U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

REAL WORLD EVIDENCE STUDIES

NDA number:	NDA 022253/S-050
	NDA 022254/S-040
	NDA 022255/S-032
Drug Name:	Vimpat (lacosamide)
Subject:	Review of real-world evidence submission for lacosamide labeling supplement
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1 EXECUTIVE SUMMARY

Background: Vimpat (lacosamide; LCM), a slow sodium channel antagonist, is currently approved for the treatment of partial-onset seizures (POS) and primary generalized-tonic-clonic seizures (PGTCS) in patients 4 years and older for all formulations. It is currently approved for the treatment of POS in patients 1 month of age and older[1] and adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older[2,3,4]. Vimpat dosage in adult patients can be started with an 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. UCB Biopharma SRL, the sponsor of Vimpat, conducted a real-world evidence (RWE) study EP0147 which aims to examine the safety profile of the loading dose of LCM in a pediatric population using data from electronic healthcare databases. The sponsor is seeking inclusion of the loading dosing regime in the label in pediatric patients.

The purpose of this review is to assess, from a statistical perspective, if the RWE study EP0147 provides sufficient evidence to support the relative safety of the proposed loading dose regime as compared to the recommended dose. Following the *Framework for FDA's real-world evidence program* [5], we considered (1) data fit-for-purpose, (2) adequacy of study design, and (3) study conduct, as well as interpretation of study findings, in our assessment of the regulatory question.

Study Design and Methods: The RWE study EP0147 was a retrospective, non-interventional cohort study of pediatric patients (<17 years old) that used electronic health records (EHR) data from the PEDSnet data network (see Section 4.3 for more details on the PEDSnet data) including individuals with at least one encounter in a PEDSnet participating site (b) (4)

The primary objective was to estimate incidence of safety-related study outcomes after intravenous (IV) treatment with higher than the recommended LCM doses (i.e., the treatment; henceforth, the loading dose) compared to pediatric patients treated with the recommended initial/maintenance LCM dose (i.e., the reference or active comparator; henceforth, the recommended dose). There were 11 primary outcomes which consists of the following eight Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs):

- cardiac disorders

[1] Vimpat (lacosamide) approval letter. October 28, 2008. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022253lbl.pdf (accessed March 7, 2023)
[2] Vimpat (lacosamide) label May 19, 2022 https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022254Orig1s044,022253Orig1s054,022255Orig1s036lbl.pdf (accessed March 7, 2023)
[3] Vimpat (lacosamide) supplement approval, October 14, 2021 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/022253Orig1s049,022254Orig1s039,022255Orig1s031ltr.pdf (accessed March 7, 2023)
[4] Vimpat (lacosamide) supplement approval, November 16, 2020 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/022253Orig1s046,%20s048;%20022254Orig1s036,%20s038;%20022255Orig1s027,%20s030ltr.pdf (accessed March 7, 2023)
[5] https://www.fda.gov/media/120060/download (accessed March 7, 2023)

- 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,

as well as the following three Standardized MedDRA Queries (SMQs):

- drug reaction with eosinophilia and systemic symptoms syndrome
- severe cutaneous adverse reactions
- hypersensitivity

The secondary objectives were: 1) to estimate and compare the incidence of the selected medical events among the SOCs and SMQs listed in Table 1 (Section 4.2) in the loading dose group to those in the recommended dose group, and 2) to estimate the effect of increasing loading dose on the incidence of the 11 primary outcomes, compared to that of the recommended dose.

Incidence rate ratios (IRRs) estimated from Poisson regression via inverse probability of treatment weighting (IPTW) approach, which could account for observed confounding, were used to evaluate the effect of the loading dose on the selected study outcomes, as compared to those in the recommended dose.

Results:

(1) Data fit-for-purpose: The *Framework for FDA's real-world evidence program* states that the strength of RWE submitted in support of a regulatory decision depends on the reliability (data accrual and data quality control/assurance) and relevance of the underlying data. We found the data in general are reliable. However, we found a potential issue with the data relevance. Section 9.15.5 of the study report provides amendments made to the study protocol where it states that "*information about the number of seizures or lectroencephalogram results were not part of the PEDSnet structured data and were removed from chart review data collection or use in propensity scoring*." As the information, particularly the number of seizures, could represent underlying severity of seizures for IV LCM indication, missing such information may lead to lack of data relevance and unmeasured confounding issues.

(2) Adequacy of study design: We adapt the target trial framework[6] to evaluate whether the study design based on real-world data is appropriate to approximate a hypothetical randomized controlled trial, if possible, to address the study question of interest. The target trial framework dictates that the following trial protocol components should be properly emulated in an observational study to draw valid causal inference: eligibility criteria, treatment strategies, treatment assignment, start and end of follow-up, outcomes, causal contrasts, and the statistical analysis plan. We made slight modifications to some of these components so that they could be more relevant to the representation of the RWE study EP0147. Summary of the evaluation of the

[6] Hernán, Miguel A., and James M. Robins. "Using big data to emulate a target trial when a randomized trial is not available." American journal of epidemiology 183.8 (2016): 758-764

RWE study EP0147 design, based on the target trial framework, is presented in Table 20 (Section 5.1.2). Our evaluation revealed that the study design has the following limitations:
(1) The selected primary outcomes at SOC level might be too broad and likely be subject to high level of noise resulting in bias towards the null.
(2) The issue of unmeasured and residual confounding was not fully accounted for in statistical analysis, and the impact of the unmeasured/residual confounding was not assessed.

In addition, FDA re-examined the power of this study as we found that the sponsor's initial power analysis was based on some invalid assumptions.[7] The goal of the FDA's power analysis was to verify whether the current sample size is sufficient to detect an unacceptable level of risk in the loading dose group, if it is present. The FDA's power analysis revealed that the current sample size is not sufficient to detect at least a two-fold increase in the risk of (1) injury, poisoning and procedural complications, (2) DRESS, and (3) hypersensitivity in the loading dose group compared to the recommended dose group. Additionally, it was determined that RWE study EP0147 is not sufficiently powered to detect at least a two-fold increase in the risk of more specific AE outcomes (i.e. outcomes that are more granular than outcomes based on broad MedDRA SOCs).

(3) Study conduct and regulatory standards: The sponsor submitted data and analysis codes which enabled FDA to validate data quality and replicate the sponsor's analysis. FDA's validation/replication effort confirmed the reproducibility of the sponsor's analyses. This meets regulatory requirements from a statistical perspective.

(4) Study findings and interpretation: There were two cohorts – one for patients ≥1 month to <17 years old; cohort 1) and the other for neonate patients (<1 month old; cohort 2).

Cohort 1 consists of 686 patients in which 215 (31.3%) were administered the loading dose as initial doses and 471 (68.7%) were administered the recommended dose. The decision of administering the loading dose vs. the recommended dose as initial dose was significantly associated with various factors including patients' age, race, duration of observation before index visit, insurance type, PEDSnet health system, weight, and many pre-existing health conditions. The loading dose, on average, were administered to healthier patients who had less pre-existing conditions. Primary IPTW Poisson regression analyses showed no significant differences in incidence of AE rates between the two dose groups. Although not significant, the loading dose group generally showed lower incidence rates of the primary outcomes compared to those in the recommended dose group. This is somewhat expected given the fact that the loading dose group consisting of healthier patients having less pre-existing conditions. These results, which were derived from the protocol-specified primary analyses, were subject to residual confounding, particularly by many pre-existing conditions that were not part of the pre-specified confounders. FDA requested an additional, sensitivity IPTW analysis that further adjusts for the (not pre-specified) uncontrolled observed confounders. Although findings from this analysis were consistent with the primary analyses results in that the loading dose group generally showed lower rates of AEs, the issue of residual confounding still remained.

[7] Of note, the submission of the power analysis results was not notified to DB VII and thus DB VII was unable to assess the adequacy of the sponsor's power analysis. See Section 4.4.7 of this review for more details.

During the follow-up, proportions of death and staying hospitalized (i.e., not discharged) were higher in the loading dose group (7.9% vs. 6.4% for death and 27.4% vs. 22.1% for staying hospitalized; not significantly different). In IPTW analysis of mortality, IRR was 1.18 (95% confidence interval= 0.57, 2.42) indicating higher mortality rate in the loading dose group compared to that in the recommended dose group. As these results indicate that patients in the loading dose group might perform worse or not as good as those in the recommended dose group over the course of follow up, we encountered contradicting findings - the loading dose group started with healthier patients (indicated by confounding) and showed better or no worse AE outcomes at the end of the study follow-up (indicated by IPTW analyses), but did not perform well in terms of death and hospitalization. From a statistical perspective, the source of the discrepancy was not identifiable.

Cohort 2 consisted of 16 patients in the recommended dose group and 12 in the loading dose group. Results from cohort 2 analyses were generally consistent with those from cohort 1, however the small sample size limited the ability to interpret findings.

Summary and Conclusion:

Following *the Framework for FDA's real-world evidence program*, we considered (1) data fit-for-purpose, (2) adequacy of study design, and (3) adequacy of study conduct, as well as the interpretation of study findings to determine whether the evidence generated from the RWE study EP0147 is sufficient to address the regulatory question on the proposed labeling. Summary of our evaluation is shown in Table 22 (Section 6) of this review and copied below:

Review criteria	Considerations	Issues
Data fit-for-purpose	Reliability	None
	Relevance	Number of seizures or lectroencephalogram results not available in PEDSnet. This could lead to unmeasured confounding issue.
Adequacy of study design	Target trial emulation	Analyses based on SOCs might be subject to high level of noise resulting in bias towards the null. Issue of unmeasured and residual confounding exists.
	Power analysis	Not adequately powered to detect a two-fold increase of risk for some primary outcomes and more specific adverse outcomes.
Whether study conduct meets regulatory requirements	Data validation	None
	Analysis replication	None
Interpretation of study findings		Patients in the loading dose group were healthier at baseline and showed better or no worse AE

		outcomes but were more likely to die or stay hospitalized during the follow-up.

Both data and design have some limitations, whereas study conduct meets regulatory requirements. Reconciling two different implications about patients in the loading dose group (patients in this group were healthier at baseline and performed better in terms of selected AE outcomes, but they did not perform better or no worse in terms of death and discharge during the follow up) was challenging. From a statistical perspective, the limitations observed result in uncertainties as to whether the RWE study EP0147 provides sufficient scientific evidence on the safety of the proposed loading dose.

