 2.99)
Torsade de pointes Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Ventricular arrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Ventricular fibrillation Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Ventricular tachyarrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 6,291 0.16 (0.00, 0.89)	None
Palpitations Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Stevens-Johnson syndrome Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 6,291 0.16 (0.00, 0.89)	None
Toxic epidermal necrolysis Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Angioedema		
Patient count of events	None	None
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
Urticaria		
Patient count of events	[redacted]	None
Patient-days of observation	6,251	
Incident rate per 1000 patient-days (95% CI)	0.64 (0.17, 1.64)	
Pruritus		
Patient count of events	[redacted]	[redacted]
Patient-days of observation	6,255	2,998
Incident rate per 1000 patient-days (95% CI)	0.64 (0.17, 1.64)	0.33 (0.01, 1.86)
Rash		
Patient count of events	24	18
Patient-days of observation	5,910	2,749
Incident rate per 1000 patient-days (95% CI)	4.06 (2.60, 6.04)	6.55 (3.88, 10.35)
Dizziness		
Patient count of events	[redacted]	[redacted]
Patient-days of observation	6,219	2,993
Incident rate per 1000 patient-days (95% CI)	0.96 (0.35, 2.10)	0.33 (0.01, 1.86)
Somnolence		
Patient count of events	22	[redacted]
Patient-days of observation	6,006	2,929
Incident rate per 1000 patient-days (95% CI)	3.66 (2.30, 5.55)	2.05 (0.75, 4.46)
Paresthesias		
Patient count of events	None	None
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
Loss of consciousness		
Patient count of events	[redacted]	None
Patient-days of observation	6,280	
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	
Syncope		
Patient count of events	None	None
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
Appetite disorder		
Patient count of events	[redacted]	None

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Patient-days of observation	6,289	
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	
Decreased appetite		
Patient count of events	[redacted]	[redacted]
Patient-days of observation	6,226	2,948
Incident rate per 1000 patient-days (95% CI)	1.45 (0.66, 2.74)	1.02 (0.21, 2.97)
Diet refusal		
Patient count of events	[redacted]	None
Patient-days of observation	6,269	
Incident rate per 1000 patient-days (95% CI)	0.32 (0.04, 1.15)	
Hypophagia		
Patient count of events	[redacted]	None
Patient-days of observation	6,263	
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	
Food aversion		
Patient count of events	None	None
Patient days of observation		
Incident rate per 1000 patient-days (95% CI)		
Chest pain		
Patient count of events	[redacted]	[redacted]
Patient-days of observation	6,253	2,995
Incident rate per 1000 patient-days (95% CI)	0.32 (0.04, 1.16)	0.67 (0.08, 2.41)
Gait disturbances		
Patient count of events	[redacted]	[redacted]
Patient-days of observation	6,214	2,982
Incident rate per 1000 patient-days (95% CI)	1.13 (0.45, 2.32)	0.67 (0.08, 2.42)
Injection site erythema		
Patient count of events	None	[redacted]
Patient-days of observation		3,000
Incident rate per 1000 patient-days (95% CI)		0.33 (0.01, 1.86)
Injection site irritation		
Patient count of events	None	None
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
Injection site pain		
Patient count of events	None	None
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval

10.4.2.2 Patients aged <30 days

Only one AE was reported in the recommended dose cohort, ie, cardiac arrest and the crude incidence rate per 1000 person-days was 12.86 (95% CI: 3.50, 32.93) and no AE was reported in the loading dose cohort (Table 22).

Table 22: Crude incidence rates of specific AE diagnoses by initial dose cohort in patients aged <30 days

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=16)	Loading dose cohort (N=12)
AV block Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
AV block complete Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
AV block 1st degree Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
AV block 2nd degree Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Arrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Bradyarrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Bradycardia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Cardiac fibrillation Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=16)	Loading dose cohort (N=12)
Cardiac flutter Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Tachyarrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Atrial fibrillation Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Atrial flutter Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Cardiac arrest Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 311 12.86 (3.50, 32.93)	None
Torsade de pointes Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Ventricular arrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Ventricular fibrillation Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Ventricular tachyarrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Palpitations Patient count of events	None	None

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=16)	Loading dose cohort (N=12)
Patient-days of observation Incident rate per 1000 patient-days (95% CI)		
Stevens-Johnson syndrome Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Toxic epidermal necrolysis Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Angioedema Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Urticaria Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Pruritus Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Rash Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Dizziness Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Somnolence Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Paresthesias Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=16)	Loading dose cohort (N=12)
Loss of consciousness Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Syncope Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Appetite disorder Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Decreased appetite Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Diet refusal Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Hypophagia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Food aversion Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Chest pain Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Gait disturbances Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Injection site erythema Patient count of events	None	None

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=16)	Loading dose cohort (N=12)
Patient-days of observation Incident rate per 1000 patient-days (95% CI)		
Injection site irritation Patient count of events Patient days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Injection site pain Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval

10.4.3 Crude incidence rates of AEs that physicians attributed to LCM by diagnostic categories

10.4.3.1 Patients aged ≥1 month to <17 years

The crude incidence rates per 1000 person-days of overall AEs that physicians attributed to LCM in the recommended and loading dose cohorts were 0.98 (95% CI: 0.36, 2.12) and 1.37 (95% CI: 0.37, 3.51), respectively.

In the recommended dose cohort, the crude incidence rates ranged from 0.16 (95% CI: 0.00, 0.89) for nervous system disorders and metabolism and nutrition disorders to 0.32 (95% CI: 0.04, 1.16) for cardiac disorders and skin and subcutaneous disorders, each. No AEs were observed for psychiatric disorders, injury, poisoning and procedural complications, general disorders and administration site conditions, investigations of ECG indicating long PR, DRESS syndrome, severe cutaneous adverse reactions, and hypersensitivity.

In the loading dose cohort, the crude incidence rates ranged from 0.33 (95% CI: 0.01, 1.86) in metabolism and nutrition disorders to 0.68 (95% CI: 0.08, 2.45) in nervous system disorders. No AEs were observed for cardiac disorders, psychiatric disorders, injury, poisoning and procedural complications, general disorders and administration site conditions, investigations of ECG indicating long PR, DRESS syndrome, severe cutaneous adverse reactions, and hypersensitivity (Table 23).

Table 23: Crude incidence rates of AEs that physicians attributed to LCM by diagnostic categories by initial dose cohort in patients aged ≥1 month to ≤17 years

Adverse drug reaction by diagnostic categories (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Overall AE Total number of events Unique patients with events Patient-days of observation	[redacted] [redacted] 6,147	[redacted] [redacted] 2,920

Adverse drug reaction by diagnostic categories (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Incident rate per 1000 patient-days (95% CI)	0.98 (0.36, 2.12)	1.37 (0.37, 3.51)
Cardiac disorders		
Total number of events	[redacted]	None
Unique patients with events	[redacted]	
Patient-days of observation	6,222	
Incident rate per 1000 patient-days (95% CI)	0.32 (0.04, 1.16)	
Skin and subcutaneous tissue disorders		
Total number of events	[redacted]	[redacted]
Unique patients with events	[redacted]	[redacted]
Patient-days of observation	6,223	2,974
Incident rate per 1000 patient-days (95% CI)	0.32 (0.04, 1.16)	0.34 (0.01, 1.87)
Nervous system disorders		
Total number of events	[redacted]	[redacted]
Unique patients with events	[redacted]	[redacted]
Patient-days of observation	6,294	2,948
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	0.68 (0.08, 2.45)
Metabolism and nutrition disorders		
Total number of events	[redacted]	[redacted]
Unique patients with events	[redacted]	[redacted]
Patient-days of observation	6,293	2,998
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	0.33 (0.01, 1.86)
Psychiatric disorders		
Total number of events	None	None
Unique patients with events		
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
Injury, poisoning and procedural complications		
Total number of events	None	None
Unique patients with events		
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
General disorders and administration site conditions	None	None
Total number of events		
Unique patients with events		
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		
Investigations of ECG indicating long PR		

Adverse drug reaction by diagnostic categories (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
DRESS Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Severe cutaneous adverse reactions Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None
Hypersensitivity Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval; DRESS= Drug reaction with eosinophilia and systemic symptoms syndrome

10.4.3.2 Patients aged <30 days

No AEs were reported in neonates that physicians attributed to LCM.

10.4.4 Crude incidence rates of AEs diagnoses that physicians attributed to LCM by specific AEs

10.4.4.1 Patients aged ≥1 month to <17 years

In the recommended dose cohort, the crude incidence rates per 1000 person-days ranged from 0.16 (95% CI: 0.00, 0.89) for bradycardia, prolonged QT interval, pancreatitis and somnolence to 0.32 (95% CI: 0.04, 1.16) for rash. No AEs were observed for vomiting and nystagmus.

In the loading dose cohort, the crude incidence rates per 1000 person-days ranged from 0.33 (95% CI: 0.01, 1.86) for vomiting to 0.34 (95% CI: 0.01, 1.88) for somnolence. No AEs were observed for bradycardia, prolonged QT interval, and pancreatitis (Table 24).

Table 24: Crude incidence rates of AEs that physicians attributed to LCM by specific AE diagnoses by in patients aged ≥1 month to <17 years

Specific AE diagnoses (MedDRA)	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Bradycardia		
Unique patients with events	[redacted]	None
Patient-days of observation	6,258	
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	
Prolonged QT interval		
Unique patients with events	[redacted]	None
Patient-days of observation	6,259	
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	
Pancreatitis		
Unique patients with events	[redacted]	None
Patient-days of observation	6,293	
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	
Vomiting		
Unique patients with events	None	[redacted]
Patient-days of observation		2,998
Incident rate per 1000 patient-days (95% CI)		0.33 (0.01, 1.86)
Nystagmus		
Unique patients with events	None	[redacted]
Patient-days of observation		2,985
Incident rate per 1000 patient-days (95% CI)		0.34 (0.01, 1.87)
Somnolence		
Unique patients with events	[redacted]	[redacted]
Patient-days of observation	6,294	2,963
Incident rate per 1000 patient-days (95% CI)	0.16 (0.00, 0.89)	0.34 (0.01, 1.88)
Rash		
Unique patients with events	[redacted]	[redacted]
Patient-days of observation	6,223	2,974
Incident rate per 1000 patient-days (95% CI)	0.32 (0.04, 1.16)	0.34 (0.01, 1.87)

AE=Adverse event; CI=Confidence interval

10.4.4.2 Patients aged <30 days

No AEs were reported that physicians attributed to LCM by categories.

10.4.5 Incidence rate ratios for AE diagnostic categories

Before adjustment, the loading dose was associated with a significant 44% decreased risk of cardiac disorders compared with the recommended dose (IRR: 0.56; 95% CI: 0.35, 0.87). After adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant differences in AE diagnostic categories were observed between the recommended and loading dose cohorts (Table 25).

Table 25: Unadjusted and adjusted incidence rate ratios for AE diagnostic categories by initial dose in patients aged ≥1 month to <17 years

	Loading vs Recommended Dose			
AE diagnostic categories (MedDRA)	**Unadjusted incidence rate ratio (95% CI)**	**p-value unadjusted**	**Adjusted incidence rate ratio[1] (95% CI)**	**p-value adjusted**
Any AE	0.78 (0.61, 1.01)	0.061	0.88 (0.60, 1.30)	0.521
Cardiac disorders	0.56 (0.35, 0.87)	0.011	0.63 (0.35, 1.14)	0.125
Skin and subcutaneous tissue disorders	0.96 (0.58, 1.57)	0.868	1.15 (0.62, 2.13)	0.654
Nervous system disorders	0.67 (0.42, 1.07)	0.092	0.73 (0.40, 1.32)	0.291
Metabolism and nutrition disorders	0.76 (0.47, 1.23)	0.260	0.96 (0.50, 1.83)	0.900
Psychiatric disorders	0.90 (0.50, 1.62)	0.732	0.91 (0.37, 2.25)	0.842
Injury, poisoning and procedural complications	0.88 (0.34, 2.29)	0.796	0.63 (0.20, 1.97)	0.429
General disorders and administration site conditions	0.72 (0.45, 1.18)	0.193	0.73 (0.30, 1.80)	0.493
Investigations of ECG indicating long PR	n/a		n/a	
DRESS	0.70 (0.07, 6.71)	0.756	0.73 (0.07, 7.10)	0.785
Severe cutaneous adverse reactions	n/a		n/a	
Hypersensitivity	n/a	0.994	n/a	n/a

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval; DRESS= Drug reaction with eosinophilia and systemic symptoms syndrome; ECG=Electrocardiogram; n/a=Not applicable or no data
[1] Determined using Poisson regression with inverse probability treatment weights.

10.4.6 Incidence rate ratios for specific AE diagnoses

Before adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant differences in specific AEs were observed between the recommended and loading dose cohorts except bradycardia, i.e. the loading dose was associated with a significant 65% decreased risk of bradycardia compared with the recommended dose (IRR: 0.35; 95% CI: 0.14, 0.91). After adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant differences in specific AEs were observed between the recommended and loading dose cohorts except rash, for which the risk was increased by two-fold in the loading dose cohort compared with the recommended dose cohort (adjusted IRR 2.11; 95% CI: 1.02, 4.38) and cardiac arrest, for which the loading dose

was associated with a significant 78% decreased risk of cardiac arrest compared with the recommended dose (adjusted IRR: 0.22; 95% CI: 0.06, 0.87) (Table 26).

