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Carisbamate treatment of adult and pediatric patients with Lennox-Gastaut syndrome: A phase 1 pharmacokinetic, safety, and tolerability study

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ABSTRACT

Objective: To characterize the single- and multiple-dose pharmacokinetics, safety, and tolerability of carisbamate oral suspension in adult and pediatric patients with Lennox-Gastaut syndrome (LGS).
Methods: This phase 1, open-label study (NCT03731715) enrolled patients into four age cohorts: Cohort I (C-I), ≥ 18 years; Cohort II (C-II), 12 to < 18 years; Cohort III (C-III), 6 to < 12 years; Cohort IV (C-IV), 2 to < 6 years (C-IV withdrawn due to inability to enroll patients). On Day 1, patients received a single dose of carisbamate: 200 mg (C-I), 140 mg (C-II), 60 mg (C-III), followed by twice-daily multiple-dosing Days 3–17: 100 mg (C-I), 70 mg (C-II), 30 mg (C-III). Pharmacokinetic parameters were determined using noncompartmental analysis. Safety was also assessed.
Results: Eighteen patients (C-I: n = 8; C-II: n = 3; C-III: n = 7) were included; 16 (89%) completed the study. Following single doses, carisbamate was rapidly absorbed (t_{max}, 1–2 h post-dose), with a mean $t_{1/2}$ of ~12 h in C-I and C-II and ~8 h in C-III. After single- and multiple-doses, mean C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ increased dose-proportionally. Total carisbamate exposures were comparable across cohorts after dose normalization. Mean (SD) accumulation ratios following multiple dosing were 1.66 (0.15; C-I) and 1.69 (0.06; C-II). Treatment-emergent adverse events (TEAEs) occurred in 66.7% of patients, most commonly nervous system TEAEs (22.2%). One severe TEAE (affective disorder) occurred, and one patient discontinued due to an AE (sedation). No serious TEAEs or deaths occurred.
Conclusions: : In this small phase 1 PK/safety study, carisbamate appeared to exhibit linear, dose-proportional pharmacokinetic parameters in pediatric and adult LGS patients at doses of 60–200 mg/day and was generally well tolerated during short-term treatment.

1. Introduction

Lennox-Gastaut syndrome is a severe childhood-onset epilepsy characterized by multiple drug-resistant seizure types (classically including tonic and atonic seizures), slow spike-wave complexes on electroencephalogram (EEG), and intellectual disability (Asadi-Pooya, 2018). Typically presenting between ages 2 and 8, LGS accounts for up to 4% of childhood epilepsies and is among the most challenging epilepsy syndromes to treat (Asadi-Pooya, 2018). Patients usually require lifelong therapy and often experience drug-resistant seizures despite polytherapy with antiseizure medications (ASMs). ASMs approved by the U.S. Food & Drug Administration for the treatment of seizures in LGS are clobazam, clonazepam, felbamate, lamotrigine, topiramate, rufinamide, cannabidiol, and fenfluramine (Asadi-Pooya, 2018; Auvin, 2020; Knupp et al., 2022; Vossler and Gidal, 2024). Despite the availability of multiple ASMs, effective treatment is often complicated by the heterogeneity of seizure types and the potential for significant adverse effects associated with some approved ASMs and pharmacokinetic and pharmacodynamic drug interactions (Asadi-Pooya, 2018; Verrotti et al., 2020). Thus, there remains a substantial unmet medical need for new, effective, and well-tolerated treatments for LGS.

Carisbamate (S-2-O-carbamoyl-1-*o*-chlorophenyl-ethanol; YKP509) is an alkyl-carbamate drug that has shown efficacy in preclinical animal

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models of focal and generalized seizures (Deshpande et al., 2008; François et al., 2008; Grabenstatter and Dudek, 2008; Novak et al., 2007). In focal seizures, carisbamate demonstrated efficacy in the hippocampal kindled rat model, the rat kainate-induced seizures model, and the mouse 6-Hz psychomotor seizure model (Bialer et al., 2010; Grabenstatter and Dudek, 2008; Novak et al., 2007). In generalized seizures, it has shown efficacy in the maximal electroshock model and in seizures induced by chemical convulsants such as pentylenetetrazol and picrotoxin (Deshpande et al., 2008; Novak et al., 2007). Carisbamate also dose-dependently reduced the number and duration of spike-and-wave discharges characteristic of absence seizures in the genetic absence epilepsy rats from Strasbourg (GAERS) model (François et al., 2008). In patients with photosensitive epilepsy, carisbamate has demonstrated positive effects in a photoparoxysmal response (PPR) study, providing additional evidence for potential efficacy in generalized epilepsies (Trenité et al., 2007). The antiseizure mechanism of action of carisbamate appears to be mediated, at least in part, by inhibition of the voltage-dependent central nervous system (CNS) sodium channels (Auvin, 2020). Carisbamate significantly inhibits voltage-gated sodium channels in the CNS, with IC_{50} values of 56.4 and 11.4 μM for the transient (I_{NaT}) and persistent (I_{NaP}) sodium currents, respectively (Hung et al., 2023).