While the limitations of unmeasured and residual confounding were not addressed through statistical assessment, they may be explained based on clinical judgement which we defer to the clinical review team. However, there still remains the issues of the lack of specificity in primary outcome defined by MedDRA SOC's and the lack of study power which would be most evident for looking at more specific safety outcomes. In combination, these issues have the potential to bias any observed findings, or lack of an observed finding, towards the null (i.e. determination of similar safety between the loading and recommended dose). Therefore, it is important to acknowledge that the absence of evidence of a difference in safety from the RWE study EP0147 is not evidence of absence.

With these considerations in mind, some notable safety findings from cohort 1 (patients ≥1 month to <17 years old) in the RWE study EP0147 were:

- Skin and subcutaneous tissues disorders (at SOC level; primary outcome): IRR = 1.15 with 95% CI (0.62, 2.13) based on the primary IPTW analysis and IRR = 1.36 with 95% CI (0.65, 2.82) with the sensitivity IPTW analysis that adjusted for residual confounding
- Rash (at preferred term level; secondary outcome) resulted in an IRR = 2.11 with 95% CI (1.02, 4.38)
- Mortality: IRR = 1.18 with 95% CI (0.57, 2.42)

While uncertainties remain on whether these safety findings represent real increases in risk of the loading dose relative to the recommended dose, we acknowledge that tolerance for risk is in relation to the benefit. Unfortunately, the RWE study EP0147 does not provide any comparative efficacy information to support any improvements of the loading dose relative to the recommended dose precluding a benefit-risk assessment which we acknowledge was not part of the considerations in the design of the study.

Overall, the statistical perspective is that the evidence generated from the RWE study EP0147, on its own, is not sufficiently reassuring of the safety of the loading dose relative to the recommended dose.

2 BACKGROUND

Vimpat (lacosamide; LCM), a slow sodium channel antagonist, is currently approved for the treatment of partial-onset seizures (POS) and primary generalized-tonic-clonic seizures (PGTCS) in patients 4 years and older for all formulations. It is currently approved for the treatment of POS in patients 1 month of age and older[8] and adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older[9,10,11]. 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, in *adult patients*, it may be initiated with a single loading dose of 200mg. UCB Biopharma SRL, the sponsor of Vimpat, conducted a real-world evidence (RWE) study EP0147 which aims to examine the safety profile of the loading dose of LCM in a *pediatric population* using data from electronic healthcare databases. The sponsor is seeking for an extension of LCM indication in pediatric patients if the loading dose is shown to be safe as compared to the recommended initial dose.

For more details on regulatory history and background of Vimpat, see DN II and DEPI I reviews.

3 REVIEW METHODS AND MATERIALS

We followed the *Frameworks for FDA's Real-World Evidence Program*[12] for review and evaluation of the submission. This program document delineates frameworks for evaluating real-world data (RWD) and RWE for their use in regulatory decisions, which states the following considerations:

1) Whether the RWD are fit for use
2) Whether the trial or study design is adequate
3) Whether the study conduct meets FDA regulatory requirements

To evaluate the adequacy of study design stated in 2), we adapted the target trial framework[13] and see if target trial protocol components, if applicable, have been properly emulated to minimize potential sources of bias caused by the absence of treatment randomization. We also examined whether the study is adequately powered to detect at least a two-fold increase in the loading dose as compared to the recommended dose.

We reviewed and evaluated the following materials:

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[8] Vimpat (lacosamide) approval letter. October 28, 2008. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022253lbl.pdf (accessed March 7, 2023)

[9] Vimpat (lacosamide) label May 19, 2022 https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022254Orig1s044,022253Orig1s054,022255Orig1s036lbl.pdf (accessed March 7, 2023)

[10] Vimpat (lacosamide) supplement approval, October 14, 2021 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/022253Orig1s049,022254Orig1s039,022255Orig1s031ltr.pdf (accessed March 7, 2023)

[11] Vimpat (lacosamide) supplement approval, November 16, 2020 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/022253Orig1s046,%20s048;%20022254Orig1s036,%20s038;%20022255Orig1s027,%20s030ltr.pdf (accessed March 7, 2023)

[12] https://www.fda.gov/media/120060/download (accessed March 7, 2023)

[13] Hernán, Miguel A., and James M. Robins. "Using big data to emulate a target trial when a randomized trial is not available." American journal of epidemiology 183.8 (2016): 758-764

1. Study report entitled *Evaluating the Occurrence of Adverse Events Among Pediatric Patients Exposed to Intravenous Lacosamide (Vimpat®) Using Real World Data. Report EP0147. October 23, 2020.* Submitted in \\CDSESUB1\evsprod\NDA022253\0257 Three supplemental materials for propensity score and sensitivity analysis were accompanied.

2. Study datasets and analysis programs that generated results in the study report. Datasets can be found in \\CDSESUB1\evsprod\NDA022253\0279

   Of note, neonate (patients younger than 1 month) data and the corresponding analysis code that generate the final report tables and figures were not submitted to the NDAs. The sponsor clarified that (1) FDA has waived the pediatric studies requirement for ages 0 to 1 month because necessary studies are impossible or highly impracticable (reference: 29 August 2014 Action Letter; Reference ID: 3619412), and (2) the PEDSnet governance body considers submitting patient-level data might be at a high-risk of patient identification due to the small number of patients in this cohort.

3. Proposed labeling submitted in \\CDSESUB1\evsprod\NDA022253\0280\m1\us\114-labeling\draft\labeling

4. FDA's information request (IR) sent to the sponsor on October 28, 2022 upon the study report review, and the sponsor's response submitted in
   \\CDSESUB1\EVSPROD\nda022253\0293\m1\us\111-information-amendment\stn-2023-00402-response-14dec2022-22253-s050-ir.pdf
   \\CDSESUB1\EVSPROD\nda022253\0293\m1\us\111-information-amendment\stn-2023-00402-response-14dec2022-ir-analyses.pdf

5. FDA's IR on December 14, 2022 and the sponsor's response available in:
   \\CDSESUB1\EVSPROD\nda022253\0288\m1\us\111-information-amendment\clin-information-ir-statistics.pdf

4 REVIEW RESULTS

4.1 STUDY OVERVIEW

The RWE study EP1047 was a retrospective cohort study that used electronic health records (EHR) data from the PEDSnet data network.

4.2 STUDY OBJECTIVES

The **primary objective** was to estimate the incidence of study outcomes in pediatric patients after intravenous (IV) treatment with higher than the recommended LCM doses (i.e., the treatment; henceforth, the loading dose) compared to pediatric patients treated with recommended initial/maintenance LCM dose (i.e., the reference or active comparator; henceforth, the recommended dose). The protocol lists 11 primary outcomes which consists of

the following eight Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs):

- 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,

as well as the following three Standardized MedDRA Queries (SMQs):

- drug reaction with eosinophilia and systemic symptoms syndrome (DRESS)
- severe cutaneous adverse reactions
- hypersensitivity

The **secondary objectives** were:
1. To estimate the incidence of the selected medical events among the SOCs and SMQs listed in Table 1 (i.e., secondary outcomes) in pediatric patients in the loading dose group compared to those in the recommended dose group.
2. To estimate the effect of increasing IV loading dose on the incidence of the 11 primary outcomes, compared to that of the recommended dose.

Reviewer Comment: *The study reports do not include results for the secondary objective 2. Given this objective was an attempt to explore a dose-response relationship rather than evaluating safety signal related to the increasing loading dose, we defer the evaluation on the necessity of the information and its impact on the interpretation of the study findings to the clinical team.*

Table 1. Medical events of interest for the secondary objective 1

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

4.3 **DATA SOURCE**

The RWE study EP0147 used the PEDSnet database (version 3.7) that includes individuals with at least one encounter with a PEDSnet institution (b) (4). 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 (see Section 9.2 of the study report).

The PEDSnet database contains data stored in *the Observational Medical Outcomes Partnership/Observational Health Data Sciences and Informatics* (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-datamodel.

Reviewer Comment: *FDA's guidance on Data Standards for Drug and Biological Product Submissions Containing Real-World Data Guidance for Industry[14] states that the sponsor should submit study data, including those derived from RWD sources, in a way that it conforms to data standards supported by FDA such as Clinical Data Interchange Standards Consortium's (CDISC's) Study Data Tabulation Model (SDTM). The guidance also states that study data derived from RWD can be transformed to SDTM datasets and submitted to FDA in an applicable drug submission, with adequate documentation of the conformance methods used and their rationale. Examples of mapping health care data to CDISE SDTM is provided in Appendix of the guidance.*

Currently, OMOP/OHDSI is not part of FDA supported data format and thus the submitted PEDSnet data does not conform to FDA's data standards. However, given the evolving nature and the availability of regulatory standards for RWD/RWE submissions, FDA neglected the existence of this guidance at the time of the sponsor's data submission and did not advise the sponsor to conform to the guidance. Of note, the study report (dated October 23, 2020) was submitted to the agency, without submission of the PEDSnet data, before the guidance was available. FDA advised to submit accompanying RWD and the sponsor submitted the data on 6/30/2022, as legacy data sets.

4.4 STUDY DESIGN

We utilized the target trial framework to describe study design in this Section, which could aid identification of pitfalls of causal inference based on an observational study (if any) as well as potential sources of bias coming from the use of RWD. The target trial framework dictates the following trial protocol components should be properly stated and emulated in the observational study: eligibility criteria, treatment strategies, treatment assignment, start and end of follow-up, outcomes, causal contrasts, and the statistical analysis plan. We made some modifications on these components to better reflect study-specific characteristics and regulatory practice; for example, start and end of follow-up was modified to index date and follow-up in this section. In addition, we describe other variables (i.e., variables other than treatment or outcome) and power analysis in part of design components.

4.4.1 Eligibility and Study Cohorts

The RWE study EP0147 considered two cohorts - **cohort 1:** patients aged ≥1month to <17years; **cohort 2:** patients aged <30 days. These two cohorts are mutually exclusive as patients' age were determined based on their earliest lifetime IV LCM exposure, regardless of subsequent IV LCM treatment episodes at a later date.