Table 26: Unadjusted and adjusted incidence rate ratios for specific AE diagnoses by initial dose cohort in patients aged ≥1 month to ≤17 years

Specific AE Diagnoses (MedDRA)	Loading vs Recommended Dose cohorts			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
AV block	n/a	n/a	n/a	n/a
AV block complete	n/a	n/a	n/a	n/a
AV block 1st degree	n/a	n/a	n/a	n/a
AV block 2nd degree	n/e	n/e	n/e	n/e
Arrhythmia	n/a	n/a	n/a	n/a
Bradyarrhythmia	2.12 (0.13, 33.87)	0.596	0.47 (0.03, 7.55)	0.591
Bradycardia	0.35 (0.14, 0.91)	0.031	0.46 (0.16, 1.37)	0.166
Cardiac fibrillation	n/a	n/a	n/a	n/a
Cardiac flutter	n/a	n/a	n/a	n/a
Tachyarrhythmia	0.55 (0.18, 1.67)	0.294	0.31 (0.10, 1.01)	0.052
Atrial fibrillation	n/a	n/a	n/a	n/a
Atrial flutter	n/a	n/a	n/a	n/a
Cardiac arrest	0.52 (0.15, 1.85)	0.314	0.22 (0.06, 0.87)	0.031
Torsade de pointes	n/a	n/a	n/a	n/a
Ventricular arrhythmia	n/a	n/a	n/a	n/a
Ventricular fibrillation	n/a	n/a	n/a	n/a
Ventricular tachyarrhythmia	n/a	n/a	n/a	n/a
Palpitations	n/a	n/a	n/a	n/a
Stevens-Johnson syndrome	n/a	n/a	n/a	n/a
Toxic epidermal necrolysis	n/a	n/a	n/a	n/a
Angioedema	n/a	n/a	n/a	n/a
Urticaria	n/a	n/a	n/a	n/a
Pruritus	0.52 (0.06, 4.67)	0.562	0.67 (0.07, 6.10)	0.722

Specific AE Diagnoses (MedDRA)	Loading vs Recommended Dose cohorts			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
Rash	1.61 (0.88, 2.97)	0.125	2.11 (1.02, 4.38)	0.045
Dizziness	0.35 (0.04, 2.88)	0.327	0.12 (0.01, 1.29)	0.080
Somnolence	0.56 (0.23, 1.38)	0.209	0.67 (0.19, 2.29)	0.521
Paresthesias	n/a	n/a	n/a	n/a
Loss of consciousness	n/a	n/a	n/a	n/a
Syncope	n/a	n/a	n/a	n/a
Appetite disorder	n/a	n/a	n/a	n/a
Decreased appetite	0.70 (0.19, 2.60)	0.600	1.38 (0.27, 7.06)	0.703
Diet refusal	n/a	n/a	n/a	n/a
Hypophagia	n/a	n/a	n/a	n/a
Food aversion	n/a	n/a	n/a	n/a
Chest pain	2.09 (0.29, 14.85)	0.461	0.55 (0.07, 4.14)	0.562
Gait disturbances	0.60 (0.12, 2.87)	0.519	0.17 (0.03, 1.15)	0.070
Injection site erythema	n/e	n/e	n/e	n/e
Injection site irritation	n/a	n/a	n/a	n/a
Injection site pain	n/a	n/a	n/a	n/a

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval; n/a=Not applicable or no data; n/e=Small sample size and confidence intervals not making sense
[1] Determined using Poisson regression with inverse probability treatment weights.

10.4.7 Mortality

10.4.7.1 Patients aged ≥1 month to <17 years

As described in Table 15, 47 deaths were reported in total in the recommended (6.4%) and loading (7.9%) dose cohorts during the follow up. Crude mortality rates per 1000 person-days in the recommended and loading dose cohorts were 4.77 (95% CI: 3.22, 6.80) vs 5.67 (95% CI: 3.30, 9.06), respectively. After adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant increased incidence rate ratios were observed in the loading dose cohort when compared with the recommended dose cohort (adjusted IRR: 1.18; 95% CI: 0.57, 2.42).

Out of total 47 fatalities, no death was attributed to LCM, though 22 patients were on LCM at the time of death. Time after the index date to death ranged from 0 to 36 days. The age at

death ranged from <1 to 16 years. [redacted] deaths (12.8%) were due to multiple organ failure, status epilepticus and cardiorespiratory arrest, individually and [redacted] deaths (6.4%) were due to hypoxic ischemic encephalopathy and anoxic encephalopathy, individually (Table 27). All 47 patients were critically ill patients having other comorbidities and were on other comedications (Appendix 1).

Table 27: Description of fatal events during the follow-up period in patients aged ≥1 month to <17 years

Patient	Cause of death*	Death ascribed to LCM (Y/N)	Time after index date to death (days)	Age at death (years)	Patient on LCM on date of death (Y/N)
1	Hemophagocytic lymphohistiocytosis	N	9	[redacted]	N
2	Cerebral infarction	N	0		Y
3	Cerebral herniation	N	2		N
4	Progressive multifocal leukoencephalopathy	N	1		N
5	Subdural intracranial hemorrhage	N	0		Y
6	Traumatic intracranial subdural hematoma	N	4		Y
7	Apnea	N	17		Y
8	Multiple organ failure	N	17		Y
9	Multiple organ failure	N	14		N
10	Hypoxic ischemic encephalopathy	N	4		Y
11	Glioblastoma	N	19		Y
12	Vascular insufficiency of intestine	N	27		N
13	Motor vehicle accident	N	4		N
14	Anoxic encephalopathy	N	2		Y
15	Invasive aspergillosis	N	12		N
16	Status epilepticus	N	3		Y
17	Hypoxic ischemic encephalopathy	N	19		Y
18	Necrotizing enterocolitis	N	35		N
19	Status epilepticus	N	0		Y
20	Multiple organ failure	N	5		N
21	Multiple organ failure	N	26		N
22	Anoxic encephalopathy	N	7		Y
23	Cardiorespiratory arrest	N	4		N
24	Multiple organ failure	N	23		N

Patient	Cause of death*	Death ascribed to LCM (Y/N)	Time after index date to death (days)	Age at death (years)	Patient on LCM on date of death (Y/N)
25	Cardiorespiratory arrest	N	10	[redacted]	N
26	Cardiorespiratory arrest	N	3		Y
27	Sepsis	N	19		N
28	Pseudomonas meningitis	N	12		N
29	Hemorrhage of abdominal cavity structure	N	36		N
30	Traumatic brain injury	N	7		N
31	Status epilepticus	N	11		N
32	Multiple organ failure	N	1		N
33	Anoxic encephalopathy	N	1		Y
34	Status epilepticus	N	2		Y
35	Hypoxic ischemic encephalopathy	N	18		Y
36	Cardiorespiratory arrest	N	11		Y
37	Cardiorespiratory arrest	N	8		Y
38	Status epilepticus	N	7		Y
39	Cardiac arrest	N	4		Y
40	Acute disseminated encephalomyelitis	N	29		N
41	Retinoblastoma	N	6		N
42	Cardiorespiratory arrest	N	3		N
43	Neuroblastoma	N	14		N
44	Cerebral herniation	N	3		Y
45	Status epilepticus	N	7		N
46	Perforation of intestine	N	6		Y
47	Hepatic failure	N	4		N

LCM=Lacosamide; N=No; Y=Yes
* Cause of Death is based on chart reviewer findings as death certificate data was not available. In some cases only immediate or preliminary cause of death was given. When possible, the most specific diagnosis was selected from the chart reviewers findings as decided by PEDSnet Clinical Informatician and Study Co-Investigator (Dr. [redacted])
Note: Other Medications on Date of Death & Other Comorbid Conditions during Encounter are in the Appendix 2.

10.4.7.2 Age <30 days

As described in Table 16, [redacted] deaths were reported in total in the recommended (31.2%) and loading (16.7%) dose cohorts during the follow up. Crude mortality rates per 1000 person-days in the recommended and loading dose cohorts were 14.75 (95% CI: 4.81, 34.08) vs 7.14

(95% CI: 0.87, 25.56), respectively. Due to small sample size, incidence rate ratios were not computed for patients aged <30 days.

Out of total [redacted] fatalities, no death was attributed to LCM though two patients were on LCM on the date of death. Time to death ranged from 1 to 15 days and age at death ranged from 5 to 38 days. Out of [redacted], [redacted] deaths were due to cardiorespiratory arrest, 2 were due to Meningitis caused by *Streptococcus agalactiae* and one was due to central sleep apnea syndrome (Table 28). All these [redacted] patients with deaths had other comorbidities like cardiac, respiratory, infections and congenital anomalies etc (Appendix 2).

Table 28: Description of fatal events during the follow-up period in patients aged <30 days

Patient	Cause of Death*	Death ascribed to LCM (Y/N)	Time to death (days)	Age at death (days)	Patient on LCM on date of death (Y/N)
48	Cardiorespiratory arrest	N	3	[redacted]	N
49	Central sleep apnea syndrome	N	4		Y
50	Cardiorespiratory arrest	N	3		N
51	Meningitis caused by *Streptococcus agalactiae*	N	1		N
52	Meningitis caused by *Streptococcus agalactiae*	N	3		N
53	Cardiorespiratory arrest	N	15		Y
54	Cardiorespiratory arrest	N	10		N

LCM=Lacosamide; N=No; Y=Yes
* Cause of Death is based on chart reviewer findings as death certificate data was not available. In some cases only immediate or preliminary cause of death was given. When possible, the most specific diagnosis was selected from the chart reviewers findings as decided by PEDSnet Clinical Informatician and Study Co-Investigator.

Note: Other Medications on Date of Death & Other Comorbid Conditions during Encounter are in the Appendix 2.

10.5 Sensitivity analyses

To summarize the change in incidence rates across all AEs, the following tables with the new incidence rates from the proposed sensitivity analyses were created. Where space permitted, the 3 analyses were combined into a single table to show the analyses side-by-side.

These 3 sensitivity analyses performed were:

1. Omit Non-Neuro PMCA: patients with pre-existing medical events as determined by the PMCA chronic conditions were excluded. However, the patients with pre-existing PMCA neurologic conditions were still included.
2. 7-day follow-up limit: the maximum follow-up time was shortened from index date + 37 days down to index date + 7 days from the index date, such that any AEs that happened outside that shortened window were not included in the incidence rates.
3. Omit prior AE: for a given AE, any patients with history of with the same category of AE diagnosis were excluded.

10.5.1 Incidence rates of AEs diagnostic categories

10.5.1.1 Patients aged ≥1 month to <17 years

10.5.1.1.1 Omit non-neuro PMCA

After excluding patients with pre-existing medical events as determined by PMCA chronic conditions, the incidence rates per 1000 person-days for overall AEs were 62.94 (95% CI: 51.97, 75.56) in the recommended dose cohort and 62.58 (95% CI: 46.73, 82.06) in the loading dose cohort. The incidence rates per 1000 person-days ranged from 0.55 (95% CI: 0.07, 1.98) for hypersensitivity to 17.56 (95% CI: 13.03, 23.15) for cardiac disorders in the recommended dose cohort and 0.58 (95% CI: 0.01, 3.25) for DRESS to 12.25 (95% CI: 7.26, 19.37) for skin and subcutaneous disorders in the loading dose cohort. No AEs were reported for investigations of ECG indicating long PR and severe cutaneous adverse reactions in the recommended dose cohort and for investigations of ECG indicating long PR, severe cutaneous adverse reactions, and hypersensitivity in the loading dose cohort (Table 29).

10.5.1.1.2 7-day follow-up limit

The maximum follow-up time was shortened from index date + 37 days down to index date + 7 days from the index date, such that any AEs that happened outside that shortened window were not included in the incidence rates. The incidence rates per 1000 person-days of overall AEs were 91.33 (95% CI: 77.64, 106.73) in the recommended dose cohort and 77.40 (95% CI: 59.47, 99.02) in the loading dose cohort. The incidence rate per 1000 person-days ranged from 0.43 (95% CI: 0.01, 2.39) for hypersensitivity to 50.78 (95% CI: 38.93, 65.10) for cardiac disorders in the recommended dose cohort and 1.96 (95% CI: 0.24, 7.06) for injury, poisoning and procedural complications to 30.11 (95% CI: 18.13, 47.02) for cardiac disorders in the loading dose cohort. No events were reported for investigations of ECG indicating long PR and severe cutaneous adverse reactions in the recommended dose cohort and for investigations of ECG indicating long PR, severe cutaneous adverse reactions, DRESS and hypersensitivity in the loading dose cohort (Table 29).

10.5.1.1.3 Omit prior AE

For a given AE, any patients with history of with the same category of AE diagnosis was excluded. The incidence rates per 1000 person-days of overall AEs were 58.02 (95% CI: 50.11, 66.84) in the recommended dose cohort and 47.51 (95% CI: 37.67, 59.13) in the loading dose cohort. The incidence rates ranged from 0.48 (95% CI: 0.10, 1.40) for DRESS and hypersensitivity to 14.96 (95% CI: 11.77, 18.75) for cardiac disorders in the recommended dose cohort and 0.33 (95% CI: 0.01, 1.86) for DRESS to 8.90 (95% CI: 5.64, 13.36) for metabolism and nutrition disorders in the loading dose cohort. No events were reported for investigations of ECG indicating long PR and severe cutaneous adverse reactions in the recommended dose cohort and for investigations of ECG indicating long PR, severe cutaneous adverse reactions and hypersensitivity in the loading dose cohort (Table 29).