The pharmacokinetics of carisbamate have been previously assessed in healthy adult and elderly volunteers (Levy et al., 2008; Yao et al., 2006; Zannikos et al., 2009). Following single and multiple doses between 100 and 750 mg, carisbamate plasma concentrations and exposure increased in a linear and dose-proportional manner (Yao et al., 2006). Carisbamate was rapidly absorbed with a mean t_{max} of 1.5–2 h. In a meta-analysis of four placebo-controlled trials of carisbamate in patients aged > 16 years with treatment-resistant focal seizures, adjunctive carisbamate demonstrated statistically significant reductions in seizure frequency and a higher than 50% responder rates at doses between 300 and 1600 mg/day (Lu et al., 2021). The safety profile of carisbamate has been characterized in over 4500 patients across various indications. Adverse events (AEs) have been generally mild-to-moderate, with the most common AEs being CNS-related (eg, dizziness, somnolence) (Lu et al., 2021). Dose-related, reversible elevations in liver enzymes (alanine transaminase [ALT] ≥ 3-times upper limit of normal [ULN]) were observed infrequently at doses ≥ 800 mg daily (Faught et al., 2008). No cases of severe liver injury (Hy's Law) or liver failure occurred.

In August of 2017, carisbamate was granted orphan drug status for the treatment of Lennox-Gastaut syndrome by the FDA (US Food and Drug Administration, 2017). Before undertaking large-scale efficacy trials in the LGS population, it was necessary to assess the pharmacokinetic (PK) profile of carisbamate across different age groups of patients with LGS. Here, we report on the results of a phase 1, open-label study designed to characterize the PK profile of carisbamate oral suspension after single and multiple doses in pediatric and adult patients with LGS and to evaluate the drug's tolerability and safety in this population.

2. Methods

2.1. Study design

This was a phase 1 open-label, single- and multiple- dose study (ClinicalTrials.gov NCT03731715) conducted to evaluate the PK, safety, and tolerability of an oral carisbamate suspension in patients with LGS. The study consisted of a 28-day screening period, a 2-day baseline period (prior to Day 1), and an 87-day treatment period, which included a single-dose administration period (Days 1–3), followed by a multiple-dose administration period (Days 3–17) and a subsequent twice-daily dose-adjustment period (Days 18–87), during which the total daily doses could be adjusted up or down based on the investigator's assessment (Fig. 1).

The study protocol called for sequential enrollment of four age-based cohorts: Cohort I (C-I), ≥ 18 years; Cohort II (C-II), 12 to < 18 years; Cohort III (C-III), 6 to < 12 years; and Cohort IV (C-IV), 2 to < 6 years. However, enrollment into C-IV was ultimately withdrawn due to unsuccessful attempts to enroll eligible patients in this age group for almost 2 years, in part due to the COVID−19 pandemic.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. The protocol was approved by the appropriate Institutional Review Boards or Independent Ethics Committee at each of the 7 US study sites (Table 1). Prior to any study-related procedures, written informed consent was obtained from adult patients or from the legal guardian/legally authorized representative for pediatric patients and for adult

Table 1
Study Institutional Review Boards or Independent Ethics Committees.

Site(s)	Name	Location
0101002, 0101018	Advarra, Inc	6940 Columbia Gateway Drive, Suite 110 Columbia, MD 21046
0101003	University of Utah IRB	Research Administration Building 75 South 2000 East Salt Lake City, UT 84112
0101006	Dartmouth-Hitchcock Medical Center Committee for the Protection of Human Subjects	63 South Main Street, Room 302 Hanover, NH 03755
0101009	Oregon Health and Science University IRB	3181 SW Sam Jackson Park Rd - L106R1 Portland, OR 97239
0101010	Johns Hopkins eIRB	1620 McElderry Street Reed Hall B130 Baltimore, MD 21205
0101011	University of Pennsylvania Office of Regulatory Affairs IRB	3800 Spruce Street, First Floor Room 151 Philadelphia, PA 19104

IRB, Institutional Review Board.

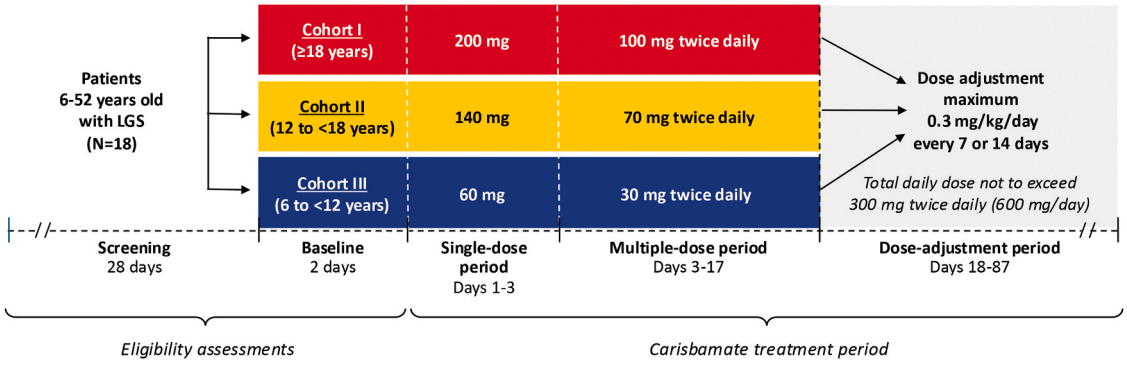

Fig. 1. Study design. LGS, Lennox-Gastaut syndrome.

patients with severe developmental intellectual disabilities. Additional, age-appropriate written or verbal assent was also obtained from children and adolescents.