Inclusion/exclusion criteria were:

- All patients in the PEDSnet database

[14] https://www.fda.gov/media/153341/download (accessed April 17, 2023)

- 1 or more IV LCM administration
- No exposure to either oral or IV LCM 3 months before the index date (where the index date was the date/time of initiation of a new IV LCM treatment episode corresponding to a recommended initial dosage or a higher initial dosage; see Section 4.4.4), as determined in the PEDSnet database
- Aged ≥1month to <17 years at the index date (for cohort 1) or age< 30 days (for cohort 2) at the index date
- Excluded if oral or IV LCM was administered 3 months before the index date (for cohort 1) or between birth to the index date (for cohort 2), as identified by chart reviewers

The study conducted chart reviews of unstructured data to validate eligibility criteria.

4.4.2 Treatment of Interest and Active Comparator

Primary treatment of interest (i.e., primary exposure) was higher IV LCM doses than recommended (i.e., the loading dose). Active comparator was the recommended initial/maintenance LCM dose (i.e., the recommended dose).

The recommended dose of IV LCM was defined as follows:

Table 2. Recommended dose of IV LCM by weight and age*

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
**Source: Study report Table 1, page 23*

The loading dose, which is the same as in the adult population, was defined as follows:

Table 3. Loading dose of IV LCM by weight and age*

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
**Source: Study report Table 2, page 23*

Additional exposure variables of interest included details of LCM administration such as 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 these primary and additional exposure variables was extracted from PEDSnet database and further verified with patient charts (see Section 5.1. of the study report).

4.4.3 Treatment Assignment

Treatment assignment was non-random and is likely based on physicians' discretion. See Table 9 as well as Tables 23 and 24 in Appendix for differences in patient characteristics between the loading dose and the recommended dose groups.

4.4.4 Index Date and Follow-Up

The index date for the loading dose group was the date/time of initiation of a new IV LCM treatment episode with an initial dose higher than the recommended IV LCM. The index date for the recommended dose group was the date/time of initiation of a new IV LCM treatment episode/receipt corresponding to a recommended initial dosage or a slow up titration. The follow-up began from the index date which is the same as the cohort entry date. The follow-up ended 38 days from the index date (i.e., index date plus following 37 days) if none of below censoring events happened within the 38 days period:

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

4.4.5 Outcomes

The primary outcomes were the first occurrence of the selected adverse events (AEs) which include eight SOCs and three SMQs listed in Section 4.2. For example, if a patient experienced rash and then later pruritus, only the incidence event of rash would contribute to the skin and subcutaneous disorders SOC. The outcomes were captured from the patient chart recorded in medical charts. See Section 5.1 of this review regarding reliability of the outcome ascertainment and validation. The secondary outcomes include the first occurrence of the selected medical events listed in Table 1, which are more specific than the primary outcomes.

Reviewer Comment: *In MedDRA data hierarchy, SOC is the highest level of classification representing the most general categories of concepts and terms. While they are commonly used as one component of typical safety assessment in drug development, they are accompanied by the assessment of more specific adverse events (e.g. MedDRA preferred terms) which are primarily used to identify any potential safety signals. Given the lack of specificity at the SOC level, it would be expected that primary outcomes would be reported that are unrelated to treatment exposure. Consequently, analyses based on SOCs might be subject to high level of noise which may result in inference towards the null. In the current setting of assessing overall safety of the loading dose relative to the recommended dose, sources of bias towards the null would be highly concerning.*

Sample size considerations for more specific definitions of adverse outcomes are discussed in Section 5.3.2.

4.4.6 Other Variables

Variables other than exposures and outcomes 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, various information regarding medication patterns (e.g., counts of IV LCM administrations, the use of other anti-epileptic drugs [AEDs], etc.), and calendar year of the index date. The study report states that details on chronic condition body systems can be found in the published article.[15]

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

4.4.7 Power Analysis

In the initial review of the study protocol, DB VII found that the sponsor had a plan to recruit 400 pediatric patients without considering a formal sample size estimation or power analysis (Statistical Review and Evaluation, dated August 21, 2019). FDA requested a formal sample size estimation with justifications for assumptions to be made. In the response letter (dated 03/05/2020), the sponsor provided power analysis results based on the following assumptions:

Assumption 1. Available sample size: A screening of the database allowed for the identification of 681 patients with at least one injection of LCM at higher than recommended dose. Therefore, power calculations assumed the following treatment group sizes:

Table 4. Sample size considered in the Sponsor's power calculation*

Population	Recommended dosing	High dosing	Total
Without neonates	474	207	681
With neonates	489	220	709

**Source: The sponsor's response (dated March 5, 2020) to FDA's information request, page 2.*

Assumption 2. Rates of AEs at population level would be 0.5%, 1% and 2.5%, based on prior trial data for LCM. The sponsor did not provide a reference for the prior data nor to which outcome the background rate would be suspected to be at the stated rates.

Additional assumptions:
3. Both groups of LCM treated patients are identical (as if randomized) except for the dosing (recommended vs high).

[15] Simon, Tamara D., et al. "Pediatric medical complexity algorithm: a new method to stratify children by medical complexity." Pediatrics 133.6 (2014): e1647-e1654

4. The study is only interested in changes in one direction (one-tailed; e.g. higher dose will have a higher rate of adverse events).
5. The number of AEs is likely to be 5 or less (based on rates of AEs and our total population sizes), so Fisher's exact test would be the most appropriate test to use.
6. The study only powers for differences across the total cohort. Subgroup analyses will be a secondary analysis.

Based on these assumptions, power analysis results were as follows:
(1) Without neonates:

Table 5. The sponsor's power analysis results without neonates*

Fisher's exact test used						
Alpha of 0.05 used with all powers						
	Detectable vs baseline rate of adverse event			Odds Ratio		
Power	**2.50%**	**1.00%**	**0.50%**	**2.50%**	**1.00%**	**0.50%**
0.6	5.82%	3.51%	2.62%	2.40962615	3.60492131	5.34568307
0.65	6.10%	3.72%	2.80%	2.53137909	3.82338474	5.72598096
0.7	6.42%	3.97%	3.03%	2.67672964	4.09299822	6.21324131
0.75	6.74%	4.26%	3.29%	2.81691269	4.4006273	6.77472114
0.8	**7.12%**	**4.59%**	**3.61%**	**2.99088475**	**4.7642309**	**7.44438451**
0.85	7.60%	5.01%	4.00%	3.20605646	5.21666961	8.28605267
0.9	8.22%	5.56%	4.53%	3.49370494	5.8313486	9.44091433
0.95	9.21%	6.46%	5.40%	3.95608346	6.83877227	11.3554055

**Source: The sponsor's response (dated March 5, 2020) to FDA's information request, page 3.*

(2) With neonates:

Table 6. The sponsor's power analysis results with neonates*

Fisher's exact test used						
Alpha of 0.05 used with all powers						
	Detectable vs baseline rate of adverse event			Odds Ratio		
Power	**2.50%**	**1.00%**	**0.50%**	**2.50%**	**1.00%**	**0.50%**
0.6	5.72%	3.46%	2.56%	2.36535365	3.54540483	5.2209075
0.65	5.98%	3.65%	2.73%	2.48247738	3.75156229	5.57802441
0.7	6.27%	3.87%	2.94%	2.61087431	3.98511189	6.02042477
0.75	6.60%	4.14%	3.19%	2.75535218	4.27927341	6.55557851
0.8	**6.97%**	**4.46%**	**3.49%**	**2.92349285**	**4.62640066**	**7.19347165**
0.85	7.43%	4.86%	3.86%	3.12959712	5.05794451	7.99389732
0.9	8.03%	5.39%	4.37%	3.40467104	5.6431984	9.09064805
0.95	8.98%	6.25%	5.20%	3.84603114	6.60090113	10.9060908

**Source: The sponsor's response (dated March 5, 2020) to FDA's information request, page 3.*

There are statistical issues with the assumptions made for these power analyses which might be critical to evaluate the adequacy of the study design. See Section 5.2.2 of this review for more discussion.

***Reviewer Comment**: Power calculations were not shared with the statistical review team prior to the current submission and thus DB VII was unable to assess the adequacy of the sponsor's power analysis prior to NDA submission. Rather, Division of Neurology Products (DNP) provided the following comment [16]: "Since we would have anticipated an open-label, single-arm study to satisfy the PMRs, having a RWE study design with adequate power for hypothesis testing is not necessary. However, the two cohorts will give us a contemporaneous comparison to see how the events of interest noted in the study align with those already in the labeling (for adult formulations and for the pediatric oral formulation) and within the ongoing study of IV use in pediatric patients."*

4.4.8 Statistical Analysis

4.4.8.1 Summary Measures for population characteristics

For the study population characteristics (age, gender, race/ethnicity, payer at index date, and PEDSnet health system site), means and standard deviations, medians and interquartile range, minimum and maximum values were used to describe continuous variables. Frequencies and percentages were used to describe categorical variables. T-test was used to examine differences in means. Mann-Whitney test was used to examine differences in medians. Fisher's exact test was used for all binary/categorical variables.

4.4.8.2 Analysis of outcomes

Several incidence rates were computed. First, the overall incidence rate of any AE occurrence was calculated. Second, individual incidence rate and 95% confidence interval (CI) for each of the primary outcomes were calculated. Third, incidence rate for each subcategory of the primary outcomes (i.e., secondary outcome AEs) and associated 95% CIs were calculated. For each incidence rate calculation, the numerator was the total number of (unique) 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 from the index date to either the date of the event (if the event happened) or to the date of last follow-up (if the event did not happen).

Regression Analyses

Poisson regressions using log(follow-up days) as an offset were used to calculate crude (i.e., unadjusted) incidence rate ratios (IRRs) and corresponding 95% CIs. Since the sample size was small for patients aged <30 days, IRRs were not computed for this age group.

In the adjusted analysis, inverse probability of treatment weighting (IPTW) was implemented to the Poisson regression to account for observed confounding. Propensity score of receiving a

[16] Review memo by Division of Pediatric and Maternal Health (DPMH): https://darrts fda.gov/darrts/ViewDocument?documentId=090140af8052cfd9&showAsPdf=true and corresponding meeting minutes DPMH reference in their memo: https://darrts fda.gov/darrts/ViewDocument?documentId=090140af805297c1

loading dose, as compared to a recommended dose, was estimated via logistic regression using the following covariates (henceforth referred to as *confounders*):
• 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.