Table 29: Incidence rates of AEs diagnostic categories by initial dose in patients aged ≥1 month to <17 years

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Total number of patients	471	215	266	117	471	215
Overall AE*						
Total number of events	283	96	269	99	453	146
Unique patients with events	115	52	158	63	192	80
Patient-days of observation	1,827	831	1,730	814	3,309	1,684
Total follow-up	3,660	1,718	2,339	1,034	6,295	3,000
Incident rate per 1000 patient-days (95% CI)	62.94 (51.97, 75.56)	62.58 (46.73, 82.06)	91.33 (77.64, 106.73)	77.40 (59.47, 99.02)	58.02 (50.11, 66.84)	47.51 (37.67, 59.13)
Cardiac disorders						
Total number of events	64	14	74	26	96	25
Unique patients with events	50	12	62	19	75	19
Patient-days of observation	2,848	1,493	1,221	631	5,013	2,631
Incident rate per 1000 patient-days (95% CI)	17.56 (13.03, 23.15)	8.04 (4.15, 14.04)	50.78 (38.93, 65.10)	30.11 (18.13, 47.02)	14.96 (11.77, 18.75)	7.22 (4.35, 11.28)
Skin and subcutaneous tissue disorders	34	18	26	12	51	22
Total number of events	28	18	26	12	42	21
Unique patients with events	3,161	1,469	1,835	903	5,570	2,728
Patient-days of observation	8.86 (5.89, 12.80)	12.25 (7.26, 19.37)	14.17 (9.26, 20.76)	13.29 (6.87, 23.21)	7.54 (5.43, 10.19)	7.70 (4.77, 11.77)
Incident rate per 1000 patient-days (95% CI)						
Nervous system disorders						
Total number of events	60	16	48	16	82	22

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Unique patients with events	47	14	42	14	63	21
Patient-days of observation	3,003	1,510	1,751	784	5,409	2,669
Incident rate per 1000 patient-days (95% CI)	15.65 (11.50, 20.81)	9.27 (5.07, 15.56)	23.99 (17.29, 32.42)	17.86 (9.76, 29.96)	11.65 (8.95, 14.90)	7.87 (4.87, 12.03)
Metabolism and nutrition disorders						
Total number of events	38	19	46	18	82	28
Unique patients with events	31	15	39	17	63	23
Patient-days of observation	3,203	1,401	1,721	744	5,368	2,584
Incident rate per 1000 patient-days (95% CI)	9.68 (6.58, 13.74)	10.71 (5.99, 17.66)	22.66 (16.11, 30.98)	22.85 (13.31, 36.58)	11.74 (9.02, 15.02)	8.90 (5.64, 13.36)
Psychiatric disorders						
Total number of events	22	[redacted]	23	12	44	17
Unique patients with events	20		22	12	37	16
Patient-days of observation	3,384	1,604	2,042	876	5,799	2,784
Incident rate per 1000 patient-days (95% CI)	5.91 (3.61, 9.13)	5.61 (2.57, 10.65)	10.77 (6.75, 16.31)	13.70 (7.08, 23.93)	6.38 (4.49, 8.79)	5.75 (3.28, 9.33)
Injury, poisoning and procedural complications						
Total number of events	11	[redacted]	[redacted]	[redacted]	15	[redacted]
Unique patients with events	[redacted]				14	
Patient-days of observation	3,469	1,687	2,184	1,023	6,048	2,947
Incident rate per 1000 patient-days (95% CI)	2.88 (1.38, 5.30)	1.78 (0.37, 5.20)	3.21 (1.29, 6.60)	1.96 (0.24, 7.06)	2.31 (1.27, 3.88)	2.04 (0.75, 4.43)
General disorders and administration site conditions						

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Total number of events	49	16	42	13	77	24
Unique patients with events	35	13	36	[redacted]	53	19
Patient-days of Observation	3,168	1,492	1,780	873	5,530	2,700
Incident rate per 1000 patient-days (95% CI)	11.05 (7.70, 15.37)	8.71 (4.64, 14.90)	20.22 (14.17, 28.00)	11.45 (5.49, 21.07)	9.58 (7.18, 12.54)	7.04 (4.24, 10.99)
Investigations of ECG indicating long PR	None	None	None	None	None	None
Total number of events						
Unique patients with events						
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
DRESS						
Total number of events	[redacted]	[redacted]	[redacted]	None	[redacted]	[redacted]
Unique patients with events						
Patient-days of observation	3,630	1,714	2,337		6,265	2,996
Incident rate per 1000 patient-days (95% CI)	0.83 (0.17, 2.42)	0.58 (0.01, 3.25)	0.43 (0.01, 2.38)		0.48 (0.10, 1.40)	0.33 (0.01, 1.86)
Severe cutaneous adverse reactions						
Total number of events	None	None	None	None	None	None
Unique patients with events						
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Hypersensitivity						

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Total number of events Unique patients with events	[redacted]	None	[redacted]	None	[redacted]	None
Patient-days of observation	3,650		2,334		6,279	
Incident rate per 1000 patient-days (95% CI)	0.55 (0.07, 1.98)		0.43 (0.01, 2.39)		0.48 (0.10, 1.40)	

AE=Adverse event; CI=Confidence interval; DRESS= Drug reaction with eosinophilia and systemic symptoms syndrome; ECG=Electrocardiogram; MedDRA= Medical Dictionary for Regulatory Activities; PMCA=Pediatric Medical Complexity Algorithm
*: Overall AEs were calculated as the first of any event a patient had during the follow-up period. Only the first event of any kind experienced by a patient was counted. For example, if a patient had a cardiac and a skin event on different dates, only the first event is counted in the overall incidence rate.

For each AE diagnosis category, the first event of any diagnosis in that category was identified, and only time towards the first event was counted.

10.5.1.2 Patients aged <30 days

10.5.1.2.1 Omit non-neuro PMCA

The incidence rates per 1000 person-days of overall AEs were 36.04 (95% CI: 15.56, 71.01) and 8.85 (95% CI: 1.07, 31.97) in the recommended and loading dose cohorts, respectively. The incidence rates of AE diagnostic categories ranged from 3.10 (95% CI: 0.08, 17.25) for general disorders and administration site conditions to 18.25 (95% CI: 5.93, 42.59) for cardiac disorders in the recommended dose cohort and from 3.91 (95% CI: 0.10, 21.76) for metabolism and nutrition disorders to 4.00 (95% CI: 0.10, 22.29) for hypersensitivity in the loading dose cohort.

In the recommended dose cohort, no AEs were reported for skin and subcutaneous disorders, psychiatric disorders, injury, poisoning and procedural complications, investigations of ECG indicating long PR, severe cutaneous adverse reactions, DRESS, and hypersensitivity.

In the loading dose cohort, no AEs were observed for cardiac disorders, skin and subcutaneous disorders, nervous system disorders, psychiatric disorders, injury, poisoning and procedural complications, general disorders and administration site conditions, investigations for ECG indicating long PR, severe cutaneous adverse reactions, and DRESS(Table 30).

10.5.1.2.2 7-day follow-up limit

The incidence rates per 1000 person-days of overall AEs was 92.11 (95% CI: 37.03, 189.77) and 12.99 (95% CI: 0.33, 72.36) in the recommended and loading dose cohorts, respectively. The incidence rates ranged from 12.20 (95% CI: 0.31, 67.95) for metabolism and nutrition disorder to 72.73 (95% CI: 19. 82, 186.21) for cardiac disorders in the recommended dose cohort and 21.28 (95% CI: 0.54, 118.55) for hypersensitivity in the loading dose cohort.

In the recommended dose cohort, no AEs were reported for skin and subcutaneous disorders, psychiatric disorders, injury, poisoning and procedural complications, general disorders and administration site conditions, investigations of ECG indicating long PR, severe cutaneous adverse reactions, DRESS, and hypersensitivity.

In the loading dose cohort, no AEs were observed for cardiac disorders, skin and subcutaneous disorders, nervous system disorders, metabolism and nutrition disorders, psychiatric disorders, injury, poisoning and procedural complications, general disorders and administration site conditions, investigations for ECG indicating long PR, severe cutaneous adverse reactions, and DRESS(Table 30).

10.5.1.2.3 Omit prior AE

The incidence rates per 1000 person-days of overall AEs was 36.04 (95% CI: 15.56, 71.01) and 8.85 (95% CI: 1.07, 31.97) in the recommended and loading dose cohorts, respectively.

In the recommended dose cohort, incidence rate per 1000 person-days ranged from 3.10 (95% CI: 0.08, 17.25) for general disorders and administration site disorders to 18.25 (95% CI: 5.93, 42.59) for cardiac disorders. No AEs were observed in skin and subcutaneous tissue disorders, psychiatric disorders, injury, poisoning and procedural complications, investigations of ECG indicating long PR, DRESS, severe cutaneous adverse reactions, and hypersensitivity.

In the loading dose cohort, incidence rate per 1000 person-days ranged from 3.91 (95% CI: 0.10, 21.76) for metabolism and nutrition disorders to 4.00 (95% CI: 0.10, 22.29) for hypersensitivity. No AEs were observed for cardiac disorders, skin and subcutaneous disorders, nervous system disorders, psychiatric disorders, injury, poisoning and procedural

complications, general disorders and administration site conditions, ECG indicating long PR, severe cutaneous adverse reactions, DRESS, and hypersensitivity (Table 30).

Table 30: Incidence rates of AEs diagnostic categories by initial dose cohort in patients aged <30 days

Sensitivity analysis	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Total number of patients	16	12	16	12	16	12
Overall AE*						
Total number of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unique patients with events						
Patient-days of observation	222	226	76	77	222	226
Incident rate per 1000 patient-days (95% CI)	36.04 (15.56, 71.01)	8.85 (1.07, 31.97)	92.11 (37.03, 189.77)	12.99 (0.33, 72.36)	36.04 (15.56, 71.01)	8.85 (1.07, 31.97)
Cardiac disorders						
Total number of events	[redacted]	None	[redacted]	None	[redacted]	None
Unique patients with events						
Patient-days of observation	274		55		274	
Incident rate per 1000 patient-days (95% CI)	18.25 (5.93, 42.59)		72.73 (19.82, 186.21)		18.25 (5.93, 42.59)	
Skin and subcutaneous tissue disorders						
Total number of events	None	None	None	None	None	None
Unique patients with events						
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Nervous system disorders						
Total number of events	[redacted]	None	[redacted]	None	[redacted]	None
Unique patients with events						

Sensitivity analysis	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Patient-days of observation Incident rate per 1000 patient-days (95% CI)	297 6.73 (0.82, 24.33)		50 40.00 (4.84, 144.49)		297 6.73 (0.82, 24.33)	
Metabolism and nutrition disorders Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 312 6.41 (0.78, 23.16)	[redacted] 256 3.91 (0.10, 21.76)	[redacted] 82 12.20 (0.31, 67.95)	None	[redacted] 312 6.41 (0.78, 23.16)	[redacted] 256 3.91 (0.10, 21.76)
Psychiatric disorders Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Injury, poisoning and procedural complications Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
General disorders and administration site conditions						

Sensitivity analysis	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 323 3.10 (0.08, 17.25)	None	None	None	[redacted] 323 3.10 (0.08, 17.25)	None
Investigations of ECG indicating long PR Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
DRESS Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Severe cutaneous adverse reactions Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None

Sensitivity analysis	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Hypersensitivity						
Total number of events	None	[redacted]	None	[redacted]	None	[redacted]
Unique patients with events						
Patient-days of observation		250		47		250
Incident rate per 1000 patient-days (95% CI)		4.00 (0.10, 22.29)		21.28 (0.54, 118.55)		4.00 (0.10, 22.29)

AE=Adverse event; CI=Confidence interval; DRESS= Drug reaction with eosinophilia and systemic symptoms syndrome; ECG=Electrocardiogram; PMCA=Pediatric Medical Complexity Algorithm

*: Overall AEs were calculated as the first of any event a patient has during the follow-up period. Only the first event of any kind experienced by a patient was counted. For example, if a patient had a cardiac and a skin event on different dates, only the first event was counted in the overall incidence rate.

For each AE diagnosis category, the first event of any diagnosis in that category was recorded, and time towards the first event was counted.

10.5.2 Incidence rates of specific AE diagnoses

10.5.2.1 Patients aged ≥1 month to <17 years

10.5.2.1.1 Omit non-neuro PMCA

The incidence rates per 1000 person-days ranged from 0.16 (95% CI: 0.00, 0.89) for Stevens-Johnson syndrome to 4.75 (95% CI: 2.72, 7.72) for rash in the recommended dose cohort and from 0.58 (95% CI 0.01, 3.26) for dizziness to 10.05 (95% CI: 5.63, 16.58) for rash in the loading dose cohort (Table 31).

10.5.2.1.2 7-day follow up limit

The incidence rates per 1000 person-days ranged from 0.43 (95% CI: 0.01, 2.42) for hypophagia and diet refusal to 9.26 (95% CI: 5.58, 14.47) for bradycardia in the recommended dose cohort and from 0.97 (95% CI: 0.02, 5.43) for dizziness to 9.78 (95% CI: 4.47, 18.57) for rash in the loading dose cohort (Table 31).

10.5.2.1.3 Omit prior AE

The incidence rates per 1000 person-days ranged from 0.16 (95% CI: 0.00, 0.89) for bradyarrhythmia, ventricular tachyarrhythmia, loss of consciousness, appetite disorder, hypophagia, and chest pain to 4.56 (95% CI: 3.00, 6.63) for bradycardia in the recommended dose cohort and from 0.33 (95% CI: 0.01, 1.86) for pruritus, dizziness, and injection site erythema to 6.17 (95% CI: 3.59, 9.88) for rash in the loading dose cohort (Table 31).