2.2. Participants

Eligible patients were males or females aged ≥ 2 years at the time of consent with a confirmed diagnosis of LGS with onset (for C-I and C-II) prior to 11 years of age. LGS diagnosis required evidence of more than one type of generalized seizure, including drop seizures (atonic, tonic, or myoclonic), and a previous EEG reporting abnormal background activity accompanied by < 2.5 Hz spike-and-slow-wave complexes meeting International League Against Epilepsy (ILAE) diagnostic criteria for LGS (Scheffer et al., 2017). Patients were required to receive stable doses of 1–3 concomitant ASMs for ≥ 30 days prior to the screening visit (Visit 1). Stable vagus nerve stimulation (implanted ≥ 5 months prior with stable parameters for ≥ 30 days) or a stable ketogenic diet (for ≥ 30 days) were permitted but did not count toward the ASM limit. Patients had to be able to ingest the carisbamate oral suspension.

Key exclusion criteria included: history of status epilepticus within 12 weeks of the screening visit (Visit 1); progressive neurological disease; prior treatment with carisbamate; any clinically significant or acute disease or medical condition or abnormal findings on physical exam, electrocardiogram (ECG), or laboratory tests at screening; or use of concomitant medications that might affect carisbamate PK parameters or that might compromise study participation. These included vigabatrin or other medications known to be CYP3A inducers (eg, phenobarbital, phenytoin, rifampin) or uridine−5′- diphosphoglucuronosyltransferase (UGT) inducers (eg, carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine). Patients taking cannabidiol for ≤ 14 days before screening were also excluded. Patients being treated with felbamate were required to have a stable dose for ≥ 60 days prior to Visit 1.

2.3. Study treatment

Patients received carisbamate as an oral suspension (20 mg/mL). Starting doses were based on preclinical (murine) toxicology data converted to human equivalent doses, targeting exposures below those associated with AEs in prior adult studies but within the potentially efficacious estimated target range. On Day 1, patients received a single dose of carisbamate: 200 mg for C-I, 140 mg for C-II, and 60 mg for C-III (Fig. 1). From Day 3 through Day 17 (multiple-dose period), patients received the corresponding total daily dose administered in two divided carisbamate doses: 100 mg twice daily (C-I), 70 mg twice daily (C-II), and 30 mg twice daily (C-III). From Day 18 through Day 87 (weight-based dose-adjustment period), the carisbamate dose could be increased based on investigator judgment regarding safety and tolerability, in increments up to a maximum of 0.3 mg/kg/day per adjustment approximately every 7 or 14 days (Fig. 1). The maximum allowed total daily dose was not to exceed the pediatric equivalent dose corresponding to an adult exposure achieved with 600 mg/day (or 300 mg twice daily), a dose level within the dose range that has demonstrated efficacy and safety in previous focal seizure studies (data on file). Patients continued their stable concomitant ASMs throughout the study. After the end of the weight-based dose-adjustment period, patients had the option to enroll in an open-label extension study.

2.4. PK sampling

Blood samples for PK analysis were collected at specified time points relative to dosing during the single-dose and multiple-dose periods for C-I, C-II, and C-III. During the single-dose administration period (Days 1–3) samples were collected pre-dose (30 min before dose) on Day 1, and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 h post-dose for C-I and C-II (for C-III, the sampling time points were the same except without the 1.5-hour sample). During the multiple-dose period (Days 3–17), steady-state PK sampling was performed on Day 17, following 14 days of twice-daily dosing; and for C-I and C-II, samples were collected pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h post-dose. For C-III, samples were collected on Day 17 only at pre-dose and at 2 h post-dose (due to blood volume constraints). During the dose-adjustment period (Days 18–87), trough (pre-dose) samples were collected on Days 45 and 73 for all cohorts (to be used in a separate population PK [PopPK] analysis not reported here). Acceptable collection windows were defined as follows: ≥ 30 min before dosing for pre-dose, ±5 min for 0.5–1.5 h post-dose, ±10 min for 2–12 h post-dose, and ±30 min for 24–48 h post-dose. Blood samples for carisbamate concentrations were placed on ice and processed for plasma according to procedures outlined in a laboratory manual.

2.5. PK endpoints

PK assessments were conducted during the single-dose and multiple-dose periods (through Day 17). For single-dose total (S- + R- enantiomers) carisbamate PK assessments, the primary endpoints consisted of maximum observed concentration (C_{max}), area under the plasma concentration-time curve (AUC) from time 0 to the time of the last measurable concentration ($AUC_{0\text{-last}}$) and AUC from time 0 extrapolated to infinity ($AUC_{0\text{-inf}}$). Secondary PK parameters included: time to reach C_{max} (t_{max}), apparent clearance (CL/F; oral clearance where CL is clearance and F is bioavailability), apparent volume of distribution during the terminal phase (Vz/F), apparent terminal half-life ($t_{1/2}$; calculated from ln[2]/λz, where λz is the apparent terminal rate constant calculated by log-linear regression of the terminal segment of the drug plasma concentration-time curve).

For the multiple-dose period, following 14 days of twice-daily dosing, the total carisbamate PK assessments included the following endpoints (for C-I and C-II only): area under the plasma concentration-time curve over the dosing interval at steady-state ($AUC_{0\text{-tau}}$) and C_{max} at steady-state ($C_{max,ss}$). Additional PK endpoints included oral clearance at steady-state (CL_{ss}/F), apparent volume of distribution at steady-state (Vz_{ss}/F), and accumulation ratios (AR). The AR was calculated as the ratio of $AUC_{0–12\ h}$ on Day 17 to $AUC_{0–12\ h}$ after the single dose, in those subjects where the ratio calculation was possible based on adequate data availability. Because of limited blood sampling in C-III, the PK endpoints were limited to concentrations at 2 h and C_{trough}.