Reviewer Comment: *Although not listed in the study report, we found that a binary covariate representing patients being in ICU at the time of initial dose of IV LCM was included in the propensity score model. This covariate seems to represent patients' underlying health condition which might impact on the decision on IV LCM dosing as well as patient outcomes after the LCM administration, we consider such a protocol deviation acceptable. In addition, this factor was imbalanced between the two dose groups at baseline at p-value 0.10 level (see Table 24).*

4.4.8.3 Missing values

All questions in the study used Research Electronic Data Capture system (REDCap) and were designed as required fields. No blank values were allowed on any electronic case report forms (eCRFs) marked as 'Complete'.

4.4.8.4 Sensitivity analyses

Several sensitivity analyses were conducted to assess the impact of parameters selected for defining the eligibility criteria, exposure, outcomes, and the study period:

- 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 happened outside the 7 days window were excluded.
- Excluded patients with pre-existing medical events determined by the PMCA chronic conditions, except PMCA neurologic conditions.
- Excluded patients who had history of any primary outcome diagnosis.

4.4.8.5 Statistical Software

Statistical analysis and production of tables, figures, patient data listings, and statistical output used R software version 3.6.3. Additional R packages used include:

- 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

4.4.9 Amendment to Statistical Analysis Plan

Section 9.15.5 of the study report states that the following amendments were made to data presented and analyses planned in the protocol:

1) 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.
2) 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. The study report says that 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.
3) 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 complete 37 days after the index date with no event (administrative censoring). 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.
4) Seizure history details: Information about the number of seizures or lectroencephalogram results were not part of the PEDSnet structured data and were removed from chart review data collection or use in propensity scoring.
5) 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.
6) Couple planned sensitivity analyses were not conducted and the report provides the following descriptions: "*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."

These changes were reflected in the final study report.

Reviewer Comment: *These amendments were not submitted prior to the study report submission and as such were not reviewed for their adequacy. From a statistical perspective, the sponsor's rationale for the amendment 3) is reasonable. We acknowledge the changes to 4) and 5) given the data limitation. However, the amendment 4) would raise data relevance and unmeasured confounding issues. See Section 5.1.1 for more discussion on the data relevance. The other amendments require clinical judgement to determine whether they are acceptable.*

4.5 STUDY RESULTS

In the PEDSnet database, there were (b) (4) pediatric patients among which 1,504 received at least one administration of IV LCM. See below Tables 7 and 15 for a stepwise selection process for creating two study cohorts - (1) Cohort 1 consisting of patients ≥1 month to <17 years old, and (2) cohort 2 consisting of patients <30 days (i.e., neonates). Steps 1 and 2 in Table 7 describe processes to get at all eligible patients without age restriction. Step 3 depicts application of the age restriction separately to each cohort. Steps 4 and 5 describe application of the eligible criteria.

This review separately presents results for cohort 1 (patients ≥1 month to <17 years old) and cohort 2 (patients <30 days; neonates) in Section 4.5.1 and 4.5.2, respectively.

4.5.1 Cohort 1: Patients ≥1 month to <17 years old

4.5.1.1 Sample Size, demographics and other baseline characteristics

There were 686 patients in this cohort that were available for final analysis, as shown in Table 7:

Table 7. Cohort 1: Cohort formation steps and number of patients remaining/excluded at each step*

Step	Cohort 1 Selection criterion	Number of patients remaining	Number of patients excluded
1	Total number of patients in PEDSnet database	(b) (4)	0

2	1 or more IV LCM administration	1,504	(b) (4)
3	IV LCM administration at ≥1 month and <17 years of age	1,248	256
4	No exposure to either oral or IV LCM before index date (determined by PEDSnet database analysis)	769	479
5	Patients remaining after chart review identified patients that actually did not meet all inclusion/exclusion criteria	686	83

**Source: Study report Table 3, page 32*

Of 686 patients, 215 (31.3%) were administered the loading dose as initial doses and 471 (68.7%) were administered the recommended dose. These doses were administered according to the age and weight criteria shown in Section 4.4.2 of this review. Among patients in the recommended dose group, the majority were those who weighed less than 30kg and were aged ≥6 months (70.3%; Table 8). In the loading dose group, there was no outstanding weight-age category and proportions of patients across weight-age categories distributed similarly ranging from 20.9% (for those whose weight ≥50kg) to 27.9% (weight ≥30 to <50kg).

Table 8. Number of patients in each group stratified by weight-age category*

	Recommended dose group, n (%) (N=471)	Loading dose group, 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)

**Source: Study report Table 7, page 35*

Table 9 presents the following demographic/baseline characteristics between the two dose groups: age, duration of observation before index visit, gender, race/ethnicity, payer, PEDSnet health system. They are all part of pre-specified confounders except duration of observation before index visit. There are other confounders that are presented in Table 23 (pre-existing health conditions) and Table 24 (counts of unique AEDs before the index date). In terms of p-value at 0.05 level, the two groups significantly differed by age distribution, duration of observation before index visit, race/ethnicity, payer, and PEDSnet health system.

Information on additional baseline characteristics (i.e., other than pre-specified confounders) are also presented in Tables 23 to 24 in Appendix. The information includes baseline clinical characteristics and medication patterns.

Reviewer Comment: *The study report does not provide standardized mean difference (SMD) but reports p-value as a way to indicate covariate (im)balance. This is inconsistent with descriptions in Section 9.15.2.6 (Evaluation of propensity score balance) of the study report where it says that this study planned to use SMD of 0.35 as a cut-point to determine imbalance.*

The study report states that "[A]lthough there is no commonly accepted threshold for a meaningful difference between cohorts, a cut-point of 0.35 was used in this study." However, this is not true and conventional choices of a cut-point - either 0.1 or 0.2 - are well-supported by existing literature. [17,18]

There were inconsistencies between p-values and SMDs for indicating covariate imbalance. In particular, there were some cases where p-values were greater than 0.05 (i.e., indicating balance) but SMD were greater than 0.2 (i.e., indicating imbalance) such as race (p=0.139 vs. SMD=0.223), prior_obs_cat (p=0.112 vs. SMD 0.224) in the original, unweighted cohort (see the sponsor's response to FDA's December 14, 2022 IR). Of note, it is unclear what "prior_obs_cat" variable represents. If we consider SMD=0.35 as a cut point to determine imbalance as suggested by the sponsor, p-values and SMDs are all consistent. However, again, SMD=0.35 is a highly subjective choice with no rationale/justification provided and we suspect that the choice might have been based upon convenience rather than science.

Although the study report does not mention it, SMD information can be found in a supplementary material.

Table 9. Demographic characteristics between the recommended and the loading dose groups*

Characteristic	Recommended dose cohort, n (%) (N=471)	Loading dose cohort, n (%) (N=215)	p-value
Age at index date, years, mean (SD)	6.90 (4.84)	7.63 (6.08)	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)	1 (0.5)	
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)	

[17] Normand, Sharon-Lise T., et al. "Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores." Journal of clinical epidemiology 54.4 (2001): 387-398.
[18] Austin, Peter C. "Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies." Pharmaceutical statistics 10.2 (2011): 150-161.

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)	6 (2.8)	
Hispanic/Latino	74 (15.7)	24 (11.2)	
American Indian or Alaska Native	0 (0.0)	3 (1.3)	
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)	8 (3.7)	
D	56 (11.9)	30 (14.0)	
E	64 (13.6)	15 (7.0)	
F	40 (8.5)	20 (9.3)	
G	5 (1.1)	7 (3.3)	
H	1 (0.2)	2 (0.9)	

SD=Standard deviation
**Source: Study report Table 9, page 37*

4.5.1.2 Duration of follow-up and Censoring

Duration of follow-up was similar between the two dose groups (Table 10). In general, proportion of patients who (1) died was higher, (2) discharged was lower, and (3) transferred was higher in the loading dose group. The results indicate that more patients in the loading dose group might perform no better or even worse than those in the recommended group.

Reviewer Comment: *Of note, these results are inconsistent with primary analyses results in that healthier patients are more likely to be administered the loading dose group and they generally show lower rates of the primary AE outcomes compared to those in the recommended dose group. See Section 5.3.3 for more discussion.*

Table 10. Duration of follow-up and reason for censoring*

Characteristic	Recommended dose cohort (N=471)	Loading dose cohort (N=215)
Duration of follow-up period (days)		
Mean (SD)	13 (13)	14 (14)
Median (IQR)	8 (2, 23)	7 (2, 27)
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)
Transferred to another hospital or a post-acute care setting	9 (1.9)	5 (2.3)
37 days transpired in hospital	65 (13.8)	37 (17.2)

IQR=Interquartile range; SD=Standard deviation

**Source: Study report Table 15, page 54*

4.5.1.3 Who gets the loading dose vs. the recommended dose? (Confounding)

According to Table 9 and Tables 23 to 24, the decision of the loading dose vs. the recommended dose as initial dose were significantly different by patients' age, race, duration of observation before index visit, payer (insurance type), PEDSnet health system (Table 9), weight, pre-existing health conditions (Table 23) including number of unique AEDs given any time before the index date (Table 24). Index date information was not provided in the study report due to PEDSnet data policy issue. See Section 5.3.4 for more details.

Reviewer Comment: *Although there were some differences between the two groups, it was unclear who gets the loading dose vs. the recommended dose based on the aforementioned, protocol-specified confounders. However, it became evident when we look at the other clinical factors that are not part of pre-specified confounders. See below.*

Uncontrolled confounding (i.e., not-prespecified in the protocol): From Table 23, the following pre-existing conditions (denoted as "top 50 conditions prior to the index date" in the table) are significantly different between the two groups – *seizure, epilepsy, constipation, developmental delay, fever, delay in physiological development, postoperative state, vomiting, acute upper respiratory infection, disorder of brain, feeding problem, gastroesophageal reflux disease, viral disease, dysphagia, seizure disorder, cough, feeding difficulties and mismanagement, incoordination, dehydration, disorder of psychological development, delayed milestone, past history of procedure, gastrostomy, gastrostomy present, history of gastrostomy, pediatric failure to thrive.* The loading dose group had significantly lower proportion of patients for all of these conditions. From the sponsor's response to FDA's IR, we also observed that prior outpatient record was significantly less frequent in the loading dose group.