Table 31: Incidence rates of specific AE diagnoses by initial dose cohort in patients aged ≥1 month to <17 years

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Total number of patients	471	215	266	117	471	215
AV block Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
AV block Complete Patient count of events Patient-days of observation Incident rate per 1000 patient-days	None	None	None	None	None	None
AV block 1st degree Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
AV block 2nd degree Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	[redacted] 1,000 1.00 (0.03, 5.57)	None	[redacted] 2,966 0.34 (0.01- 1.88)
Arrhythmia Patient count of events Patient days of observation	[redacted] 3,645	None	[redacted] 2,328	None	[redacted] 6,280	None

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Incident rate per 1000 patient-days (95% CI)	0.55 (0.07, 1.98)		0.43 (0.01, 2.39)		0.32 (0.04, 1.15)	
Bradyarrhythmia						
Patient count of events	[redacted]	[redacted]	[redacted]	None	[redacted]	[redacted]
Patient-days of observation	3,659	1,693	2,338		6,294	2,975
Incident rate per 1000 patient-days (95% CI)	0.27 (0.01, 1.52)	0.59 (0.01, 3.29)	0.43 (0.01, 2.38)		0.16 (0.00, 0.89)	0.34 (0.01, 1.87)
Bradycardia						
Patient count of events	16	[redacted]	19	[redacted]	27	[redacted]
Patient-days of observation	3,442	1,649	2,051	971	5,922	2,907
Incident rate per 1000 patient-days (95% CI)	4.65 (2.66, 7.55)	1.82 (0.38, 5.32)	9.26 (5.58, 14.47)	3.09 (0.64, 9.03)	4.56 (3.00, 6.63)	1.72 (0.56, 4.01)
Cardiac fibrillation						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Cardiac flutter						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Tachyarrhythmia						
Patient count of events	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-days of observation	3,426	1,626	2,187	942	6,053	2,908

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Incident rate per 1000 patient-days (95% CI)	3.50 (1.81, 6.12)	2.46 (0.67, 6.30)	4.12 (1.88, 7.81)	4.25 (1.16, 10.87)	2.31 (1.26, 3.88)	1.38 (0.37, 3.52)
Atrial fibrillation						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Atrial flutter						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Cardiac arrest						
Patient count of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-days of observation	3,524	1,718	2,167	970	6,123	2,936
Incident rate per 1000 patient-days (95% CI)	2.55 (1.17, 4.85)	0.58 (0.01, 3.24)	4.15 (1.90, 7.88)	3.09 (0.64, 9.04)	1.80 (0.90, 3.21)	1.02 (0.21, 2.99)
Torsade de pointes						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Ventricular arrhythmia						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Incident rate per 1000 patient-days (95% CI)						
Ventricular fibrillation Patient count of events Patient days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Ventricular tachyarrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 3,656 0.27 (0.01, 1.52)	None	[redacted] 2,335 0.43 (0.01, 2.39)	None	[redacted] 6,291 0.16 (0.00, 0.89)	None
Palpitations Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Stevens-Johnson syndrome Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 6,291 0.16 (0.00, 0.89)	None	None	None	None	None
Toxic epidermal necrolysis Patient count of events Patient-days of observation	None	None	None	None	None	None

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Incident rate per 1000 patient-days (95% CI)						
Angioedema						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Urticaria						
Patient count of events	[redacted]	None	[redacted]	None	[redacted]	None
Patient-days of observation	3,621		2,330		6,256	
Incident rate per 1000 patient-days (95% CI)	0.83 (0.17, 2.42)		0.43 (0.01, 2.39)		0.48 (0.10, 1.40)	
Pruritus						
Patient count of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-days of observation	3,628	1,716	2,327	1,032	6,263	2,998
Incident rate per 1000 patient-days (95% CI)	0.83 (0.17, 2.42)	0.58 (0.01, 3.25)	0.86 (0.10, 3.10)	0.97 (0.02, 5.40)	0.48 (0.10, 1.40)	0.33 (0.01, 1.86)
Rash						
Patient count of events	16	15	[redacted]	[redacted]	[redacted]	[redacted]
Patient-days of observation	3,366	1,492	2,145	920	5,933	2,755
Incident rate per 1000 patient-days (95% CI)	4.75 (2.72, 7.72)	10.05 (5.63, 16.58)	4.66 (2.24, 8.57)	9.78 (4.47, 18.57)	3.88 (2.46, 5.82)	6.17 (3.59, 9.88)
Dizziness						
Patient count of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-days of observation	3,587	1,711	2,276	1,027	6,219	2,993

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Incident rate per 1000 patient-days (95% CI)	1.39 (0.45, 3.25)	0.58 (0.01, 3.26)	2.20 (0.71, 5.13)	0.97 (0.02, 5.43)	0.96 (0.35, 2.10)	0.33 (0.01, 1.86)
Somnolence						
Patient count of events	14	[redacted]	17	[redacted]	20	[redacted]
Patient-days of observation	3,481	1,647	2,142	994	6,034	2,929
Incident rate per 1000 patient-days (95% CI)	4.02 (2.20, 6.75)	3.04 (0.99, 7.08)	7.94 (4.62, 12.71)	3.02 (0.62, 8.82)	3.31 (2.02, 5.12)	2.05 (0.75, 4.46)
Paresthesias						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Loss of consciousness						
Patient count of events	[redacted]	None	None	None	[redacted]	None
Patient-days of observation	3,645				6,280	
Incident rate per 1000 patient-days (95% CI)	0.27 (0.01, 1.53)				0.16 (0.00, 0.89)	
Syncope						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Appetite disorder						
Patient count of events	[redacted]	None	None	None	[redacted]	None
Patient-days of observation	3,654				6,289	

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Incident rate per 1000 patient-days (95% CI)	0.27 (0.01, 1.52)				0.16 (0.00, 0.89)	
Decreased appetite						
Patient count of events	[redacted]					
Patient-days of observation	3,622	1,666	2,293	1,005	6,226	2,948
Incident rate per 1000 patient-days (95% CI)	0.83 (0.17, 2.42)	1.80 (0.37, 5.26)	2.62 (0.96, 5.70)	1.99 (0.24, 7.19)	1.45 (0.66, 2.74)	1.02 (0.21, 2.97)
Diet refusal						
Patient count of events	None	None	[redacted]	None	[redacted]	None
Patient-days of observation			2,306		6,269	
Incident rate per 1000 patient-days (95% CI)			0.43 (0.01, 2.42)		0.32 (0.04, 1.15)	
Hypophagia						
Patient count of events	[redacted]	None	[redacted]	None	[redacted]	None
Patient-days of observation	3,628		2,307		6,263	
Incident rate per 1000 patient-days (95% CI)	0.28 (0.01, 1.54)		0.43 (0.01, 2.42)		0.16 (0.00, 0.89)	
Food aversion						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Chest pain						
Patient count of events	None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-days of observation		1,713	2,320	1,029	6,276	2,995

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Incident rate per 1000 patient-days (95% CI)		1.17 (0.14, 4.22)	0.43 (0.01, 2.40)	1.94 (0.24, 7.02)	0.16 (0.00, 0.89)	0.67 (0.08, 2.41)
Gait disturbances						
Patient count of events	[redacted]					
Patient-days of observation	3,598	1,703	2,289	1,031	6,239	2,982
Incident rate per 1000 patient-days (95% CI)	1.39 (0.45, 3.24)	0.59 (0.01, 3.27)	2.18 (0.71, 5.10)	0.97 (0.02, 5.40)	0.96 (0.35, 2.09)	0.67 (0.08, 2.42)
Injection site erythema						
Patient count of events	None	None	None	None	None	[redacted]
Patient-days of observation						3,000
Incident rate per 1000 patient-days (95% CI)						0.33 (0.01, 1.86)
Injection site irritation						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Injection site pain						
Patient count of events	None	None	None	None	None	None
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval; MedDRA= Medical Dictionary for Regulatory Activities; PMCA=Pediatric Complexity Medical Algorithm

10.5.2.2 Patients aged <30 days

10.5.2.2.1 Omit non-neuro PMCA

The incidence rates per 1000 person-days for the specific AE diagnoses were 12.86 (95% CI: 3.50, 32.93) for cardiac arrest in the recommended dose cohort and no AE was reported for the loading dose cohort (Table 32).

10.5.2.2.2 7-day follow-up limit

The incidence rates for the specific AE diagnoses were 32.61 (95% CI: 6.72, 95.30) for cardiac arrest in the recommended dose cohort and no AE was reported for the loading dose cohort (Table 32).

10.5.2.2.3 Omit prior AE

The incidence rates for the specific AE diagnoses were 12.86 (95% CI: 3.50, 32.93) for cardiac arrest in the recommended dose cohort and no AE was reported for the loading dose cohort (Table 32).

Table 32: Incidence rates of specific AE diagnoses by initial dose cohort in patients aged <30 days

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Total number of patients	16	12	16	12	16	12
AV block Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
AV block complete Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
AV block 1st degree Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
AV block 2nd degree Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Arrhythmia Patient count of events	None	None	None	None	None	None

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Patient-days of observation Incident rate per 1000 patient-days (95% CI)						
Bradyarrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Bradycardia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Cardiac fibrillation Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Cardiac flutter Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Tachyarrhythmia Patient count of events	None	None	None	None	None	None

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Patient-days of observation Incident rate per 1000 patient-days (95% CI)						
Atrial fibrillation Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Atrial flutter Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Cardiac arrest Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	[redacted] 311 12.86 (3.50, 32.93)	None	[redacted] 92 32.61 (6.72, 95.30)	None	[redacted] 311 12.86 (3.50, 32.93)	None
Torsade de pointes Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Ventricular arrhythmia Patient count of events	None	None	None	None	None	None

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Patient-days of observation Incident rate per 1000 patient-days (95% CI)						
Ventricular fibrillation Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Ventricular tachyarrhythmia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Palpitations Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Stevens-Johnson syndrome Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Toxic epidermal necrolysis Patient count of events	None	None	None	None	None	None

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Patient-days of observation Incident rate per 1000 patient-days (95% CI)						
Angioedema Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Urticaria Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Pruritus Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Rash Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Dizziness Patient count of events	None	None	None	None	None	None

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Patient-days of observation Incident rate per 1000 patient-days (95% CI)						
Somnolence Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Paresthesias Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Loss of consciousness Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Syncope Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Appetite disorder Patient count of events	None	None	None	None	None	None

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Patient-days of observation Incident rate per 1000 patient-days (95% CI)						
Decreased appetite Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Diet refusal Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Hypophagia Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Food aversion Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Chest pain Patient count of events	None	None	None	None	None	None

Sensitivity analyses	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Patient-days of observation Incident rate per 1000 patient-days (95% CI)						
Gait disturbances Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Injection site erythema Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Injection site irritation Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Injection site pain Patient count of events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval; MedDRA= Medical Dictionary for Regulatory Activities; PMCA=Pediatric Medical Complexity Algorithm

10.5.3 Count of other AEs

10.5.3.1 Patients aged ≥1 month to <17 years

Counts of other AEs (not part of specified AE list) are given in below table.

10.5.3.1.1 Omit non-neuro PMCA

The highest number of AEs were 8 for tachycardia in the recommended dose cohort and 4 for vomiting in loading dose cohort (Table 33).

10.5.3.1.2 7-day follow-up limit

The highest number of AEs were 12 for tachycardia in the recommended dose cohort and 6 for low blood pressure, tachycardia, and feeling agitated in loading dose cohorts (Table 33).

10.5.3.1.3 Omit prior AE

The highest number of AEs were 15 for vomiting in the recommended dose cohort and 9 for feeling agitated in loading dose cohort (Table 33).

Table 33: Counts of other AEs in patients aged ≥1 month to <17 years

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Cardiac disorder	**Disorder of atrioventricular (not morphologically mitral or tricuspid) valve**	None	None	None	None	0	[redacted]
	Heart failure	[redacted]		None	None	None	None
	Hypertensive disorder, systemic arterial			[redacted]			
	Infective endocarditis			None	None	[redacted]	
	Left ventricular cardiac dysfunction			None	None		
	Left ventricular hypertrophy			None	None		
	Low blood pressure			[redacted]	[redacted]		
	Prolonged QT interval						
	Shock co-occurrent and due to anaphylaxis						
	Sinus arrest	None	None				
	Tachycardia	[redacted]		12		13	
General disorders and	**Abdominal compartment syndrome**			None	None	[redacted]	
	Acute conjunctivitis			[redacted]	0		

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
administration site conditions	**Acute injury of kidney**	[redacted]					
	Anemia						
	Apnea						
	Aspiration pneumonia	None	None	None	None	[redacted]	
	Bacteremia	[redacted]					
	Bleeding from nose	0	[redacted]	None	None		
	Blood in urine	None	None	[redacted]	0		
	Candidiasis of mouth	[redacted]					
	Corneal ulcer						
	Excessive salivation						
	Exposure keratoconjunctivitis	None	None	None	None		
	Febrile neutropenia	None	None	None	None		
	Fever	[redacted]					
	Fracture of femur	None	None	[redacted]			
	Functional gait instability	None	None				
	Gait disturbances	[redacted]					
	Gastroparesis			None	None		
	Hematochezia	None	None	None	None		
	Hemosiderin pigmentation	[redacted]					

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Hydrocele of testis	[redacted]					
	Hydronephrosis						
	Hypervolemia						
	Hypothermia	None	None	[redacted]			
	Hypoxia	[redacted]					
	Increased blood leukocyte number						
	Intestinal obstruction co-occurrent and due to decreased peristalsis	None	None				
	Kidney stone	[redacted]					
	On examination, penile discharge			None	None	[redacted]	
	Physical deconditioning			None	None		
	Pneumatosis coli			None	None		
	Pneumonia			[redacted]			
	Pulmonary aspiration						
	Recurrent dislocation of hip			None	None		
	Respiratory distress	None	None	[redacted]		None	None
	Respiratory failure	[redacted]					