2.6. Bioanalytical methods and PK analysis

Plasma concentrations of carisbamate were measured using two validated high-performance liquid chromatography assays with tandem mass spectrometric detection (HPLC-MS/MS; Sciex API 4000, Danaher Corp, Toronto, Canada). The lower limit of quantitation for carisbamate in plasma was in the low microgram-per-milliliter range in both assays, which is sufficiently sensitive to quantify levels up to 48 h post-dose at the lowest dose tested. Plasma samples from all three cohorts were analyzed using a chiral assay (performed by Q^2 Solutions, now part of IQVIA Laboratories, Bridgewater, NJ, USA); total carisbamate concentrations were estimated post hoc by summing the measured S- and R-enantiomer concentrations at each time point. For C-I and C-II, a second set of plasma samples were analyzed using an achiral method (Worldwide Clinical Trials [Research Triangle Park, NC, USA] Procedure ATM−2352) to directly determine total carisbamate (S- + R-enantiomers) concentrations.

PK parameters were derived from the plasma carisbamate concentration–time data using noncompartmental analysis methods with Phoenix WinNonlin software (Version 6.4 or higher; Certara, Radnor, PA, USA). Dose proportionality of carisbamate exposure was evaluated by descriptive comparisons of dose-normalized C_{max} and AUC across the different dose levels and age cohorts. No inferential statistical comparison was planned due to the small cohort sizes.

2.7. Safety assessments

Safety and tolerability were evaluated in all patients who received at least one dose of carisbamate. Assessments included monitoring and recording of all treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation during the 87-day study duration. Concomitant medications were recorded. Clinical laboratory tests (hematology, serum chemistry, urinalysis), vital signs (blood pressure, heart rate, respiratory rate, temperature), 12-lead ECGs, and physical and neurological examinations were performed at scheduled intervals. For pediatric patients, laboratory reference ranges specific to age groups were used. At the end of study visit, overall change in status was assessed using the Parent/Caregiver Global Impression of Change (CaGI-C) questionnaire.

2.8. Statistical analysis

The safety analysis set included all patients who received at least one dose of carisbamate. Demographic, baseline characteristics, disposition, study drug exposure, and safety data were summarized using descriptive statistics by cohort and overall. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 21.1) and summarized by system organ class (SOC) and preferred term (PT). Concomitant medications were coded using the World Health Organization (WHO) Drug dictionary (September 2018) and tabulated. Missing safety data were not imputed. The PK analysis set included all patients who received at least one dose of carisbamate and had at least one quantifiable total carisbamate concentration during the PK assessment period.

The sample size was chosen based on practical considerations for a phase 1 trial in a rare disease and was not based on formal power calculations. The focus was on obtaining sufficient PK data to adequately characterize the PK of total carisbamate rather than on statistical power. The decision to stop dose escalation in individual patients was based on tolerability, and the decision to not enroll C-IV (ages 2 to <6) was made during the study due to slow enrollment and external circumstances (the onset of the COVID−19 pandemic, which impacted trial participation for young children).

PK parameters derived from the noncompartmental analysis were summarized using descriptive statistics by cohort. Individual and mean plasma concentration-time profiles were plotted on linear and semi-logarithmic scales. No formal inferential statistical testing was pre-specified or necessary for comparisons between cohorts for PK and safety parameters and due to the small sample sizes of LGS patients enrolled in each cohort.

3. Results

3.1. Baseline characteristics and participant disposition

A total of 27 patients were screened. Eighteen were enrolled into the study across the three cohorts, received at least one dose of carisbamate, and were included in both the PK and safety analysis sets: C-I (adults ≥ 18 years; n = 8); C-II (adolescents 12 to < 18 years; n = 3); C-III (children 6 to < 12 years; n = 7. Of the 18 patients, 16 (88.9%) completed the full 87-day treatment period and all protocol-specified evaluations. Two patients (11.1%) did not complete the study: one adult patient in C-I withdrew on Day 19 due to an AE (sedation), and one pediatric patient in C-III discontinued on Day 50 at the investigator's decision (this patient had experienced worsening of baseline behavioral issues, as described below, and it was decided to stop treatment for clinical reasons).

Baseline demographic and clinical characteristics of the patients for each cohort are summarized in Table 2. All enrolled patients had a history of more than one type of generalized seizure, including drop seizures (atonic, tonic, or myoclonic). The total number of reported seizures (per 28 days) was higher in C-III (mean [SD]: 254.2 [394.24]) compared with C-II (103.8 [103.34]) and C-I (37.2 [78.02]). The mean number of ongoing concomitant medications taken during study treatment was 2.4 in C-I, 2.3 in C-II, and 2.3 in C-III. The most frequent concomitant ASMs taken during the study were clobazam (n = 14; 77.8%), diazepam (n = 9; 50.0%), lorazepam (n = 6; 33.3%), felbamate and rufinamide (n = 5; 27.8%), and lamotrigine and valproate (n = 4; 22.2%).

Table 2
Baseline demographics.