Reviewer Comment: *All of these confirm that the loading dose might have been considered and administered to healthier patients. Indication for IV LCM administration was significantly different between the loading and the recommended dose groups as well, although no obvious pattern was observed from this factor. Again, these factors were not part of protocol-specified confounders. Considering clinical nature of these factors, they are highly likely to be confounders and thus the primary IPTW analysis which doesn't account for these factors are highly likely subject to residual confounding.*

4.5.1.4 Outcome analysis results

Analysis of primary outcomes

Crude incidence rates of the primary AEs and other relevant information (such as total number of events, unique patients with events, etc.) for the two groups are presented in Table 11. *Total number of events* in the table includes multiple events occurred from a single patient so it is always equal to or larger than *number of unique patients with events* (i.e., number of the first event). *Patient days of observation for incidence* in the table represents the total number of days from the index date until event occurrence or censoring. Incidence rate was calculated by taking *unique patients with events* divided by *patient-days of observation for incidence*.

Table 12 presents crude (denoted as "*unadjusted*") and IPTW adjusted (denoted as "*adjusted*") IRRs, where the recommended dose group was used as the reference group (i.e., IRR<1 meaning that the loading dose has lower AE rate). As indicated by the differences in clinical characteristics between the two dose groups, all incidence rates of the primary AEs were lower in the loading dose group. Based on the IRRs, no noticeable differences were observed with relatively wide confidence intervals for each of the 11 specified primary outcomes. However, the magnitude of effect estimates generally decreases (i.e., moved towards the null value) after confounding control.

Table 11. Crude incidence rates of AEs between the two dose groups*

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)
Injury, poisoning and procedural complications		
Total number of events	15	7
Unique patients with events	14	6
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	3	1
Unique patients with events	3	1
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	3	None
Unique patients with events	3	
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.

**Source: Study report Table 19, page 63*

Table 12. Unadjusted and IPTW adjusted rate ratios for AEs by the two dose groups*,**

	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.

**Source: Study report Table 25, page 80*

*** No analyses accounted for multiplicity. Here, "p-value unadjusted" represent p-value for unadjusted incidence rate ratio and "p-value adjusted" represents p-value for adjusted incidence rate ratio.*

Reviewer Comment: *No inferential analyses in this study adjusted for multiplicity. In drug safety studies, the greater concern is with controlling for Type II errors (concluding a product is safe when it might have an adverse effect, or false negatives).* [19] *Various guidelines support this and even state that adjusting for multiplicity could be counterproductive for safety studies.* [20] *Therefore, it is acceptable to not adjust for multiplicity, and instead use a level of P<0.05 to explore the possibility of a real adverse effect.* [18, 21]

Additional Analysis requested by FDA

Due to the residual confounding issue described in Section 4.5.1.3, FDA requested an additional, sensitivity IPTW analysis adjusting for all factors in Tables 9, 23, and 25. Table 13 presents the protocol-specified primary IPTW and the sensitivity IPTW analysis results.

Table 13. Comparison between the protocol-specified primary IPTW analysis results and an FDA requested sensitivity IPTW analysis results*

AE	Primary IPTW IRR (95% CI)	Sensitivity IPTW IRR (95% CI)	Note
Cardiac disorders	0.63 (0.35, 1.14)	0.79 (0.41, 1.52)	Towards the null
Skin and subcutaneous tissue disorders	1.15 (0.62, 2.13)	1.36 (0.65, 2.82)	Signal increased

[19] Management of Safety Information from Clinical Trials, a Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group, 2005.

[20] Points to Consider on Multiplicity Issues in Clinical Trials by the Committee for Proprietary Medicinal Products, 2002

[21] Note for Guidance on Statistical Principles for Clinical Trials- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Topic E 9 Statistical Principles for Clinical Trials by the Committee for Proprietary Medicinal Products, 1998.

Nervous system disorders	0.73 (0.40, 1.32)	0.64 (0.34, 1.21)	Away from the null
Metabolism and nutrition disorders	0.96 (0.50, 1.83)	0.61 (0.32, 1.19)	Away from the null
Psychiatric disorders	0.91 (0.37, 2.25)	0.74 (0.34, 1.64)	Away from the null
Injury, poisoning and procedural complications	0.63 (0.20, 1.97)	0.63 (0.19, 2.07)	Away from the null
General disorders and administration site conditions	0.73 (0.30, 1.80)	0.65 (0.32, 1.30)	Away from the null
Investigations of ECG indicating long PR	NA	NA	
DRESS	0.73 (0.07, 7.10)	3.28 (0.34, 31.44)	Direction changed
Severe cutaneous adverse reactions	NA	NA	
Hypersensitivity	NA	NA	

**Source: Study report Table 25, page 80, and the sponsor's response to FDA's IR (December 14, 2022) Table 24, page 43; results combined and reproduced by reviewer.*

Although the substance of IPTW analysis results remained unchanged (i.e., no difference in primary AEs between the two dose groups), the sensitivity IPTW analysis results do indicate some residual confounding in the pre-specified, primary IPTW analysis. For cardiac disorders, IRR went up more towards the null value of 1. For DRESS, the direction of the effect estimate even changed from 0.73 to 3.28.

This sensitivity IPTW analysis was still subject to residual confounding. The following factors were still imbalanced at SMD=0.2 level after the weighting:

- age, site, weight,
- indication for LCM
- constipation, fever, delay in physiological development, postoperative state, vomiting, feeding problem, gastroesophageal reflux disease, viral disease, feeding difficulties and mismanagement, incoordination, disorder of psychological development, and gastrostomy present.

Analysis of secondary outcomes

Counts of other AEs are presented in Table 17, page 55 of the study report. Trends are generally the same that the loading dose group mostly had lower incidence rates.

Crude incidence rates by specific AE diagnoses such as AV block, AV block complete, AV block 1st degree, etc. are presented in Table 21, page 67 of the study report. AE diagnoses with counts≥10 in either of the group include the following: Bradycardia (29 in the recommended vs. 5 in the loading), Tachyarrhythmia (15 vs. 4), cardiac arrest (12 vs. 3), rash (24 vs. 18), and somnolence (22 vs. 6). Unadjusted and adjusted IRRs for the specific AE diagnoses are presented in Table 14 below. Trends are generally the same as primary outcome analyses (the

loading dose group has lower incidence rates whenever information is available, except for rash where IRR from IPTW analysis= 2.11 with 95% CI=(1.02, 4.38)).

Information on crude incidence rates of AEs that physicians attributed to LCM is available in the study report (Table 23, page 76).

Table 14. Unadjusted and adjusted IRRs of specific AE diagnoses between the two dose groups*,**

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
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.

**Source: Study report Table 26, page 81.*

***** No analyses accounted for multiplicity. Here, "p-value unadjusted" represent p-value for unadjusted incidence rate ratio and "p-value adjusted" represents p-value for adjusted incidence rate ratio.*

Mortality

There were 47 deaths during the follow-up among which 30 (6.4% out of n=471) occurred in the recommended dose group and 17 (7.9% out of n=215) occurred in the loading dose group (see Table 10). Crude mortality rate per 1000 person-days in the recommended and loading dose

groups was 4.77 (95% CI = 3.22, 6.80) and 5.67 (95% CI = 3.30, 9.06), respectively. After adjusting for pre-specified confounders via IPTW, mortality rates remained higher in the loading dose relative to the recommended dose (adjusted IRR: 1.18; 95% CI = 0.57, 2.42).

4.5.1.5 Sensitivity analyses for cohort 1

1. 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 group and 62.58 (46.73, 82.06) in the loading dose group.

Crude incidence rates of AEs in the loading dose group generally increased in the sensitivity analysis (Table 15). Although incidence rates of AEs in the loading dose group remained lower than or similar to those in the recommended dose group, the rates became higher for skin and subcutaneous issue disorders and metabolism and nutrition disorders in the loading dose group, which is different from the primary, crude analysis results. In IPTW analysis (comparing Table 25 [page 80] with Table 37 [page 140] of the study report), direction of IRR changed from less than 1 to greater than 1 for metabolism and nutrition disorders (0.96 to 1.10) and psychiatric disorders (0.91 to 1.05). The direction of IRR for skin and subcutaneous issue disorders remained unchanged but the magnitude changed and moved further away from the null (1.15 to 1.47). None of IRRs were significant.

Table 155. Changes in crude incidence rates (per 1000 patient-days) and 95% CIs from the primary to this sensitivity analysis*

	Primary Analysis			Sensitivity Analysis	
	Recommended Dose IR (95% CI)	Loading Dose IR (95% CI)		Recommended Dose IR (95% CI)	Loading Dose IR (95% CI)
Overall	64.44 (55.88, 73.95)	50.00 (39.82, 61.98)		62.94 (51.97, 75.56)	62.58 (46.73, 82.06)
Cardiac disorders	17.23 (13.74, 21.33)	9.52 (6.10, 14.16)		17.56 (13.03, 23.15)	8.04 (4.15, 14.04)
Skin and subcutaneous issue disorders	8.91 (6.59, 11.78)	8.52 (5.40, 12.79)		8.86 (5.89, 12.80)	12.25 (7.26, 19.37)
Nervous system disorders	13.21 (10.30, 16.69)	8.78 (5.57, 13.18)		15.65 (11.50, 20.81)	9.27 (5.07, 15.56)
Metabolism and nutrition disorders	11.74 (9.02, 15.02)	8.90 (5.64, 13.36)		9.68 (6.58, 13.74)	10.71 (5.99, 17.66)
Psychiatric disorders	6.38 (4.49, 8.79)	5.75 (3.28, 9.33)		5.91 (3.61, 9.13)	5.61 (2.57, 10.65)
Injury, poisoning and procedural complications	2.31 (1.27, 3.88)	2.04 (0.75, 4.43)		2.88 (1.38, 5.30)	1.78 (0.37, 5.20)

General disorders and administration site conditions	11.48 (8.80, 14.72)	8.29 (5.19, 12.55)		11.05 (7.70, 15.37)	8.71 (4.64, 14.90)
DRESS	0.48 (0.10, 1.40)	0.33 (0.01, 1.86)		0.83 (0.17, 2.42)	0.58 (0.01, 3.25)
Hypersensitivity	0.48 (0.10, 1.40)	None		0.55 (0.07, 1.98)	None

**Source: Study report Table 19 (page 63) and Table 29 (page 87). Results combined and reproduced by reviewer.*

2. When the maximum follow-up time was shortened from 37 days post index date to only 7 days, crude incidence rates of AEs in the loading dose group remained lower than or similar to those in the recommended dose group (study report Table 29, page 87). In IPTW analysis, direction of IRR changed from less than 1 to greater than 1 for psychiatric disorders again (0.91 to 1.18). The magnitude of IRR for skin and subcutaneous issue disorders again moved further away from the null (1.15 to 1.28).