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Respiratory insufficiency	[redacted]		None	None	[redacted]	
	Respiratory obstruction			None	None		
	Retention of urine	None	None	[redacted]		None	None
	Septic shock	[redacted]		None	None	[redacted]	
	Shock	None	None	[redacted]			
	Stridor	[redacted]		None	None		
	Subconjunctival hemorrhage	None	None	None	None		
	Superior vena cava syndrome	None	None	None	None		
	Systemic lupus erythematosus	[redacted]		None	None		
	Tinnitus			0	[redacted]		
	Torsion of ovary			None	None		
	Tracheitis			[redacted]			
	Urinary tract infectious disease						
	Vascular insufficiency of intestine	None	None				
	Venous thrombosis due to central venous access device	[redacted]					
	Ventilator-acquired pneumonia						
	Vocal cord palsy			None	None		

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Injury, poisoning, and procedural complication	**Accidental poisoning by alcohol**	[redacted]					
	Acute deep venous thrombosis of right femoral vein						
	Closed fracture of fifth metacarpal	None	None	[redacted]			
	Compartment syndrome of lower limb	[redacted]		None	None	[redacted]	
	Complication of intravascular line			[redacted]			
	Deep venous thrombosis of left lower extremity						
	Deep venous thrombosis of left upper extremity			None	None		
	Dislocation of temporomandibular joint	None	None	[redacted]			
	Erythema at injection site	0	[redacted]	None	None		
	Fall from bed	None	None	[redacted]	0		
	Isoflurane poisoning	0	[redacted]	None	None		
	Magnetic resonance imaging of cervical spine abnormal	None	None	[redacted]	0		
	Malignant hyperthermia	[redacted]	0	None	None		

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Thromboembolism of vein	[redacted]					
	Thrombosis of cephalic vein		0	None	None		
	Thrombosis of jugular vein	None	None	None	None		
	Venous thrombosis due to central venous access device						
Metabolism and nutrition disorders	**Abdominal discomfort**	None	None	None	None		
	Constipation						
	Diabetes insipidus						
	Diarrhea						
	Dysphagia						
	Failure to gain weight						
	Feeding difficulties and mismanagement	None	None	None	None		
	Gastroesophageal reflux disease			None	None		
	Gastrostomy hemorrhage			None	None		
	Hematochezia			None	None		
	Hepatic failure			None	None		
	Hyperammonemia	None	None				
	Hyperglycemia						

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Hyperkalemia	None	None	[redacted]			
	Hypernatremia	0	[redacted]				
	Hypoglycemia	None	None				
	Hypokalemia	None	None				
	Hyponatremia	[redacted]	0				
	Increased aspartate transaminase level	None	None	None	None	[redacted]	0
	Intestinal obstruction co-occurrent and due to decreased peristalsis	[redacted]					
	Lactic acidosis	[redacted]		None	None	[redacted]	
	Loose stool			[redacted]			
	Metabolic acidosis						
	Nausea	None	None	None	None		
	Necrotizing enterocolitis in fetus OR newborn (disorder)	[redacted]		None	None		
	Pancreatitis			[redacted]	0		
	Severe protein-calorie malnutrition			None	None		
	Small bowel obstruction	None	None	[redacted]			

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Syndrome of inappropriate vasopressin secretion	[redacted]		None	None	[redacted]	
	Unable to eat			[redacted]	[redacted]		
	Vitamin D deficiency	None	None	None	None		
	Volvulus of the small bowel	None	None	None	None		
	Vomiting	[redacted]		[redacted]			
	Weight loss						
Nervous system disorders	**Akathisia**			None	None		
	Anoxic encephalopathy			[redacted]	0		
	Apraxia			None	None		
	Aseptic meningitis			None	None		
	Autoimmune encephalitis caused by N-methyl D aspartate receptor antibody			[redacted]			
	Bilateral hearing loss	None	None				
	Brain disorder resulting from a period of impaired oxygen delivery to the brain	0	[redacted]				
	Central fever	[redacted]	0	None	None		
	Cerebral edema	0	[redacted]				

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Cerebral infarction	None	None	None	None	[redacted]	
	Cerebrovascular accident	[redacted]		[redacted]	0		
	Chorea			None	None		
	Choreoathetosis			None	None		
	Cortical visual impairment			[redacted]			
	Delirium						
	Diplopia						
	Disorder of autonomic nervous system						
	Disorder of brain	None	None				
	Dizziness	[redacted]					
	Dyskinesia					None	None
	Dysmetria					[redacted]	
	Dyssomnia			None	None		
	Dystonia			[redacted]			
	Encephalitis	None	None				
	Esotropia	[redacted]		None	None		
	Expressive dysphasia			[redacted]			
	Headache disorder						

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Hemorrhagic cerebral infarction	None	None	None	None	[redacted]	
	Hypoxic ischemic encephalopathy	None	None	0	[redacted]		
	Impairment of mental alertness	None	None	None	None		
	Incoherent speech	[redacted]	0	[redacted]	0		
	Increased muscle tone	None	None	None	None		
	Insomnia	[redacted]	0	None	None		
	Intracranial hemorrhage	None	None	[redacted]	0	None	None
	Intracranial hypotension	[redacted]	0	[redacted]	0	[redacted]	0
	Left hemiparesis	None	None	None	None		0
	Lethargy	[redacted]	0	[redacted]	0		0
	Low pressure headache	None	None	[redacted]	0	None	None
	Meningitis	[redacted]	0	None	None	[redacted]	
	Movement disorder		0	[redacted]	0		
	Muscular hypertonicity	None	None	None	None		
	Nystagmus	None	None	0	[redacted]		
	On examination - fixed, dilated pupils	None	None	[redacted]	0	None	None

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Posterior reversible encephalopathy syndrome	None	None	0	[redacted]	None	None
	Raised intracranial pressure	None	None	None	None	[redacted]	
	Rasmussen syndrome	[redacted]	0	None	None		
	Slurred speech	None	None	None	None		
	Spasticity	[redacted]		0	[redacted]		
	Spinal stenosis in cervical region			[redacted]	0		
	Spinal subdural hematoma			[redacted]	0		
	Stupor			None	None		
	Subdural hygroma			[redacted]	0		
	Tremor			None	None		
	Weakness of left arm			None	None		
	Weakness of left facial muscle			[redacted]	0		
	Weakness of left leg			[redacted]	0		
Psychiatric disorders	**Adjustment disorder with disturbance of conduct**			None	None		
	Aggressive behavior			None	None		
	Altered mental status			[redacted]			
	Anxiety	None	None				

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Attention deficit hyperactivity disorder	None	None	None	None	[redacted]	0
	Catatonia	[redacted]					
	Clouded consciousness	None	None				
	Delirium	[redacted]					
	Depressed mood						
	Developmental regression						
	Feeling agitated					12	[redacted]
	Feeling irritable						
	Hallucinations						
	Impulsive character			None	None		
	Mood swings			[redacted]	[redacted]		
	Outbursts of anger			None	None		
Skin and subcutaneous tissue disorders	**Anasarca**			[redacted]	0		
	Broken skin			[redacted]	0		
	Cellulitis			None	None		
	Dermal mycosis						
	Erythema of skin	None	None				
	Fat necrosis of breast	[redacted]	0	None	None		

Sensitivity Analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
	Impetigo bullosa	None	None	None	None	None	None
	Inflammatory disease of mucous membrane	None	None	None	None	[redacted]	
	Lip ulcer	None	None	[redacted]			
	Oral lesion	None	None				
	Peeling of skin	None	None	None	None	None	None
	Petechia	None	None	[redacted]	0	[redacted]	
	Phlegmon	[redacted]		None	None		
	Pressure ulcer			[redacted]			
	Skin necrosis						
	Skin nodule			None	None		
	Swelling of oral cavity structure			None	None		
	Ulcer of anus	None	None	None	None		
	Ulcer on tongue	[redacted]		[redacted]			
	Wound granuloma						

AE=Adverse event; PMCA=Pediatric Medical Complexity Algorithm; SNOMED-CT= Systematized nomenclature of medicine-clinical terms

10.5.3.2 Patients aged <30 days

Counts of other AEs (not part of specified AE list) are given in below (Table 34).

10.5.3.2.1 Omit non-neuro PMCA

The highest number of AEs were 2 for vomiting in the recommended dose cohort and 1 for necrotizing enterocolitis in fetus or newborn (disorder) in the loading dose cohort (Table 34).

10.5.3.2.2 7-day follow-up limit

The highest number of AEs were 1 for pulmonary hypertension, vomiting, spinal epidural hematoma, subdural intracranial hematoma in the recommended dose cohort and no event was reported in the loading dose cohort (Table 34).

10.5.3.2.3 Omit prior AE

The highest number of AEs were 2 for vomiting in the recommended dose cohort and 1 for necrotizing enterocolitis in fetus or newborn (disorder) in the loading dose cohort (Table 34).

Table 34: Counts of other AEs in patients aged <30 days

Sensitivity analyses		1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE Diagnostic Categories	**Other AEs (SNOMED-CT)**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Cardiac conditions	**Low blood pressure**	[redacted]					
	Pulmonary hypertension						
General disorders and administration site conditions	**Aspiration pneumonia**						
Metabolism and nutrition disorders	**Necrotizing enterocolitis in fetus OR newborn (disorder)**						
	Vomiting						
Nervous system disorders	**Spinal epidural hematoma**						
	Subdural intracranial hematoma						

AE=Adverse event; PMCA=Pediatric Medical Complexity Algorithm; SNOMED-CT= Systematized nomenclature of medicine-clinical terms

10.5.4 Incidence rates for AEs that physicians attributed to LCM by diagnostic categories

10.5.4.1 Patients aged ≥1 month to <17 years

10.5.4.1.1 Omit non-neuro PMCA

The incidence rates per 1000 days for overall AEs were 1.42 (95% CI: 0.46, 3.32) in the recommended dose cohort and 1.81 (95% CI: 0.37, 5.30) in loading dose cohort. The incidence rates per 1000 person-days ranged from 0.27 (95% CI: 0.01, 1.52) for nervous system disorders and metabolism and nutrition disorders to 0.56 (95% CI: 0.07, 2.01) for cardiac disorders and skin and subcutaneous tissue disorders in the recommended dose cohort and from 0.58 (95% CI: 0.01, 3.25) for metabolism and nutrition disorders to 1.20 (95% CI: 0.15, 4.34) for nervous system disorders in the loading dose cohort (Table 35).

10.5.4.1.2 7-day follow-up limit

The incidence rates per 1000 days for overall AEs were 2.74 (95% CI: 1.00, 5.96) in the recommended dose cohort and 4.19 (95% CI: 1.14, 10.74) in the loading dose cohort. The incidence rates per 1000 person-days ranged from 0.43 (95% CI: 0.01, 2.38) for nervous system disorders and metabolism and nutrition disorders to 0.88 (95% CI: 0.11, 3.19) for cardiac disorders and skin and subcutaneous tissue disorders in the recommended dose cohort and from 0.97 (95% CI: 0.02, 5.40) for metabolism and nutrition disorders to 2.04 (95% CI: 0.25, 7.36) for nervous system disorders in the loading dose cohort (Table 35).

10.5.4.1.3 Omit prior AE

The incidence rates per 1000 days for overall AEs were 0.81 (95% CI: 0.26, 1.89) in the recommended dose cohort and 1.37 (95% CI: 0.37, 3.51) in the loading dose cohort. The incidence rates per 1000 person-days ranged from 0.16 (95% CI: 0.00, 0.89) for cardiac disorders, nervous system disorders and metabolism and nutrition disorders to 0.32 (95% CI: 0.04, 1.16) for skin and subcutaneous tissue disorders in the recommended dose cohort and from 0.33 (95% CI: 0.01, 1.86) for metabolism and nutrition disorders to 0.68 (95% CI: 0.08, 2.45) for nervous system disorders in the loading dose cohort (Table 35).

Table 35: Count of AEs that physicians attributed to LCM by diagnostic categories by initial dose in patients aged ≥1 month to <17 years

	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Overall AE						
Total number of events	[redacted]					
Unique patients with events						
Patient-days of observation	3,513	1,653	2,191	954	6,183	2,920
Incident rate per 1000 patient-days (95% CI)	1.42 (0.46, 3.32)	1.81 (0.37, 5.30)	2.74 (1.00, 5.96)	4.19 (1.14, 10.74)	0.81 (0.26, 1.89)	1.37 (0.37, 3.51)
Cardiac disorders						
Total number of events	[redacted]	None	[redacted]	None	[redacted]	None
Unique patients with events						
Patient-days of observation	3,587		2,266		6,258	
Incident rate per 1000 patient-days (95% CI)	0.56 (0.07, 2.01)		0.88 (0.11, 3.19)		0.16 (0.00, 0.89)	
Skin and subcutaneous tissue disorders						
Total number of events	[redacted]					
Unique patients with events						
Patient-days of observation	3,588	1,692	2,267	1,008	6,223	2,974
Incident rate per 1000 patient-days (95% CI)	0.56 (0.07, 2.01)	0.59 (0.01, 3.29)	0.88 (0.11, 3.19)	0.99 (0.03, 5.53)	0.32 (0.04, 1.16)	0.34 (0.01, 1.87)
Nervous system disorders						
Total number of events	[redacted]					
Unique patients with events						

	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Patient-days of observation	3,659	1,666	2,338	982	6,294	2,948
Incident rate per 1000 patient-days (95% CI)	0.27 (0.01, 1.52)	1.20 (0.15, 4.34)	0.43 (0.01, 2.38)	2.04 (0.25, 7.36)	0.16 (0.00, 0.89)	0.68 (0.08, 2.45)
Metabolism and nutrition disorders						
Total number of events	[redacted]					
Unique patients with events						
Patient-days of observation	3,658	1,716	2,337	1,032	6,293	2,998
Incident rate per 1000 patient-days (95% CI)	0.27 (0.01, 1.52)	0.58 (0.01, 3.25)	0.43 (0.01, 2.38)	0.97 (0.02, 5.40)	0.16 (0.00, 0.89)	0.33 (0.01, 1.86)
Psychiatric disorders						
Total number of events	None	None	None	None	None	None
Unique patients with events						
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
Injury, poisoning and procedural complications	None	None	None	None	None	None
Total number of events						
Unique patients with events						
Patient-days of observation						
Incident rate per 1000 patient-days (95% CI)						
General disorders and administration site conditions	None	None	None	None	None	None
Total number of events						

	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)						
Investigations of ECG indicating long PR Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
DRESS Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Severe cutaneous adverse reactions Total number of events Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)	None	None	None	None	None	None
Hypersensitivity Total number of events	None	None	None	None	None	None

	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
AE diagnostic categories (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Unique patients with events Patient-days of observation Incident rate per 1000 patient-days (95% CI)						

AE=Adverse event; CI=Confidence interval; DRESS=Drug reaction with eosinophilia and systemic symptoms syndrome; ECG=Electrocardiogram; MedDRA= Medical Dictionary for Regulatory Activities; PMCA=Pediatric Medical Complexity Algorithm

10.5.4.2 Patients aged <30 days

10.5.4.2.1 Omit non-neuro PMCA

After omission of non-neuro PMCA, the incidence rates per 1000 person-days ranged from 0.27 (95% CI: 0.01, 1.52) for pancreatitis to 0.56 (95% CI: 0.07, 2.01) for rash in the recommended dose cohort and from 0.58 (95% CI 1.01, 3.25) for vomiting to 0.59 (95% CI 0.02, 3.31) for somnolence in the loading dose cohort (Table 36).