Parameter	Patients by cohort		
	Cohort I (≥ 18 years) (n = 8)	Cohort II (12 to < 18 years) (n = 3)	Cohort III (6 to < 12 years) (n = 7)
Age (years) at baseline			
Mean (SD)	31.1 (10.9)	13.7 (0.6)	8.4 (1.3)
Median (min, max)	32.0 (18.0, 52.0)	14.0 (13.0, 14.0)	9.0 (6.0, 10.0)
Gender, n (%)			
Male	4 (50.0)	2 (66.7)	4 (57.1)
Female	4 (50.0)	1 (33.3)	3 (42.9)
Race, n (%)			
Asian	1 (12.5)	0	0
Black or African American	0	1 (33.3)	2 (28.6)
White	6 (75.0)	2 (66.7)	5 (71.4)
Not reported	1 (12.5)	0	0
Ethnicity, n (%)			
Hispanic or Latino	1 (12.5)	0	1 (14.3)
Not Hispanic or Latino	7 (87.5)	3 (100.0)	6 (85.7)
BMI (kg/m^2)			
Mean (SD)	21.4 (5.6)	21.9 (6.5)	16.6 (2.3)
Median (min, max)	21.4 (13.7, 33.3)	19.4 (16.9, 29.3)	16.7 (13.2, 20.2)
Number of patients taking 1/2/3 concomitant ASMs during study treatment	1/3/4	0/2/1	0/5/2

BMI, body mass index; max, maximum; min, minimum; SD, standard deviation.

3.2. Pharmacokinetics

All enrolled patients (N = 18) contributed PK data for the single-dose phase (Days 1–3), and 16 patients contributed PK data for the multiple-dose phase (Day 17). PK profiles were fully characterized for the adult, adolescent, and child cohorts following single oral doses of carisbamate 200, 140, and 60 mg total daily dose, respectively. Fig. 2 illustrates the mean plasma total carisbamate concentration–time profiles in each cohort following a single dose on Day 1, and at steady-state on Day 17 following 14 days of treatment with 100 mg twice daily, 70 mg twice daily, and 30 mg twice daily for C-I, C-II, and C-III, respectively.

3.2.1. Single-dose pharmacokinetic parameters

Key single-dose PK parameters for total carisbamate (combined R-plus S- enantiomers) are summarized in Table 3. After a single oral dose on Day 1, carisbamate was rapidly absorbed in all age groups, with median peak carisbamate levels occurring at a t_{max} (hours post-dose) of 1.47 h (C-I), 1.5 h (C-II), and 1.1 h post-dose (C-III). Overall, peak concentration and total exposure (i.e., C_{max} and AUCs, respectively) increased with the increasing doses administered to the respective cohorts. Inter-subject variability (%CV) for C_{max} and AUC was generally low to moderate (range, 2.6–51.3%). The mean apparent terminal half-life ($t_{1/2}$) was similar between C-I (12.2 h) and C-II (11.9 h), but shorter for C-III (8.01 h).

3.2.2. Multiple-dose (steady-state) pharmacokinetic parameters

Steady-state (Day 17) PK parameters for total carisbamate are summarized in Table 4. Exposures ($C_{max,ss}$, and $AUC_{0\text{-}tau}$) increased with the increasing twice-daily doses administered to C-I and C-II. For C-III (30 mg twice daily), mean C_{trough} was 615 ng/mL and mean $C_{2\,h}$ was

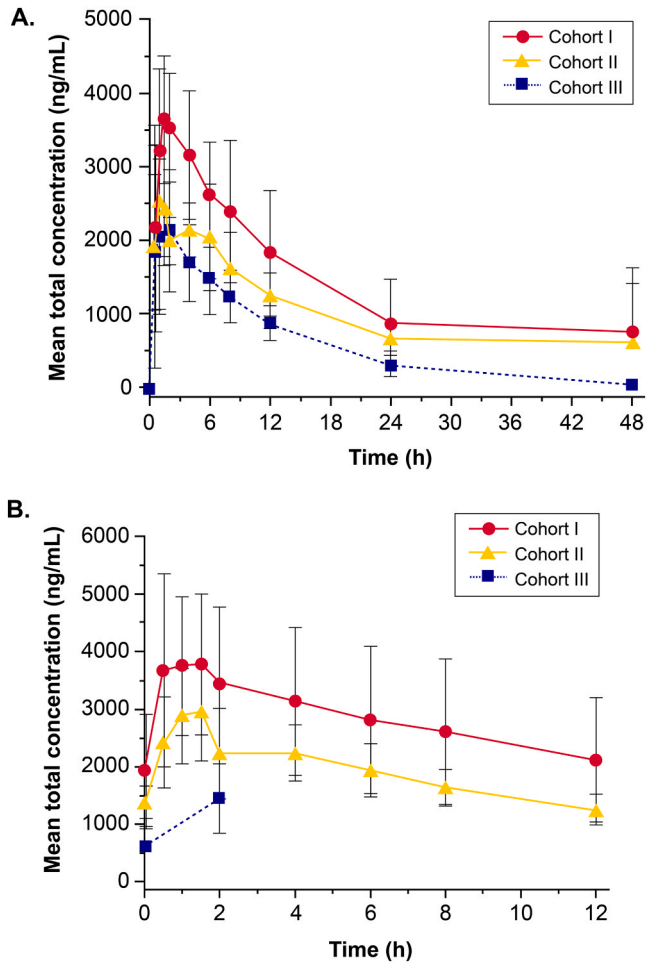

Fig. 2. Mean (±SD) plasma total (S- + R- enantiomers) carisbamate concentration-time profiles, **A**) After oral administration of a single dose of carisbamate (S-carisbamate), and **B**) After oral administration of multiple twice-daily doses of carisbamate (S-carisbamate) on study Day 17 at steady-state. Pharmacokinetic analysis set (N = 18) included subjects who received ≥ 1 dose of carisbamate and who had ≥ 1 quantifiable total carisbamate plasma concentration during the PK assessment period. Cohort I (n = 8) included subjects ≥ 18 years; Cohort II (n = 3), 12 to < 18 years; Cohort III (n = 7), 6 to < 12 years. PK-scheduled time points for Cohort III were at 0 and 2 h. For Cohort III, total carisbamate drug concentrations were estimated by adding the measured concentration of S-carisbamate and R-carisbamate at each scheduled (nominal) PK time point, while Cohorts I and II had the measured total carisbamate drug concentration. SD, standard deviation.