3. When patients with history of a prior AE diagnosis were excluded, the magnitude of IRR for skin and subcutaneous issue disorders again moved further away from the null (1.15 to 1.35).

4.5.1.6 Additional Analysis Requested by FDA

Note that the two groups were eventually at the same level of dose after the titration. Therefore, FDA thought an adequate time interval for the comparison of the AE outcomes might be from the initiation of exposure till the end of (or right after) titration. Also, given the nature of AEs, FDA found it might be helpful to look at timing of AE occurrence. Accordingly, FDA requested two additional analyses – the time interval analysis and the time to event analysis - in the December 14, 2022 IR. The sponsor responded that the time interval analysis was not possible as the end of titration date was not collected for this study. The sponsor provided time-to-event analysis results, including Kaplan-Meier plots and both unadjusted Cox and IPTW Cox regression results, in the response letter. Findings were consistent with unadjusted Poisson and IPTW Poisson regression results in that no additional noticeable signals were identified.

4.5.2 Cohort 2: Neonate Patients

4.5.2.1 Sample Size, demographics and other baseline characteristics

There were 28 patients eligible for this study. See below Table 16 for the cohort creation process.

Table 16. Cohort 2: Cohort formation steps and number of patients remaining/excluded at each step

Step	Cohort 2 Selection criterion	Number of patients remaining	Number of patients excluded
1	Total number of patients in PEDSnet database	(b) (4)	0
2	1 or more IV LCM administration	1,504	(b) (4)
3	IV LCM administration at <30 days of age	28	1,476

4	No exposure to either oral or IV LCM before index date (determined by PEDSnet database analysis)	28	0
5	Patients remaining after chart review identified patients that actually did not meet all inclusion/exclusion criteria	28	0

**Source: Study report Table 4, page 33*

Out of the 28 patients, 57.1% were administered the recommended dose and 42.9% were given loading dose as initial doses. See Table 17 for weight distribution by the dose group:

Table 17. Weight distribution by the dose group*

Weight-based sub-cohort	Recommended dose cohort, n (%) (N=16)	Loading dose cohort, n (%) (N=12)
<4kg	11 (68.8)	8 (66.7)
4 to 10kg	5 (31.2)	4 (33.3)

**Source: Study report Table 8, page 35*

See below Table 18 for demographic characteristics by the dose group:

Table 18. Cohort 2: Demographic characteristics by the dose group*

Characteristic	Recommended dose cohort, n(%) (N=16)	Loading dose cohort, n(%) (N=12)
Age at index date, days, mean (SD)	14.19 (8.78)	16.17 (10.65)
Duration of observation before index visit		
Patients with encounter before Index Visit, n (%)	5 (31.2)	3 (25.0)
Total duration, days, mean (SD)	6.60 (8.56)	7.00 (7.21)
Gender, n (%)		
Male	7 (43.8)	5 (41.7)
Female	9 (56.2)	7 (58.3)
Race/Ethnicity, n (%)		
White	11 (68.8)	8 (66.7)
Black/African-American	1 (6.2)	1 (8.3)
Asian/Native Hawaiian/Pacific Islander	0 (0.0)	0 (0.0)
Hispanic/Latino	0 (0.0)	1 (8.3)

American Indian or Alaska Native	0 (0.0)	0 (0.0)
Multiple/Other/Unknown/Refused	4 (25.0)	2 (16.7)
Payer (at index visit), n (%)		
Public	8 (50.0)	4 (33.3)
Private/Commercial	5 (31.2)	4 (33.3)
Self-Pay/Other	3 (18.8)	4 (33.4)
PEDSnet Health System, n (%)		
A	5 (31.1)	7 (58.3)
B	1 (6.3)	4 (33.3)
C	1 (6.3)	1 (8.4)
D	4 (25.0)	0 (0.0)
E	0 (0.0)	0 (0.0)
F	4 (25.0)	0 (0.0)
G	1 (6.3)	0 (0.0)
H	0 (0.0)	0 (0.0)

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.
**Source: Study report Table 10, page 38.*

See Table 12 of the study report for clinical characteristics by the dose group in this cohort and Table 14 for medication patterns. Those tables are also available in Appendix of this review.

Confounding (for the pre-specified confounding factors only): To summarize, there seems to be a slight difference in dose administration with respect to the following factors: Payer at index date, PEDSnet health system, for some of AEDs use any time before index date (e.g., 1-2 unique non-benzodiazepine AEDs), but not by age/weight at index date, sex, race/ethnicity, pre-existing health conditions by PMCA, duration of observation before index date.

Patients who had public insurance were more likely to be administered with the recommended dose and those who paid self or owned other types of insurance were more likely to be administered with the loading dose.

Other potential confounding factors: Indication for IV LCM administration, prior hospitalization/ambulatory visit in baseline period, and some of top 50 conditions prior to the index date such as feeding problem, fever of the newborn seem different between the two groups. Similar to cohort 1, neonate patients in the loading dose group had less hospitalization or ambulatory visit prior to the index date but no clear pattern was observed with respect to pre-existing conditions. Therefore, unlike the cohort 1, it is unclear whether the neonate patients in the loading dose group were healthier, similar, or worse compared to those in the recommended dose group.

4.5.2.2 Outcome analysis results

Crude incidence rates of the primary AEs between the two groups are presented in Table 19. Rates were only available for a few AEs as there were no event for most AEs. Due to the very small sample size in neonate patients, results for this cohort are provided descriptively only (i.e. IRR's from primary and sensitivity analyses are not presented).

Crude incidence rates by specific AE diagnoses such as AV block, AV block complete, AV block 1st degree, etc. are presented in Table 22 of the study report. Only four events were observed for cardiac arrest exclusively among the recommended dose group.

Table 19. Crude incidence rates of AEs by the two dose groups in cohort 2*

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	2
Unique patients with events	8	2
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	6	None
Unique patients with events	5	
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)		
Nervous system disorders		
Total number of events	2	None
Unique patients with events	2	
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	2	1
Unique patients with events	2	1
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	1	None
Unique patients with events	1	
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		
Patient-days of observation		
Incident rate per 1000 patient-days (95% CI)		

Hypersensitivity		
Total number of events	None	1
Unique patients with events		1
Patient-days of observation		250
Incident rate per 1000 patient-days (95% CI)		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.

**Source: Study report Table 20, page 65*

Mortality

Seven deaths were reported in the recommended (31.2%) and the loading (16.7%) dose groups during the follow up (Study report Table 16, page 54). Crude mortality rates per 1000 person-days in the recommended and the loading dose groups were 14.75 (95% CI: 4.81, 34.08) and 7.14 (0.87, 25.56), respectively.

5 STATISTICAL EVALUATION

Considerations for the use of RWD for generating evidence

The Framework for FDA's real-world evidence program intends to evaluate the potential use of RWE to support changes to labeling about drug product effectiveness, including adding or modifying an indication, such as a change in dose, dose regimen, or route of administration; adding a new population; or adding comparative effectiveness or safety information. The program document states that the framework will include consideration of the following:

1. Whether the RWD are fit for use
2. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
3. Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection).

Following this guidance, we considered (1) data fit-for-purpose, (2) adequacy of study design, and (3) study conduct to determine whether the RWE study EP0147 provides adequate scientific evidence to answer or to help answer the regulatory question. To evaluate the adequacy of study design, we adapted the target trial framework and examined power of the study. Finally, we incorporated interpretation of study findings to determine whether the evidence generated from the use of RWD is sufficient to support regulatory decision making, from a statistical perspective.

5.1 Data Fit-for-Purpose

Reliability: The framework for FDA's real-world evidence program states that reliability includes data accrual and data quality control. Section 9.11 (Data sources and measurement) of

the study report describes that PEDSnet data management maintains an extensive structural data quality assessment program, including data checks for missingness, data model compliance, and stability of data. Regarding missing data, the study report describes that patients are able to seek care outside of PEDSnet, which may lead to missing data. The report says 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. Even though we did not conduct study-specific examination on the data mapping, OMOP/OHDSI common data model used in this study provides mapping from data fields in EHR to MedDRA terms. The outcomes were further independently reviewed by trained professionals. In addition, the process of data transformation was documented and submitted. Therefore, it meets the requirements stated in the FDA guidance for RWE data standards. [22] Overall we considered the data reliable. See also Section 9.16.3 of the study report on additional data quality control effort.

Relevance: Section 4.4.2 of the study report states that the study conducted chart reviews of unstructured data to validate eligibility criteria and to collect data on study outcomes. Section 4.4.2 states that the information on these primary and additional exposure variables was extracted from PEDSnet database and further verified with the patient charts. Section 4.4.6 states that the information on other variables was extracted from PEDSnet database and further verified with the patient charts. Regarding misclassification, the study report states that ascertainment of outcomes was made using controlled vocabularies and further verified through chart review by trained personnel.

Although it seems that most variables representing patients' underlying medical condition, treatment assignment and uptake, outcomes and other necessary information were properly captured/ascertained and validated, we found one issue with respect to the data relevance. As stated in Section 4.4.9 of this review, some critical information regarding seizure history details such as number of seizures or lectroencephalogram results were not part of the PEDSnet structured data. As the number of seizures might represent underlying severity of the seizure for which the LCM is indicated, missing such information would raise the issue of unmeasured confounding.

5.2 Adequacy of Study Design

5.2.1 Target Trial Emulation

As described in Section 4.4, we adapt the target trial framework to evaluate whether the study design is appropriate to approximate a hypothetical randomized controlled trial, if that was possible, and to address the study question of interest. The target trial framework dictates the following trial protocol components should be properly stated: eligibility criteria, treatment strategies, treatment assignment, start and end of follow-up, outcomes, causal contrasts, and the statistical analysis plan. We made slight modifications to some of these components so that they could be more relevant to the representation of the RWE study EP0147. We also considered power of this study as an essential design component.