10.5.4.2.2 7-day follow-up limit

After limiting the follow up period to 7 days, the incidence rates per 1000 person-days ranged from 0.43 (95% CI: 0.01, 2.42) for bradycardia and prolonged QT interval, to 0.88 (95% CI: 0.11, 3.19) for rash in the recommended dose cohort and from 0.97 (95% CI: 0.02, 5.40) for vomiting to 1.00 (95% CI: 0.03, 5.59) for somnolence in the loading dose cohort (Table 36).

10.5.4.2.3 Omit prior AE

After omission of prior AEs, the incidence rates ranged from 0.16 (95% CI: 0.00, 0.89) for bradycardia, pancreatitis and somnolence to 0.32 (95% CI: 0.04, 1.16) for rash in the recommended dose cohort and from 0.33 (95% CI: 0.01, 1.86) for vomiting to 0.34 (95% CI: 0.01, 1.88) for somnolence in the loading cohort (Table 36).

Table 36: Count of AEs that physicians attributed to LCM by diagnostic categories by initial dose in patients aged <30 days

	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Bradycardia						
Unique patients with events	[redacted]	None	[redacted]	None	[redacted]	None
Patient-days of observation	3,623		2,302		6,258	
Incident rate per 1000 patient-days (95% CI)	0.28 (0.01, 1.54)		0.43 (0.01, 2.42)		0.16 (0.00, 0.89)	
Prolonged QT interval						
Unique patients with events	[redacted]	None	[redacted]	None	None	None
Patient-days of observation	3,624		2,303			
Incident rate per 1000 patient-days (95% CI)	0.28 (0.01, 1.54)		0.43 (0.01, 2.42)			
Pancreatitis						
Unique patients with events	[redacted]	None	[redacted]	None	[redacted]	None
Patient-days of observation	3,658		2,337		6,293	
Incident rate per 1000 patient-days (95% CI)	0.27 (0.01, 1.52)		0.43 (0.01, 2.38)		0.16 (0.00, 0.89)	
Vomiting						
Unique patients with events	None	[redacted]	None	[redacted]	None	[redacted]
Patient-days of observation		1,716		1,032		2,998
Incident rate per 1000 patient-days (95% CI)		0.58 (0.01, 3.25)		0.97 (0.02, 5.40)		0.33 (0.01, 1.86)

Table 36: Count of AEs that physicians attributed to LCM by diagnostic categories by initial dose in patients aged <30 days

	1 – Omit non-neuro PMCA		2 – 7-day follow-up limit		3 – Omit prior AE	
Specific AE diagnoses (MedDRA)	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**	**Recommended dose cohort**	**Loading dose cohort**
Nystagmus						
Unique patients with events	None	None	None	[redacted]	None	[redacted]
Patient-days of observation				1,019		2,985
Incident rate per 1000 patient-days (95% CI)				0.98 (0.02, 5.47)		0.34 (0.01, 1.87)
Somnolence						
Unique patients with events	None	[redacted]				
Patient-days of observation		1,681	2,338	997	6,294	2,963
Incident rate per 1000 patient-days (95% CI)		0.59 (0.02, 3.31)	0.43 (0.01, 2.38)	1.00 (0.03, 5.59)	0.16 (0.00, 0.89)	0.34 (0.01, 1.88)
Rash						
Unique patients with events	[redacted]					
Patient-days of observation	3,588	1,692	2,267	1,008	6,223	2,974
Incident rate per 1000 patient-days (95% CI)	0.56 (0.07, 2.01)	0.59 (0.01, 3.29)	0.88 (0.11, 3.19)	0.99 (0.03, 5.53)	0.32 (0.04, 1.16)	0.34 (0.01, 1.87)

AE=Adverse event; CI=Confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; PMCA=Pediatric Medical Complexity Algorithm

10.5.5 Incidence rate ratios for AE diagnostic categories after patients with omitting non-neuro PMCA

10.5.5.1 Patients aged ≥1 month to <17 years

With omission of non-neuro PMCA, before adjustment, the loading dose was associated with a significant 54% decreased risk of cardiac disorders compared with the recommended dose (IRR: 0.46; 95% CI: 0.25, 0.87). After adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant differences in AE diagnostic categories were observed between the recommended and loading dose cohorts (Table 37).

Table 37: Unadjusted and adjusted incidence rate ratios for AE diagnostic categories by initial dose in patients aged ≥1 month to <17 years after omitting patients with non-neuro PMCA

Sensitivity analyses	Loading vs Recommended Dose			
AE Diagnostic Categories (MedDRA)	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
Any AE	1.00 (0.72, 1.38)	0.983	0.83 (0.41, 1.68)	0.606
Cardiac disorders	0.46 (0.25, 0.87)	0.016	0.55 (0.20, 1.49)	0.239
Skin and subcutaneous tissue disorders	1.39 (0.77, 2.51)	0.280	1.47 (0.66, 3.26)	0.341
Nervous system disorders	0.60 (0.33, 1.08)	0.089	0.80 (0.34, 1.84)	0.593
Metabolism and nutrition disorders	1.11 (0.60, 2.05)	0.749	1.10 (0.48, 2.55)	0.820
Psychiatric disorders	0.95 (0.43, 2.09)	0.902	1.05 (0.38, 2.92)	0.921
Injury, poisoning and procedural complications	0.62 (0.17, 2.25)	0.466	0.32 (0.06, 1.63)	0.171
General disorders and administration site conditions	0.79 (0.42, 1.49)	0.470	0.94 (0.38, 2.35)	0.898
Investigations of ECG indicating long PR	n/a	n/a	n/a	n/a
DRESS	0.71 (0.07, 6.80)	0.765	0.66 (0.07, 6.59)	0.722
Severe cutaneous adverse reactions	n/a	n/a	n/a	n/a
Hypersensitivity	n/a	n/a	n/a	n/a

AE=Adverse event; CI=Confidence interval; DRESS=Drug reaction with eosinophilia and systemic symptoms syndrome; ECG=Electrocardiogram; MedDRA= Medical Dictionary for Regulatory Activities; n/a=Not applicable or no data; PMCA=Pediatric Medical Complexity Algorithm
[1]Determined using Poisson regression with inverse probability treatment weights.

10.5.6 Incidence rate ratios for AE diagnostic categories after sensitivity analysis limiting to 7-day follow-up after the index date

10.5.6.1 Patients aged ≥1 month to <17 years

By limiting the follow-up period to 7 days, before and after adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant differences in AE diagnostic categories were observed between recommended and loading dose cohorts (Table 38).

Table 38: Unadjusted and adjusted incidence rate ratios for AE diagnostic categories by initial dose in patients aged ≥1 month to <17 years after sensitivity analysis limiting to 7-day follow-up after the index date

Sensitivity analyses	Loading vs Recommended Dose			
AE diagnostic categories (MedDRA)	**Unadjusted incidence rate ratio (95% CI)**	**p-value unadjusted**	**Adjusted incidence rate ratio[1] (95% CI)**	**p-value adjusted**
Any AE	0.85 (0.64, 1.14)	0.277	0.85 (0.57, 1.27)	0.434
Cardiac disorders	0.61 (0.37, 1.03)	0.062	0.73 (0.37, 1.44)	0.365
Skin and subcutaneous tissue disorders	0.93 (0.47, 1.85)	0.846	1.28 (0.56, 2.95)	0.561
Nervous system disorders	0.69 (0.38, 1.27)	0.235	0.54 (0.24, 1.21)	0.134
Metabolism and nutrition disorders	0.91 (0.52, 1.62)	0.759	0.98 (0.45, 2.14)	0.954
Psychiatric disorders	1.15 (0.57, 2.33)	0.692	1.18 (0.40, 3.45)	0.766
Injury, poisoning and procedural complications	0.59 (0.12, 2.83)	0.508	0.19 (0.04, 1.01)	0.052
General disorders and administration site conditions	0.56 (0.28, 1.13)	0.108	0.70 (0.17, 2.94)	0.624
Investigations of ECG indicating long PR	n/a	n/a	n/a	n/a
DRESS	n/a	n/a	n/a	n/a
Severe cutaneous adverse reactions	n/a	n/a	n/a	n/a
Hypersensitivity	n/a	n/a	n/a	n/a

AE=Adverse event; CI=Confidence interval; DRESS=Drug reaction with eosinophilia and systemic symptoms syndrome; ECG=Electrocardiogram; MedDRA= Medical Dictionary for Regulatory Activities; PMCA=Pediatric Medical Complexity Algorithm; n/a=Not applicable or no data
[1]Determined using Poisson regression with inverse probability treatment weights.

10.5.7 Incidence rate ratios for AE diagnostic categories after sensitivity analyses omitting patients with prior AEs

10.5.7.1 Patients aged ≥1 month to <17 years

With omission of prior AEs, before and after adjusting for possible confounding variables by Poisson regression with inverse probability treatment weights, no statistically significant differences in AE diagnostic categories were observed between the recommended and loading dose cohorts except for cardiac disorders, ie, loading dose was associated with a significant 53% decreased risk of cardiac disorders when compared with recommended dose (adjusted IRR: 0.47; 95% CI: 0.24, 0.90) (Table 39).

Table 39: Unadjusted and adjusted incidence rate ratios for AE diagnostic categories by initial dose in patients aged ≥1 month to <17 years after sensitivity analysis omitting patients with prior AEs

	Loading vs Recommended Dose			
AE Diagnostic Categories (MedDRA)	**Unadjusted incidence rate ratio (95% CI)**	**p-value unadjusted**	**Adjusted incidence rate ratio[1] (95% CI)**	**p-value adjusted**
Any AE	0.82 (0.64, 1.07)	0.147	0.93 (0.63, 1.38)	0.71
Cardiac disorders	0.49 (0.29, 0.80)	0.005	0.47 (0.24, 0.90)	0.024
Skin and subcutaneous tissue disorders	1.02 (0.61, 1.73)	0.930	1.35 (0.71, 2.56)	0.355
Nervous system disorders	0.68 (0.41, 1.11)	0.123	0.75 (0.40, 1.40)	0.361
Metabolism and nutrition disorders	0.76 (0.47, 1.23)	0.260	0.96 (0.50, 1.83)	0.900
Psychiatric disorders	0.90 (0.50, 1.62)	0.732	0.91 (0.37, 2.25)	0.842
Injury, poisoning and procedural complications	0.88 (0.34, 2.29)	0.796	0.63 (0.20, 1.97)	0.429
General disorders and administration site conditions	0.74 (0.44, 1.24)	0.252	0.79 (0.30, 2.09)	0.632
Investigations of ECG indicating long PR	n/a	n/a	n/a	n/a
DRESS	0.70 (0.07, 6.71)	0.756	0.73 (0.07, 7.10)	0.785
Severe cutaneous adverse reactions	n/a	n/a	n/a	n/a
Hypersensitivity	n/a	n/a	n/a	n/a

AE=Adverse event; CI=Confidence interval; DRESS=Drug reaction with eosinophilia and systemic symptoms syndrome; ECG=Electrocardiogram; MedDRA= Medical Dictionary for Regulatory Activities n/a=Not applicable or no data; PMCA=Pediatric Medical Complexity Algorithm
[1]Determined using Poisson regression with inverse probability treatment weights.

10.5.8 Incidence rate ratios for specific AEs after sensitivity analysis after omitting patients with non-neuro PMCA

10.5.8.1 Patients aged ≥1 month to <17 years

With omission of patients with non-neuro PMCA, before and after adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant differences in specific AEs were observed between the recommended and loading dose cohorts except for gait disturbances, ie, loading dose was associated with a significant 93% decreased risk of gait disturbances when compared with recommended dose (adjusted IRR: 0.07; 95% CI: 0.01, 0.81) (Table 40).