1440 ng/mL, consistent with the lower daily dose administered to C-III compared to C-I and C-II. Median $t_{max,ss}$ was 0.86 h post-dose in C-I and 1.5 h post-dose in C-II. The mean apparent $t_{1/2}$ at steady-state was similar in C-I (9.05 h) and C-II (9.32 h). Mean apparent steady-state clearance (CL_{ss}/F) and volume of distribution (Vz_{ss}/F) were also similar between C-I and C-II (CL_{ss}/F: 3.25 vs 3.13 L/h; Vz_{ss}/F: 50.1 vs 42.4 L), indicating no substantial difference between adults and adolescents. The mean AR, calculated by $AUC_{0–12}$ of single dose to that of multiple dose, was consistent and similar between C-I (1.66) and C-II (1.69), suggesting an approximate 1.7-fold accumulation of total carisbamate exposure with twice-daily dosing at steady-state compared to the first dose.

3.2.3. *Dose normalization and enantiomer ratios*

Dose-normalized exposures of total carisbamate (C_{max}/dose, $AUC_{0\text{-}inf}$/dose for single dose; $C_{max,ss}$/dose, $AUC_{0\text{-}tau}$/dose for multiple dose) were generally proportional to the dose administered across the range studied (single doses 60–200 mg; multiple doses 30–100 mg twice daily). Dose-normalized exposures were similar and consistent across the three age cohorts, while C-III exhibited greater data variability and higher C_{max}/dose compared to older cohorts (C-I and C-II) after administration of single doses.

The contribution of total exposure to the R-enantiomer (the inactive metabolite resulting from the chiral inversion of the orally administered S-enantiomer) was assessed by calculating the ratios of R to total (i.e., R/R+S) carisbamate for PK parameters at steady-state (Day 17). The median enantiomer ratios for $C_{max,ss}$ in C-I/II or $C_{2\ h}$ in C-III (proxy for C_{max}) were 0.0780, 0.0582, and 0.0656, respectively; the mean enantiomer ratios for $AUC_{0\text{-}tau}$ in C-I and C-II were 0.100 and 0.0792, respectively (the C-III ratio could not be determined due to inadequate sample size); and the mean enantiomer ratios for C_{trough} in C-I, C-II, and C-III were 0.139, 0.0957, and 0.110, respectively. With the exception of the C_{trough} enantiomer ratios for C-I and C-III, the enantiomer ratios for $C_{max,ss}$, and $AUC_{0\text{-}tau}$ were ≤ 0.1 (ie, ≤10% of total carisbamate exposure), suggesting that R-enantiomer is a minor circulating enantiomer following oral administration of S-carisbamate.

Table 3
Summary of total carisbamate PK parameters following administration of a single dose of carisbamate by cohort.

Treatment group **Dose** **Age**	PK parameter	**n**	**Mean**	**SD**	**%CV**
Cohort I 200 mg ≥ 18 years	t_{max} (h)[a]	8	Median (min-max): 1.47 (0.48–2.08)		
	C_{max} (ng/mL)	8	3850.00	828.35	21.5
	$AUC_{0\text{-}last}$ (h•ng/mL)	8	62,400.00	31,861.00	51.1
	$AUC_{0\text{-}inf}$ (h•ng/mL)	6	60,200.00	30,862.60	51.3
	$t_{1/2}$ (h)	6	12.20	5.34	43.70
Cohort II 140 mg 12 to < 18 years	t_{max} (h)[a]	3	Median (min-max): 1.5 (0.5–6)		
	C_{max} (ng/mL)	3	3080.00	255.15	8.28
	$AUC_{0\text{-}last}$ (h•ng/mL)	3	47,400.00	3029.58	6.4
	$AUC_{0\text{-}inf}$ (h•ng/mL)	2	48,900.00	1272.46	2.6
	$t_{1/2}$ (h)	2	11.90	1.29	10.8
Cohort III 60 mg 6 to < 12 years	t_{max} (h)[a]	7	Median (min-max): 1.1 (0.65–4.05)		
	C_{max} (ng/mL)	7	2340.00	873.21	37.4
	$AUC_{0\text{-}last}$ (h•ng/mL)	7	26,900.00	8775.92	32.7
	$AUC_{0\text{-}inf}$ (h•ng/mL)	7	27,400.00	9260.95	33.7
	$t_{1/2}$ (h)	7	8.01	1.58	19.7

PK analysis aet included subjects who received ≥ 1 dose of carisbamate and who had ≥ 1 quantifiable total carisbamate, S- and R-carisbamate plasma concentration during the PK assessment period.
[a]t_{max} is presented as median (min-max).
%CV, coefficient of variance; $AUC0_{0\text{-}inf}$, area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}last}$, area under the plasma concentration-time curve (AUC) from time 0 to the time of the last measurable concentration; C_{max}, maximum concentration; PK, pharmacokinetic; SD, standard deviation; $t_{1/2,}$ terminal elimination half-life; t_{max}, time of maximum plasma carisbamate concentration.