[22] Data Standards for Drug and Biological Product Submissions Containing Real-World Data Guidance for Industry. https://www fda.gov/media/153341/download (accessed April 13, 2023)

See Table 20 for summary of our evaluation on the adequacy of each study design attribute based on the target trial framework.

Table 20. Design evaluation using the target trial framework

Protocol components	Target trial	Emulation in this study	Issues/Notes
Eligibility criteria	Patients aged <17years who are eligible to receive IV LCM	Same as in the target trial	The entire cohort was divided into two age groups (patients ≥1 month to <17 years old; neonates)
Treatment and comparator	Treatment: Higher IV LCM doses than recommended. Active comparator: The recommended initial/maintenance LCM dose	Same as in the target trial	
Treatment assignment	Via random mechanism	IPTW to control for confounding	There may be some unmeasured confounding related to seizure history (Section 5.1.2). Some residual confounding with respect to comorbidities in the weighted population existed (Section 4.5.4).
Start and end of follow-up	Follow-up starts at time of randomization and continues until 38 days. Censoring events were: (1) death (2) discharge from the acute care hospital setting (3) transfer to another hospital or a post-acute care setting	Follow-up started at the index date (i.e., the time of IV LCM initiation). Rest is the same as in the target trial.	
Outcomes	Adverse events are captured by the physician in the CRF and coded/mapped into MedDRA	Using MedDRA mappings, eight SOC outcomes and three SMQs outcomes served as primary outcomes	Analyses based on SOCs might be subject to high level of noise resulting in bias towards the null.

Statistical analysis	Comparing incidence rates of the 11 primary outcomes on a ratio scale (i.e., IRR)	Same as in the target trial	Unmeasured and residual confounding issues were not fully accounted for in the IPTW analyses, including both primary and sensitivity analyses requested by FDA.

From Table 20, the emulation effort seems challenging due to issues with selected outcomes at SOC level as well as potential presence of unmeasured and residual confounding. No sensitivity analysis to examine the impact of the unmeasured/residual confounding was planned in design stage. In summary, the study design had some limitations and potential impact of the limitations was not quantified.

5.2.2 Power Analysis

In this study, there were 686 patients where 215 (31.3%) were administered the loading dose and 471 (68.7%) were administered the recommended dose as initial doses. These numbers are similar to the numbers considered in the assumption 1 for the sponsor's power analysis described in Section 4.4.7. However, some other assumptions may not be appropriate for this study making it unclear to determine whether this study is adequately powered to detect at least some level of unacceptable risk. For example, the sponsor considered 0.5%, 1% and 2.5% of AE rates at population level, based on prior trial data for LCM (no reference for the AE rates provided). It is unclear which rate they represent – prevalence or incidence - and whether these rates represent a specific AE or grouping of AE's (e.g. MedDRA SOC). From the observed data in the RWE study EP0147, using the primary non-specific SOC outcomes and the three SMQ outcomes, incidence rates across these outcomes varied a lot - some with rates outside the range of 0.5% to 2.5% (e.g., incidence rate for DRESS is 0.33 per 1000py (i.e., 0.03% per py) in the loading dose group; see Section 4.5.1.4). Also, the sponsor's power analyses were based on odds ratio rather than IRR which was the metric used in the study report.

Therefore, FDA re-examined the power of this study as the sponsor's power analysis seemed based on some invalid assumptions. The goal of the FDA's power analysis was to verify whether the current sample size is sufficient to detect an unacceptable level of risk in the loading dose group with 80% power, if it is present. FDA used crude incidence rates observed from the recommended group (Table 11) as the base rates, and assumed that two-fold increase from the incidence rate in the loading dose group would be an unacceptable risk. We used R version 4.1.2 and *epiR* package[23] for the sample size calculation.

Results are shown in Table 21 for the protocol-defined primary outcomes. The FDA's power analysis revealed that the current sample size is not sufficient to detect at least a two-fold increase in the risk of (1) injury, poisoning and procedural complications, (2) DRESS, and (3) hypersensitivity in the loading dose group compared to the recommended dose group.

[23] https://search r-project.org/CRAN/refmans/epiR/html/epi.sscohortt.html (accessed March17, 2023)

Table 21. Post-hoc power analysis using crude incidence rates observed in the RWE EP0147 study*

AE	Crude IR in recommended dose	Required sample size in recommended dose (currently, n=471)	Required sample size in loading dose (currently, n=215)
Cardiac disorders	17.23/1000	132	60
Skin and subcutaneous tissue disorders	8.91/1000	218	99
Nervous system disorders	13.21/1000	161	73
Metabolism and nutrition disorders	11.74/1000	174	79
Psychiatric disorders	6.38/1000	291	132
Injury, poisoning and procedural complications	2.31/1000	**660**	**351**
General disorders and administration site conditions	11.48/1000	179	81
Investigations of ECG indicating long PR	0	NA	NA
DRESS	0.48/1000	**3059**	**1627**
Severe cutaneous adverse reactions	0	NA	NA
Hypersensitivity	0.48/1000	**3059**	**1627**

**Sample size calculations were based on 80% power of an one-sided test with the objective of ruling out a two-fold increase in the background AE rates (i.e., AE rates in the recommended group as reported in the second column of the table) with 38 days of maximum follow-up.*

Of note, we raised the issue of lack of specificity in selected primary SOC outcomes. If more specific outcomes such as the ones in the secondary outcomes were considered for these calculations, required sample sizes would have been much larger as the crude IRs for the secondary outcomes in the recommended dose group were much lower (e.g., crude incidence for cardiac fibrillation and cardiac flutter was zero in both groups, rate of incident cardiac arrest was 12.86 in the recommended dose group and zero in the loading dose group; see Table 14 of this review and Table 22 of the study report). This means that the RWE study EP0147 is not sufficiently powered to detect at least a two-fold increase in the risk of more specific AE outcomes.

5.3 Study Conduct and Regulatory Standards

Data Validation and Analysis Replication

The sponsor submitted data and analysis codes which satisfied regulatory requirements from a statistical perspective. FDA validated the sponsor's analyses for primary, secondary, and some sensitivity analyses, but not all sensitivity analyses. There were two noteworthy issues identified during the validation/replication process:

(1) FDA was unable to reproduce Table 25 in the study report (Table 12 in this review) using the sponsor's analysis code. Although the substance of findings (that the loading dose group generally shows lower or same level of risks than those of the recommended dose group) remained consistent, FDA observed different effect estimates and p-values from IPTW analyses. In the responses to FDA's IR on this issue, the sponsor clarified that the data submitted to FDA has different date information than those in the original PEDSnet data due to a PEDSnet policy, which induced the different effect estimates and p-values. See the sponsor's response:

"*Per the standard PEDSnet policy, the data provided to FDA is date shifted. This is a requirement of all PEDSnet dataset releases and is for the purpose of preserving patient privacy. Dates are randomly shifted within a 6-month period, either before or after the original date. Note that the dates for each patient are shifted in such a way that preserves the original time variance between dates (for example, if there was a 5-day window between the administration of LCM and the occurrence of an AE, the 5-day window will be preserved even though the exact dates of each of those events will be shifted). The propensity score re-weights the data, so the two groups will have the same statistical distribution but is based on a logistic regression which predicts group membership from covariates. One factor that goes into logistic regression is the index year; because of the date-shifting of the index date, the exact probability returned will be shifted.*"

As this is per PEDSnet policy to protect patient privacy and the difference between the two analyses are minimal, the discrepancy between sponsor's and FDA's data and analysis results is acceptable.

(2) Section 9.15.2.7 of the study report provides inconsistent descriptions on handling extreme weights. It states that

"[T]hus, extreme weights were found <u>they were replaced with the 95th percentile of weights</u> 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 <u>trimming excess weights were dropped</u>."

The underscored descriptions indicate two different approaches – weight truncation and weight trimming. In the response to FDA's December 14, 2022 IR, the sponsor clarified that the paragraph was not written clearly and no outlier/extreme weights were observed.

FDA's validation/replication effort confirms reproducibility of the sponsor's analyses. This meets regulatory requirements from a statistical perspective.

5.4 **Interpretation of Study Findings**

As described in Section 4.5.1.3, confounding results generally indicate that healthier patients are more likely to be administered the loading dose - patients in the loading group had significantly lower pre-existing conditions, less history of ambulatory visits, etc., and consequently patients in the loading dose group generally performed better in terms of the selected AE outcomes.

However, we observed contradicting results during the follow-up (Section 4.5.1.2) – patients in the loading dose group died more and were discharged less, which all indicate that they do not perform well compared to those in the recommended group. Although it is challenging to identify and locate the exact source of the discrepancy, there could be some plausible explanations. First, as this data was lack of severity information, there could be a chance that patients in the loading dose group were actually sicker but relevant information might not have been captured in the data. Along the same lines, it could have been due to lack of granularity in the primary outcome as they were captured at SOC level. If any of these are true, it implies an issue with the data relevance.

In summary, it was challenging to reconcile the two contradicting results – if there are more healthier patients in the loading group why didn't they perform better in terms of death and discharge – and isolate the cause of the inconsistency.

6 SUMMARY AND CONCLUSION

Following *the Framework for FDA's real-world evidence program*, we considered (1) data fit-for-purpose, (2) adequacy of study design, and (3) study conduct, as well as the interpretation of study findings to determine whether the evidence generated from the RWE study EP0147 is sufficient to address the regulatory question on the proposed labeling. The summary of our evaluation is shown in Table 22.

Table 22. Summary of statistical evaluation of the RWE EP1047 study

Review criteria	Considerations	Issues
Data fit-for-purpose	Reliability	None
	Relevance	Number of seizures or lectroencephalogram results not available in PEDSnet. This could lead to unmeasured confounding issue.
Adequacy of study design	Target trial emulation	Analyses based on SOCs might be subject to high level of noise resulting in bias towards the null. Issue of unmeasured and residual confounding exists.
	Power analysis	Not adequately powered to detect a two-fold increase of risk for some primary outcomes and more specific adverse outcomes.
Whether study conduct meets regulatory requirements	Data validation	None
	Analysis replication	None
Interpretation of study findings		Patients in the loading dose group were healthier at baseline and showed better or no worse AE outcomes but were more likely to

		die or stay hospitalized during the follow-up.