Table 40: Unadjusted and adjusted incidence rate ratios for specific AE diagnoses by initial dose in patients aged ≥1 month to <17 years after omitting patients with non-neuro PMCA

Specific AE Diagnoses (MedDRA)	Loading vs Recommended Dose			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
AV block	n/a	n/a	n/a	n/a
AV block complete	n/a	n/a	n/a	n/a
AV block 1st degree	n/a	n/a	n/a	n/a
AV block 2nd degree	n/e	n/e	n/e	n/e
Arrhythmia	n/a	n/a	n/a	n/a
Bradyarrhythmia	n/a	n/a	n/a	n/a
Bradycardia	0.32 (0.10, 1.09)	0.069	0.37 (0.09, 1.47)	0.158
Cardiac fibrillation	n/a	n/a	n/a	n/a
Cardiac flutter	n/a	n/a	n/a	n/a
Tachyarrhythmia	0.94 (0.29, 3.05)	0.918	0.61 (0.18, 2.10)	0.436
Atrial fibrillation	n/a	n/a	n/a	n/a
Atrial flutter	n/a	n/a	n/a	n/a
Cardiac arrest	0.70 (0.19, 2.57)	0.587	0.26 (0.06, 1.04)	0.057
Torsade de pointes	n/a	n/a	n/a	n/a
Ventricular arrhythmia	n/a	n/a	n/a	n/a
Ventricular fibrillation	n/a	n/a	n/a	n/a
Ventricular tachyarrhythmia	n/a	n/a	n/a	n/a
Palpitations	n/a	n/a	n/a	n/a

Specific AE Diagnoses (MedDRA)	Loading vs Recommended Dose			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
Stevens-Johnson syndrome	n/a	n/a	n/a	n/a
Toxic epidermal necrolysis	n/a	n/a	n/a	n/a
Angioedema	n/a	n/a	n/a	n/a
Urticaria	n/a	n/a	n/a	n/a
Pruritus	1.05 (0.10, 11.57)	0.969	1.39 (0.12, 15.62)	0.789
Rash	1.91 (0.77, 4.69)	0.161	2.81 (0.97, 8.10)	0.057
Dizziness	0.42 (0.05, 3.57)	0.425	0.13 (0.01, 1.52)	0.105
Somnolence	0.36 (0.11, 1.24)	0.107	0.29 (0.06, 1.44)	0.132
Paresthesias	n/a	n/a	n/a	n/a
Loss of consciousness	n/a	n/a	n/a	n/a
Syncope	n/a	n/a	n/a	n/a
Appetite disorder	n/a	n/a	n/a	n/a
Decreased appetite	0.70 (0.14, 3.48)	0.665	0.80 (0.11, 5.83)	0.827
Diet refusal	n/a	n/a	n/a	n/a
Hypophagia	n/a	n/a	n/a	n/a
Food aversion	n/a	n/a	n/a	n/a
Chest pain	4.20 (0.38, 46.27)	0.241	0.92 (0.08, 10.49)	0.947
Gait disturbances	0.42 (0.05, 3.57)	0.425	0.07 (0.01, 0.81)	0.033
Injection site erythema	n/a	n/a	n/a	n/a
Injection site irritation	n/a	n/a	n/a	n/a

Specific AE Diagnoses (MedDRA)	Loading vs Recommended Dose			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
Injection site pain	n/a	n/a	n/a	n/a

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval; MedDRA= Medical Dictionary for Regulatory Activities; n/a=Not applicable or no data; n/e=Not estimable or small sample size and confidence intervals not making sense; PMCA=Pediatric Medical Complexity Algorithm
[1]Determined using Poisson regression with inverse probability treatment weights.

10.5.9 Incidence rate ratios for specific AE diagnoses after sensitivity analyses limiting to 7-day follow-up after the index date

10.5.9.1 Patients aged ≥1 month to <17 years

With limitation of follow up to 7 days, before and after adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant differences in specific AE were observed between the recommended and loading dose cohorts except gait disturbances, for which the significant risk increased by 93% in patients treated with loading dose compared with the recommended dose cohort (adjusted IRR: 0.07; 95% CI: 0.01, 0.81) (Table 41).

Table 41: Unadjusted and adjusted incidence rate ratios for specific AE diagnoses by initial dose in patients aged ≥1 month to <17 years after sensitivity analysis limiting to 7-day follow-up after the index date

Specific AE Diagnoses (MedDRA)	Loading vs Recommended Dose			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
AV block	n/a	n/a	n/a	n/a
AV block complete	n/a	n/a	n/a	n/a
AV block 1st degree	n/a	n/a	n/a	n/a
AV block 2nd degree	n/e	n/e	n/e	n/e
Arrhythmia	n/a	n/a	n/a	n/a
Bradyarrhythmia	n/a	n/a	n/a	n/a
Bradycardia	0.32 (0.10, 1.09)	0.069	0.37 (0.09, 1.47)	0.158
Cardiac fibrillation	n/a	n/a	n/a	n/a
Cardiac flutter	n/a	n/a	n/a	n/a
Tachyarrhythmia	0.94 (0.29, 3.05)	0.918	0.61 (0.18, 2.10)	0.436
Atrial fibrillation	n/a	n/a	n/a	n/a
Atrial flutter	n/a	n/a	n/a	n/a
Cardiac arrest	0.70 (0.19, 2.57)	0.587	0.26 (0.06, 1.04)	0.057
Torsade de pointes	n/a	n/a	n/a	n/a
Ventricular arrhythmia	n/a	n/a	n/a	n/a
Ventricular fibrillation	n/a	n/a	n/a	n/a
Ventricular tachyarrhythmia	n/a	n/a	n/a	n/a
Palpitations	n/a	n/a	n/a	n/a

Table 41: Unadjusted and adjusted incidence rate ratios for specific AE diagnoses by initial dose in patients aged ≥1 month to <17 years after sensitivity analysis limiting to 7-day follow-up after the index date

Specific AE Diagnoses (MedDRA)	Loading vs Recommended Dose			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
Stevens-Johnson syndrome	n/a	n/a	n/a	n/a
Toxic epidermal necrolysis	n/a	n/a	n/a	n/a
Angioedema	n/a	n/a	n/a	n/a
Urticaria	n/a	n/a	n/a	n/a
Pruritus	1.05 (0.10, 11.57)	0.969	1.39 (0.12, 15.62)	0.789
Rash	1.91 (0.77, 4.69)	0.161	2.81 (0.97, 8.10)	0.057
Dizziness	0.42 (0.05, 3.57)	0.425	0.13 (0.01, 1.52)	0.105
Somnolence	0.36 (0.11, 1.24)	0.107	0.29 (0.06, 1.44)	0.132
Paresthesias	n/a	n/a	n/a	n/a
Loss of consciousness	n/a	n/a	n/a	n/a
Syncope	n/a	n/a	n/a	n/a
Appetite disorder	n/a	n/a	n/a	n/a
Decreased appetite	0.70 (0.14, 3.48)	0.665	0.80 (0.11, 5.83)	0.827
Diet refusal	n/a	n/a	n/a	n/a
Hypophagia	n/a	n/a	n/a	n/a
Food aversion	n/a	n/a	n/a	n/a
Chest pain	4.20 (0.38, 46.27)	0.241	0.92 (0.08, 10.49)	0.947
Gait disturbances	0.42 (0.05, 3.57)	0.425	0.07 (0.01, 0.81)	0.033

Table 41: Unadjusted and adjusted incidence rate ratios for specific AE diagnoses by initial dose in patients aged ≥1 month to <17 years after sensitivity analysis limiting to 7-day follow-up after the index date

Specific AE Diagnoses (MedDRA)	Loading vs Recommended Dose			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
Injection site erythema	n/a	n/a	n/a	n/a
Injection site irritation	n/a	n/a	n/a	n/a
Injection site pain	n/a	n/a	n/a	n/a

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval; n/a=Not applicable or no data; n/e=Not estimable or small sample size and confidence intervals not making sense; PMCA=Pediatric Medical Complexity Algorithm

[1] Determined using Poisson regression with inverse probability treatment weights.

10.5.10 Incidence rate ratios for specific AE diagnoses after sensitivity analyses omitting patients with prior AEs

10.5.10.1 Patients aged ≥1 month to <17 years

With omission of patients with prior AEs, before adjustment, the risk of bradycardia was significantly decreased by 62% when patients treated with the loading dose in comparison to the recommended dose (adjusted IRR: 0.38; 95% CI: 0.15, 0.98). After adjusting for possible confounding variables by Poisson regression with inverse probability treatment weights, no statistically significant differences in specific AE diagnoses were observed between the recommended and loading dose cohorts except the risk of cardiac arrest was significantly decreased by 77% when patients were treated with the loading dose in comparison to the recommended dose (adjusted IRR: 0.23, 95% CI: 0.06, 0.92) (Table 42).

Table 42: Unadjusted and adjusted incidence rate ratios for specific AE diagnoses by initial dose in patients aged ≥1 month to <17 years after sensitivity analysis omitting patients with prior AEs

Specific AE diagnoses (MedDRA)	Loading vs Recommended Dose			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
AV block	n/a	n/a	n/a	n/a
AV block complete	n/a	n/a	n/a	n/a
AV block 1st degree	n/a	n/a	n/a	n/a
AV block 2nd degree	n/e	n/e	n/e	n/e
Arrhythmia	n/a	n/a	n/a	n/a
Bradyarrhythmia	2.12 (0.13, 33.87)	0.596	0.47 (0.03, 7.55)	0.591
Bradycardia	0.38 (0.15, 0.98)	0.046	0.49 (0.17, 1.47)	0.203
Cardiac fibrillation	n/a	n/a	n/a	n/a
Cardiac flutter	n/a	n/a	n/a	n/a
Tachyarrhythmia	0.60 (0.20, 1.81)	0.361	0.34 (0.10, 1.11)	0.074
Atrial fibrillation	n/a	n/a	n/a	n/a
Atrial flutter	n/a	n/a	n/a	n/a
Cardiac arrest	0.57 (0.16, 2.04)	0.388	0.23 (0.06, 0.92)	0.038
Torsade de pointes	n/a	n/a	n/a	n/a
Ventricular arrhythmia	n/a	n/a	n/a	n/a
Ventricular fibrillation	n/a	n/a	n/a	n/a
Ventricular tachyarrhythmia	n/a	n/a	n/a	n/a
Palpitations	n/a	n/a	n/a	n/a

Specific AE diagnoses (MedDRA)	Loading vs Recommended Dose			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
Stevens-Johnson syndrome	n/a	n/a	n/a	n/a
Toxic epidermal necrolysis	n/a	n/a	n/a	n/a
Angioedema	n/a	n/a	n/a	n/a
Urticaria	n/a	n/a	n/a	n/a
Pruritus	0.70 (0.07, 6.71)	0.755	0.90 (0.09, 8.81)	0.928
Rash	1.59 (0.85, 2.98)	0.146	2.11 (1.00, 4.46)	0.051
Dizziness	0.35 (0.04, 2.88)	0.327	0.12 (0.01, 1.29)	0.08
Somnolence	0.62 (0.25, 1.54)	0.303	0.71 (0.20, 2.48)	0.591
Paresthesias	n/a	n/a	n/a	n/a
Loss of consciousness	n/a	n/a	n/a	n/a
Syncope	n/a	n/a	n/a	n/a
Appetite disorder	n/a	n/a	n/a	n/a
Decreased appetite	0.70 (0.19, 2.60)	0.6	1.38 (0.27, 7.06)	0.703
Diet refusal	n/a	n/a	n/a	n/a
Hypophagia	n/a	n/a	n/a	n/a
Food aversion	n/a	n/a	n/a	n/a
Chest pain	4.20 (0.38, 46.27)	0.241	0.92 (0.08, 10.49)	0.947
Gait disturbances	0.70 (0.14, 3.46)	0.66	0.18 (0.03, 1.29)	0.088
Injection site erythema	n/e	n/e	n/e	n/e
Injection site irritation	n/a	n/a	n/a	n/a

Specific AE diagnoses (MedDRA)	Loading vs Recommended Dose			
	Unadjusted incidence rate ratio (95% CI)	p-value unadjusted	Adjusted incidence rate ratio[1] (95% CI)	p-value adjusted
Injection site pain	n/a	n/a	n/a	n/a

AE=Adverse event; AV=Atrioventricular; CI=Confidence interval; n/a=Not applicable or no data; n/e=Not estimable or small sample size and confidence intervals not making sense; PMCA=Pediatric Medical Complexity Algorithm

[1] Determined using Poisson regression with inverse probability treatment weights.

11 DISCUSSION

11.1 Key results

The study comprised 714 patients, including 28 neonates (aged <30 days), and was conducted using the data from EHRs of large specialized pediatric hospitals in US. Of 686 patients aged ≥1 month to <17 years, 68.7% vs 31.3% were administered the iv LCM recommended dose and loading dose as initial doses, respectively. Of 28 patients aged <30 days, 57.1% vs 42.9% were administered the iv LCM recommended dose and loading dose as initial doses, respectively. In patients aged ≥1 month to <17 years, mostly (three-fourths) were diagnosed with epilepsy (focal or syndrome) and status epilepticus in both the dose cohorts. In patients aged <30 days, most of them were diagnosed with status epilepticus and seizure without diagnosis in the recommended dose cohort and seizure without diagnoses in the loading dose cohort. PMCA algorithm was used to describe the presence of chronic conditions. In patients aged ≥1 month to <17 years, presence of chronic conditions ranged from 1.3% vs 1.4% for genitourinary body system to 50.3% vs 48.8% for neurologic body system in the recommended and loading dose cohorts, respectively. In patients aged <30 days, 6.2% were reported to have chronic (neurologic) conditions in the recommended dose cohort and none of the patients reported to have any chronic condition in the loading dose cohort. Patients in both age groups were critically ill with several other comorbidities (top 50 conditions were defined). This indicates that PMCA algorithm is not valid for studying the chronic conditions in neonates.