3.3. *Safety and tolerability*

The minimum and maximum total daily dose of carisbamate administered during the dose-adjustment period was 40 and 288 mg, respectively. TEAEs are summarized in Table 5. TEAEs were reported by 12 of 18 patients (66.7%) overall and were mostly mild (n = 6 patients) or moderate (n = 5 patients) in severity. One patient (from C-III) experienced a severe TEAE, coded as affective disorder and one patient (from C-I) discontinued due to a moderate TEAE of sedation. No deaths or SAEs were reported during the study.

Table 4
Summary of PK parameters at steady-state following administration of multiple twice-daily doses of carisbamate by cohort.

Treatment group **Dose** **Age**	PK parameter (steady-state)	**n**	**Mean**	**SD**	**% CV**
Cohort I 100 mg twice daily ≥ 18 years	$t_{max,ss}$ (h)[a]	6	Median (min-max): 0.86 (0.03–4.12)		
	$C_{max,ss}$ (ng/mL)	6	4370	1509.03	34.5
	C_{trough} (ng/mL)	6	2060	995.30	48.3
	$AUC_{0\text{-}last}$ (h•ng/mL)	6	35,800	15,387.16	43.0
	$AUC_{0\text{-}tau}$ (h•ng/mL)	6	36,000	15,145.95	42.1
	$t_{1/2}$ (h)	4	9.05	1.33	14.7
	CL_{ss}/F (L/h)	6	3.25	1.44	44.2
	Vz_{ss}/F (L)	6	50.1	15.68	31.3
	AR	4	1.66	0.15	8.86
Cohort II 70 mg twice daily 12 to < 18 years	$t_{max,ss}$ (h)[a]	3	Median (min-max): 1.5 (1.48–2.32)		
	$C_{max,ss}$ (ng/mL)	3	2950	811.56	27.5
	C_{trough} (ng/mL)	3	1380	277.91	20.2
	$AUC_{0\text{-}last}$ (h•ng/mL)	3	22,700	3813.30	16.8
	$AUC_{0\text{-}tau}$ (h•ng/mL)	3	22,800	3924.23	17.2
	$t_{1/2}$ (h)	3	9.32	0.49	5.27
	CL_{ss}/F (L/h)	3	3.13	0.56	17.9
	Vz_{ss}/F (L)	3	42.4	9.88	23.3
	AR	3	1.69	0.06	3.27
Cohort III 30 mg twice daily 6 to < 12 years[b,c]	$C_{2\,h}$ (ng/mL)	7	1440	600.31	41.8
	C_{trough} (ng/mL)	7	615	309.35	50.3

PK analysis set included subjects who received ≥ 1 dose of carisbamate and who had ≥ 1 quantifiable total carisbamate, S-carisbamate, and R-carisbamate plasma concentration during the PK assessment period. The PK of total carisbamate is reported in this manuscript.
[a]t_{max} values are reported as median (min, max). [b]One subject was administered a 32-mg dose but was included in the 30-mg dose nominally. [c]Because of limited blood sampling in Cohort III, the PK steady-state endpoints were limited to concentrations at 2 h and C_{trough}.
%CV, coefficient of variance; AR, accumulation ratio calculated as the ratio of $AUC_{0–12\,h}$ on Day 17 to $AUC_{0–12\,h}$ after the single dose; $AUC_{0\text{-}last}$, area under the plasma concentration-time curve (AUC) from time 0 to the time of the last measurable concentration; $AUC_{0\text{-}tau,}$ area under the plasma concentration-time curve over the dosing interval at steady-state; $C_{2\,h}$, concentration at 2 h post-dose; $C_{max,ss}$, maximum observed plasma concentration at steady-state; C_{trough}, trough concentration at the end of the dosing interval; CL_{ss}/F, apparent (oral) clearance at steady-state; PK, pharmacokinetic; SD, standard deviation; $t_{½}$, terminal elimination half-life; $t_{max,ss}$, time of maximum plasma total carisbamate concentration at steady-state; Vz_{ss}/F, apparent volume of distribution at steady-state.

Table 5
TEAEs reported in ≥ 10% of total subjects (safety analysis set).

TEAE (n, %)	Cohort I (≥ 18 years, n = 8)	Cohort II (12 to < 18 years, n = 3)	Cohort III (6 to < 12 years, n = 7)	**Overall** (N = 18)
TEAEs	5 (62.5)	2 (66.7)	5 (71.4)	12 (66.7)
Nervous system disorders				
Headache	1 (12.5)	0	1 (14.3)	2 (11.1)
Seizure	1 (12.5)	0	1 (14.3)	2 (11.1)
Injury, poisoning, and procedural complications				
Contusion	2 (25.0)	0	0	2 (11.1)
Fall	2 (25.0)	0	1 (14.3)	3 (16.7)
General disorders and administration site conditions				
Pyrexia	0	1 (33.3)	1 (14.3)	2 (11.1)
Gastrointestinal disorders				
Constipation	1 (12.5)	0	1 (14.3)	2 (11.1)

Safety analysis set included all subjects who received at least 1 dose of carisbamate. TEAEs include any adverse event that began or worsened (increased in severity) during the treatment period for subjects who enrolled in the subsequent open-label study; for subjects who did not enroll in the open-label study, a TEAE was defined as any adverse event that began or worsened on or after date of first dose of the treatment but within 30 days after the date of the last dose.
TEAE, treatment-emergent adverse event.

There were no clinically meaningful changes in the laboratory safety tests by study endpoint in mean values for hematology, serum chemistry, or urinalysis parameters across the cohorts. Evaluations of vital signs, 12-lead ECGs, physical examinations, and neurological examinations did not reveal any safety concerns.