Both data and design have some limitations, whereas study conduct meets regulatory requirements. Reconciling two different implications about patients in the loading dose group (patients in this group were healthier at baseline and performed better in terms of most AE outcomes, but they did not perform better or no worse in terms of death and discharge during the follow up) was challenging. From a statistical perspective, the limitations observed result in uncertainties as to whether RWE study EP0147 provides adequate scientific evidence on the safety of the proposed loading dose. While the limitations of unmeasured and residual confounding were not addressed through statistical assessment, they may be explained based on clinical judgement which we defer to the clinical review team. However, there still remains the issues of the lack of specificity in primary outcome defined by MedDRA SOC's and the lack of study power which would be most evident for looking at more specific safety outcomes. In combination, these issues have the potential to bias any observed findings, or lack of an observed finding, towards the null (i.e. determination of similar safety between the loading and recommended dose). Therefore, it is important to acknowledge that the absence of evidence of a difference in safety from the RWE study EP0147 is not evidence of absence.

With these considerations in mind, some notable safety findings from cohort 1 (patients ≥1 month to <17 years old) in RWE study EP0147 were:

- Skin and subcutaneous tissues disorders (at SOC level; primary outcome): IRR = 1.15 with 95% CI (0.62, 2.13) based on the primary IPTW analysis and IRR = 1.36 with 95% CI (0.65, 2.82) with the sensitivity IPTW analysis that adjusted for residual confounding
- Rash (at preferred term level; secondary outcome) resulted in an IRR = 2.11 with 95% CI (1.02, 4.38)
- Mortality: IRR = 1.18 with 95% CI (0.57, 2.42)

While uncertainties remain on whether these safety findings represent real increases in risk of the loading dose relative to the recommended dose, we acknowledge that tolerance for risk is in relation to the benefit. Unfortunately, the RWE study EP0147 does not provide any comparative efficacy information to support any improvements of the loading dose relative to the recommended dose precluding a benefit-risk assessment which we acknowledge was not part of the considerations in the design of the study.

Overall, the statistical perspective is that the evidence generated from the RWE study EP0147, on its own, is not sufficiently reassuring of the safety of the loading dose relative to the recommended dose.

7 APPENDIX

This appendix presents various tables related to baseline/clinical characteristics and medication patterns in cohort 1 and 2.

Table 23. Baseline clinical characteristics between the two dose groups in cohort 1*

Characteristic	Recommended dose cohort, n (%) (N=471)	Loading dose cohort, n (%) (N=215)	p-value
Weight (at index date)			
<4kg	3 (0.6)	6 (2.8)	<0.001
4 to 10kg	73 (15.5)	51 (23.7)	
10 to 20kg	144 (30.6)	36 (16.8)	
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)	0.021
Status epilepticus	134 (28.5)	72 (33.5)	
Seizures with fever	5 (1.1)	3 (1.4)	
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)	6 (2.8)	0.927
Dermatologic	12 (2.5)	6 (2.8)	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	6 (1.3)	3 (1.4)	1.000
Hematologic	27 (5.7)	10 (4.7)	0.690
Immunologic	16 (3.4)	9 (4.2)	0.770
Malignancy	18 (3.8)	10 (4.7)	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)	10 (4.7)	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	4 (0.8)	1 (0.5)	0.948
Psychiatric disorders	0 (0.0)	1 (0.5)	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)	10 (4.7)	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

Source: Study report Table 11, page 41

Table 24. Medication patterns in cohort 1*

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)	9 (4.2)	
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.

**Source: Study report Table 13, page 49*

Table 25. Baseline clinical characteristics between the two dose groups in cohort 2*

Characteristic	Recommended dose cohort, n (%) (N=16)	Loading dose cohort, n (%) (N=12)	p-value
Weight (at index Date)			
<4kg	11 (68.8)	8 (66.7)	1.000
4 to 10kg	5 (31.2)	4 (33.3)	
Indication for iv LCM administration			
Epilepsy (focal, syndrome)	2 (12.5)	0 (0.0)	
Status epilepticus	5 (31.2)	1 (8.3)	0.218
Seizures without a diagnosis	6 (37.5)	9 (75.0)	
Other	3 (18.8)	2 (16.7)	
Prior hospitalization in baseline period			
At least one hospitalization before index visit	1 (6.2)	0 (0.0)	1.000
Prior ambulatory visit in baseline period			
At least one ambulatory visit before index visit	2 (12.5)	0 (0.0)	0.492
Presence of chronic conditions by body system PMCA			
Cardiovascular	0 (0.0)	0 (0.0)	
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)	1.00
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	1 (6.2)	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)	1 (8.3)	
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)	2 (16.7)	0.175
Seizure	1 (6.2)	1 (8.3)	1.000
Fever of the newborn	2 (12.5)	0 (0.0)	0.492
Localization-related(focal)(partial)idiopathic epilepsy and epileptic syndromes with seizures of localized onset	1 (6.2)	1 (8.3)	1.000
Convulsions in the newborn	1 (6.2)	1 (8.3)	1.000
Pulmonary hypertension	0 (0.0)	1 (8.3)	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)	1 (8.3)	0.429
Pericardial effusion	1 (6.2)	0 (0.0)	1.000
Respiratory failure	0 (0.0)	1 (8.3)	0.429
Swelling, edema symptom	1 (6.2)	0 (0.0)	1.000
Baby premature 33 weeks	1 (6.2)	0 (0.0)	1.000
Ischemic stroke	0 (0.0)	1 (8.3)	0.429
Fetal or neonatal effect of maternal infection	1 (6.2)	0 (0.0)	1.000
Prolonged loss of consciousness	0 (0.0)	1 (8.3)	0.429
Metabolic disease	0 (0.0)	1 (8.3)	0.429
Fever	1 (6.2)	0 (0.0)	1.000
Physical child abuse	0 ((0.0)	1 (8.3)	0.429

Characteristic	Recommended dose cohort, n (%) (N=16)	Loading dose cohort, n (%) (N=12)	p-value
Traumatic intracranial subarachnoid hemorrhage	0 (0.0)	1 (8.3)	0.429
Failure to thrive in infant	1 (6.2)	0 (0.0)	1.000
Disorder of fetus or newborn	0 (0.0)	1 (8.3)	0.429
Edema	1 (6.2)	0 (0.0)	1.000
Meningitis	0 (0.0)	1 (8.3)	0.429
Opioid dependence	0 (0.0)	1 (8.3)	0.429
Meconium aspiration syndrome	0 (0.0)	1 (8.3)	0.429
Hypoxemia	1 (6.2)	0 (0.0)	1.000
Family history of clinical finding	1 (6.2)	0 (0.0)	1.000
Opioid withdrawal	0 (0.0)	1 (8.3)	0.429
Neonatal tachycardia	1 (6.2)	0 (0.0)	1.000
Neonatal respiratory failure	0 (0.0)	1 (8.3)	0.429
Cortical hemorrhage	1 (6.2)	0 (0.0)	1.000
Hemorrhagic cerebral infarction	0 (0.0)	1 (8.3)	0.429
Bacterial meningitis	0 (0.0)	1 (8.3)	0.429
Disorder of nervous system	1 (6.2)	0 (0.0)	1.000
Cerebral hemisphere hemorrhage	1 (6.2)	0 (0.0)	1.000
Bacterial meningoencephalitis	0 (0.0)	1 (8.3)	0.429
Intraventricular (nontraumatic) hemorrhage, grade 3, of fetus and newborn	1 (6.2)	0 (0.0)	1.000
Obstructive hydrocephalus	0 (0.0)	1 (8.3)	0.429
Feeding problems in newborn	0 (0.0)	1 (8.3)	0.429
Disturbance of temperature regulation of newborn	1 (6.2)	0 (0.0)	1.000
Escherichia coli meningitis	0 (0.0)	1 (8.3)	0.429
Posthemorrhagic hydrocephalus	0 (0.0)	1 (8.3)	0.429
Vomiting	1 (6.2)	0 (0.0)	1.000
Cerebral hemorrhage	1 (6.2)	0 (0.0)	1.000
Bacteremia caused by Gram-positive bacteria	0 (0.0)	1 (8.3)	0.429
Dialysis finding	0 (0.0)	1 (8.3)	0.429
Feeding poor	0 (0.0)	1 (8.3)	0.429
Abrasion of head	0 (0.0)	1 (8.3)	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	0 (0.0)	1 (8.3)	0.429
Neonatal aspiration of milk and regurgitated food	0 (0.0)	1 (8.3)	0.429
Term birth of newborn	0 (0.0)	1 (8.3)	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

**Source: Study report Table 12, page 45*

Table 26. Medication patterns in cohort 2*

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 (%)	4 (25.0)	3 (25.0)	
2, n (%)	3 (18.8)	0 (0.0)	0.124
3, n (%)	0 (0.0)	3 (25.0)	
4+, n (%)	9 (56.2)	6 (50.0)	
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 (%)	8 (50.0)	4 (33.3)	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 (%)	2 (12.5)	3 (25.0)	
1 unique non-benzodiazepine AED, n (%)	8 (50.0)	5 (41.7)	0.775

2 unique non-benzodiazepine AEDs, n (%)	6 (37.5)	4 (33.3)	
3+ unique non-benzodiazepine AEDs, n (%)	0 (0.0)	0 (0.0)	
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 (%)	0 (0.0)	1 (8.3)	
1 unique benzodiazepine AED, n (%)	4 (25.0)	1 (8.3)	0.242
2 unique benzodiazepine AEDs, n (%)	4 (25.0)	1 (8.3)	
3+ unique benzodiazepine AEDs, n (%)	8 (50.0)	9 (75.1)	
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	0 (0.0)	0 (0.0)	
1 concomitant non-benzodiazepine AED	2 (12.5)	1 (8.3)	0.858
2 concomitant non-benzodizapine AEDs	8 (50.0)	8 (66.7)	
3+ concomitant non-benzodiazepine AEDs	6 (37.5)	3 (25.0)	
Patients on concomitant[1] benzodiazepine AEDs, n (%)			
0 concomitant benzodiazepine AED	3 (18.8)	4 (33.3)	
1 concomitant benzodiazepine AED	12 (75.0)	8 (66.7)	0.807
2 concomitant benzodiazepine AEDs	1 (6.2)	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.

**Source: Study report Table 14, page 52*

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