Overall, the patients in these cohorts were critically ill. In patients aged ≥1 month to <17 years, over half of them were treated in an ICU, while in patients aged <30 days, almost all of them were treated in an ICU. Among patients aged ≥1 month to <17 years, one third of patients were hospitalized at least once in the 3 months prior to the index date. Patients in both age groups were refractory to at least four lines of therapy. In patients aged ≥1 month to <17 years and <30 days, 47 and [redacted] deaths were reported in critically ill patients, respectively, but none of them were attributed to LCM. In patients aged ≥1 month to <17 years, in recommended dose cohort, the proportion of top 50 conditions prior to index date ranged from 8.9% for obstructive sleep apnea syndrome to 46.5% for seizures and in loading dose cohort, it ranged from 4.7% for pediatric failure to thrive to 27.9% for seizures. In patients aged <30 days, in recommended dose cohort, proportion of top 50 conditions prior to index date ranged from 0% for various conditions including feeding problem, pulmonary hypertension, etc to 12.5% with fever of newborn and in the loading dose cohort, it ranged from 0% for several conditions, ie, fever of the newborn, pericardial effusion, etc to 16.7% for feeding problem.

Crude incidence rates by AE diagnostic categories

In patients aged ≥1 month to <17 years, the crude incidence rates per 1000 person-days of overall adverse events (AEs) in the recommended and loading dose cohorts were 64.44 (95% CI: 55.88, 73.95) vs 50.00 (95% CI: 39.82, 61.98), respectively.

In patients aged <30 days, the crude incidence rates per 1000 person-days of overall AEs in the recommended and loading dose cohorts were 36.04 (95% CI: 15.56, 71.01) vs 8.85 (95% CI: 1.07, 31.97), respectively.

Crude incidence rates by specific AE diagnoses

In patients aged ≥1 month to <17 years, the crude incidence rates per 1000 person-days ranged from 0.16 (95% CI: 0.00, 0.89) for AV block, bradyarrhythmia, ventricular

tachyarrhythmia, Stevens-Johnson syndrome, loss of consciousness, appetite disorder and hypophagia each to 4.91 (95% CI: 3.29, 7.05) for bradycardia in the recommended dose cohort. The crude incidence rates per 1000 person-days ranged from 0.33 (95% CI: 0.01, 1.86) for injection site erythema, dizziness, and pruritis individually to 6.55 (95% CI: 3.88, 10.35) for rash in the loading dose cohort.

In patients aged <30 days, only one AE was reported in the recommended dose cohort, ie, cardiac arrest and the crude incidence rate per 1000 person-days was 12.86 (95% CI: 3.50, 32.93). No AE was reported in the loading dose cohort.

Crude incidence rates by AEs that physicians attributed to LCM

In patients aged ≥1 month to <17 years, the crude incidence rates per 1000 person-days of overall AEs that physicians attributed to LCM in the recommended and loading dose cohorts were 0.98 (95% CI: 0.36, 2.12) vs 1.37 (95% CI: 0.37, 3.51), respectively.

In patients aged <30 days, no AEs were reported that physicians attributed to LCM.

IRRs by categories and specific AE diagnoses

In patients aged ≥1 month to <17 years, after adjusting for possible observed confounding variables by Poisson regression with IPTW, no statistically significant increased IRRs in AE diagnostic categories and most of the specific AE diagnoses were observed between the recommended and loading dose cohorts. The risk of rash was increased by two-fold in the loading dose cohort compared with the recommended dose cohort (adjusted IRR 2.11; 95% CI: 1.02, 4.38).

In patients aged <30 days, no IRRs were calculated due to small sample size.

Mortality

In patients aged ≥1 month to <17 years, crude mortality rates per 1000 person-days in the recommended and loading dose cohorts were 4.77 (95% CI: 3.22, 6.80) and 5.67 (95% CI: 3.30, 9.06), respectively. In patients aged <30 days, crude mortality rates per 1000 person-days in the recommended and loading dose cohorts were 14.75 (95% CI: 4.81, 34.08) and 7.14 (95% CI: 0.87, 25.56), respectively.

In patients aged ≥1 month to <17 years, after adjusting for possible confounding variables by Poisson regression with IPTW, no statistically significant IRRs were observed in the loading dose cohort when compared with the recommended dose cohort (adjusted IRR: 1.18; 95% CI: 0.57, 2.42). In patients aged <30 days, no IRRs were calculated due to small sample size.

11.2 Published literature

Six previously published studies evaluated the usage and safety of LCM in children. Patients in most of the published studies were treated for status epilepticus and the sample size was small. The comparison of the current study with previously published studies is limited due to the differences in the indication of iv LCM, small sample size, and incomplete follow-up information. The brief summary of the results is given in Table 43.

Table 43: Previously published studies reporting the usage and safety of iv LCM in children

Author (Year)	Country, study period	Study design	Study population and indication	LCM iv dosage	Other AEDs	Safety (%Incidence proportion of AEs)
Ngampoopun et al (2018)	Thailand, 2016-2018	Prospective single center study	Patients with Nonconvulsive SE, acute repetitive seizures (N=11) Median age, years: 11 (range 7-16)	Average loading dose: 227mg and maintenance dose 249mg Mean loading dose 8.3mg/kg/dose; mean maintenance dose 4.6mg/kg/day	LCM used as second, third, fourth line therapy. In only one patient it was used as first line therapy. Other AEDs: LEV, CLB, CZP, VPA, TPM, LTG, PHE, DZP, PB, PPN Most patients (90.9%) received a median of 3.5 AEDs (range2-5) concomitantly	Bradycardia without PR prolongation: 9% (1/11)
Welsh et al (2017)	US, 2011-2016	Retrospective single centre study	Patients with acute seizures or SE (N=51; 29 patients were given LCM during admission and 22 patients were given LCM prior to admission) Median age, years: 5.6	Median loading dose: 2mg/kg (IQR 1.9-2.7)	LCM third, fourth- or fifth-line therapy Other AEDs: NR	Bradycardia: 2.0% (1/51) Rash: 2.0% (1/51)

Author (Year)	Country, study period	Study design	Study population and indication	LCM iv dosage	Other AEDs	Safety (%Incidence proportion of AEs)
Arkilo et al (2016)	US, 2009-2015	Retrospective single centre observational study	Patients with epilepsy (N=32) Epilepsia partialis continua 3; SE 11; Acute seizure exacerbation18 Median age: 6.5 years (range 1 month – 12 years)	Initial dose range: 1– 11mg/kg	Adjunctive therapy of ≥2 drugs. Other AEDs or concomitant medications: BZD, PHE, LEV, VPA, DZP, FOS, FBM, LTG, TRX, TPM, CLZ, PB, OXC, ZNS, LRZ	Sedation: 15.6% (5/32) Ataxia: 3.1% (1/32)
Poddar et al (2016)	US, 2011-2014	Retrospective descriptive study	Patients with SE refractory to usual treatment ie, FOS, phenobarbital, [redacted] generalized: [redacted] complex partial: [redacted] ([redacted] with secondary generalization) complex partial, myoclonic, generalized tonic: [redacted] epilepsia partialis continua [redacted] Mean age, years: 5.7 (range 3months -16 years)	Mean initial or loading dose: 8.7mg/Kg (3.3-10.0mg/kg) [redacted] out of [redacted] patients received a loading dose of 10mg/kg.	iv AEDs given 24 hours before LCM: FOS, LEV, OXC, PB, VPA	Bradycardia: 11.1% (1/9)

Author (Year)	Country, study period	Study design	Study population and indication	LCM iv dosage	Other AEDs	Safety (%Incidence proportion of AEs)
Grosso et al (2014)	Italy, 2011-2012	Retrospective multicenter observational study	Patients with SE (N=11; convulsive SE 6; Non-convulsive SE 5) Mean age, years: 9.4 (range 3–16)	Mean loading dose: 8.6mg/kg (range 6.7– 9.9)	LCM was given as add on therapy; fifth line or greater AEDs before LCM: BZD, LRZ, PHE, VPA, PB	No AEs reported
Jain and Harvey (2012)	Australia, NR	Case series	Patients with refractory tonic status SE [redacted] Median age, range, years: 16 (12-17)	Dose range: 50-100mg	LCM given as fourth line or more AEDs before LCM: CLB, LEV, LTG, MP, OXC, PB, PHE, TPM, VNS, VPA	Chorea: 33.3% (1/3) Oculogyric crisis: 33.3% (1/3)

AE(s)= Adverse event(s); AEDs=Antiepileptic drugs; BZD=Benzodiazepines; CLB=Clobazam; CLZ=Clonazepam; CZP=Carbamazepine; DZP=Diazepam; FBM=Felbamate; FOS=Fosphenytoin; IQR=Interquartile range; kg=Kilogram; LCM=Lacosamide; LEV=Levetiracetam; LRZ=Lorazepam; LTG=Lamotrigine; mg=Milligram; MP= methylprednisolone; NR=Not reported; OXC=Oxcarbazepine; PB=Phenobarbitone; PHE=Phenytoin; PPN=Perampanel; SD=Standard deviation; SE=Status epilepticus; TPM=Topiramate; TRX=Tranxene; US=United States; VNS=Vagal nerve stimulator; VPA=Valproic acid; ZNS=Zonisamide

11.3 Limitations

The study has several limitations:

Retrospective design: The study used retrospective study design thus cannot guarantee the complete reporting of any AEs. Given the validated nature of large PEDSnet database supported by patient charts, the recording of good quality clinically important AEs is expected.

Small sample size: Sample size of patients aged <30 days was 28 patients; however, larger sample sizes are unlikely to be achieved due to the off-label use of drug and late line of treatment in this age group.

Unmeasured confounding: For the comparison of the incidence rates of the selected medical events of interest between patients who were treated with a loading dose of iv LCM and those who were treated with the recommended dose of iv LCM, certain observable factors were identified which might have confounded these rates. The factors included age, gender, comorbidities, and exposure to other medications. Unmeasured confounding would only occur if there was a major confounder which was not measured and was thus involved in the adjusted model. However, the EHRs included demographic information, the medical history of the patients and any medications prescribed by the physicians. Also, there was no reason to expect differences in the recording of the medical history data and prescription of medications in patients who were treated with the loading dose LCM and recommended LCM prior to the index date.

Misclassification: Ascertainment of outcomes was made using controlled vocabularies. However, there was a risk of misclassification since there were no validated algorithms for defining these outcomes in EHR data. This risk was minimized through chart reviews which were conducted by trained healthcare personnel. Additionally, sensitivity analyses were conducted to assess the impact of the case definitions on the effect estimates. It is likely that any severe AEs would have been recorded. As noted, available data from the chart review were expected to be completed for patients in an inpatient setting. In particular, it was reasonable to expect nurses' notes to contain detailed information on patient responses and patient reported outcomes. As iv LCM was administered for patients in this study, there is a good reason to expect the recording of immediate AEs to be well documented, including those that might have been less severe such as injection site irritation/pain.

Incomplete information: Information available from outpatient or EHR reports were likely not to provide as complete information as that recorded during hospitalization. Despite this, it was likely that any severe AEs would have been recorded. Available data from the chart review were expected to be complete for patients in an inpatient setting. As iv LCM was generally administered in an inpatient setting, there was a good reason to expect the recording of immediate AEs to be well documented, including those that might have been less severe such as injection site irritation/pain.

11.4 Interpretation

The results of the study do not impact the current benefit-risk balance of LCM in patient populations aged <30 days and ≥1 month to <17 years, no evidence of new safety events was found.
In patients aged ≥1 month to <17 years, there was two-fold increased risk of rash in loading dose cohort compared with the recommended dose cohort, which is consistent with previously established safety profile. Rash is listed as an adverse drug reaction for LCM in the current label.

For some of the AE diagnostic categories and specific AE diagnoses, decreased risk was observed in patients treated with a loading dose in comparison to the recommended dose, this observation could be by chance and due to the small sample size of the loading dose cohort.

11.5 Generalizability

PEDSnet includes patients from all 50 states with high representation from 12, making this study a geographically diverse analysis of off-label iv LCM use in pediatric patients, which will facilitate a timely characterization of the safety profile of these patients and help inform the pediatric study program.

12 OTHER INFORMATION

Not applicable

13 CONCLUSION

In the present study, 686 patients aged ≥1 month to <17 years and 28 patients aged <30 days were identified from large specialized pediatric centers, who received off-label iv LCM. Of 686 patients aged ≥1 month to <17 years, 68.7% vs 31.3% were administered iv LCM at the recommended dose or a loading dose as initial doses, respectively. Of the 28 patients aged <30 days, 57.1% vs 42.9% were administered iv LCM at the recommended and loading doses as initial doses, respectively. In patients aged ≥1 month to <17 years, there was a two-fold increased risk of rash in the loading dose cohort compared with the recommended dose cohort, which is in line with the previously established safety profile. No other relevant differences were observed between the recommended and loading dose cohorts for the AE profile of LCM. In patients aged ≥1 month to <17 years and <30 days, 47 and [redacted] deaths were observed, respectively and none of them were attributed to LCM. All of these fatal cases were critically ill patients who were refractory to four other AEDs, were on other concomitant medications, and had other comorbidities. LCM has been on the market for 12 years, its safety profile is well characterized and the results of the current study do not impact the current benefit-risk balance of LCM in the patient populations aged < 30 days and ≥1 month to <17 years.

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15 APPENDICES

APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Title
1	Case report form
2	Statistical analysis plan
3	Study code sets
4	Data dictionary
5	Additional information on deaths
6	Baseline propensity score
7	Propensity scores for PMCA sensitivity analyses
8	New results after PMCA sensitivity analyses

APPENDIX 2. ADDITIONAL INFORMATION

None