At study endpoint on the single-item CaGI-C questionnaire, a total of 10/18 patients (55.6%) were reported to show improvement in overall status following the start of carisbamate treatment.

4. Discussion

This phase 1 study provided the first characterization of the PK, safety, and tolerability of carisbamate oral suspension in pediatric and adult patients 6–52 years old with LGS. The PK and safety findings in pediatric and adult patients with LGS were consistent with previous phase 2 studies of carisbamate in adult focal epilepsy that also reported dose-proportional PK and a tolerable adverse event profile (with CNS AEs being dose-limiting at the higher end of the dose range) (Yao et al., 2006). The current study extends these findings to a pediatric population with developmental epilepsy. The results showed that carisbamate appeared to exhibit predictable and dose-proportional PK exposures (C_{max} and AUCs) in this population over the dose ranges studied (single doses 60–200 mg; multiple doses 30–100 mg twice daily). Following oral suspension administration, carisbamate was rapidly absorbed with peak plasma concentrations occurring within 1–2 h post-dose, which is consistent with the findings in healthy adults (Yao et al., 2006). The mean apparent terminal $t_{1/2}$ was 11.9–12.2 h in adults and adolescents (C-I and C-II), similar to previous reports (Yao et al., 2006). A shorter mean $t_{1/2}$ of approximately 8 h was observed in children aged 6 to < 12 years (C-III), suggesting faster clearance in this younger age group. For many drugs metabolized by the liver or excreted renally, drug clearance rates are commonly higher in younger children compared to older adolescents and adults (Batchelor and Marriott, 2015; Crom et al., 1991). Despite this difference in $t_{1/2}$ between adolescents and younger children, descriptive dose-normalized exposures (AUC/dose) were comparable across the three age cohorts, indicating that the carisbamate disposition is approximately similar between pediatric (age of 6 to < 18 years) and adult populations. The time to steady-state was similar in adults and adolescents and was achieved within the 14 days on twice-daily dosing, with an accumulation ratio of approximately 1.7.

Carisbamate (the active, S-enantiomer parent drug) was the predominant form in systemic circulation following oral administration, with the R-enantiomer (the inactive, chiral inversion metabolite) representing less than 10% of the total drug exposure based on C_{max} and AUC. The C_{trough} ratio in C-I was 13.9%, although it should be noted that C_{trough} levels tend to be more variable and are dependent on when the previous dose was administered relative to the C_{trough} sampling time, leading to a slightly higher C_{trough} carisbamate concentrations and therefore a less reliable ratio. Based on the enantiomer ratios, measuring total carisbamate should provide an appropriate measure of systemic exposure for clinical development and therapeutic drug monitoring purposes, and thus it may not be necessary to quantify each chiral species of S- and R-carisbamate enantiomer to evaluate the systemic exposure of total carisbamate.

The LGS patients in this study had a high level of medical comorbidity and typically were treated with multiple concomitant ASMs. Of note, benzodiazepines, including clobazam, diazepam, and lorazepam, were among the most frequently reported concomitant ASMs in the

study. Clobazam is indicated in the US for LGS, whereas diazepam and lorazepam are typically used for acute seizures (Vossler and Gidal, 2024), which are also common in patients with LGS (i.e., repetitive, cluster seizures).

Carisbamate was generally safe and well tolerated during the short-term treatment duration. The types of TEAEs observed were typical for CNS-active drugs and were consistent with the known safety profile of carisbamate from previous studies in adult patients with focal seizures (Halford et al., 2011; Sperling et al., 2010). Nervous system disorders, such as headache and seizure (which could reflect underlying disease), was the most common category. Falls were the most frequent individual TEAE (a common issue in LGS due to drop seizures). Most TEAEs were mild or moderate in severity. Importantly, no SAEs or deaths occurred.

There were no clinically significant findings on laboratory tests, vital signs, or ECGs, and no unexpected or idiosyncratic reactions were observed. This is consistent with prior adult data indicating that carisbamate does not significantly affect liver or renal function and has no proarrhythmic effect (Halford et al., 2011; Sperling et al., 2010). Because many of the patients in this trial were on valproate and other ASMs that themselves have known adverse events, the absence of any additive toxicity (e.g., no patients developed liver enzyme elevations beyond what might be expected from valproate alone) is a positive sign for combination therapy scenarios with carisbamate. Overall, the safety profile supports further investigation of carisbamate in this challenging LGS patient population that are frequently receiving polytherapy with ASMs.

The efficacy and safety of carisbamate are being further assessed in an ongoing phase 3, randomized, double-blind, placebo-controlled study in patients with LGS ages 4–55 years (NCT05219617). To further inform the dosing regimens used in the phase 3 study, the PK data generated from this study were integrated into a previously developed PopPK model for carisbamate (data on file). Simulations were performed to predict appropriate dosing regimens to achieve target exposures across the pediatric age groups, including extrapolation to younger children (age 4 years) who were not enrolled in this PK study and did not have observed data. The model-informed dosing regimens used in the phase 3 study include flat dosing (mg per dose, not based on weight) for adults and adolescents 12 years and older and body-weight dosing (mg/kg) for LGS patients 4 to $<$ 12 years.

4.1. Study limitations

Notable study limitations included the small sample size, which is common in pediatric PK studies and studies of patients with rare diseases/disorders; the need to reduce the total volume of blood samples taken from the younger cohort, which limited the ability to fully characterize the PK parameters at steady-state following multiple dosing; and the absence of a placebo control, which limited the ability to evaluate both the short-term efficacy and safety of carisbamate. A final limitation is the absence of PK data in patients under the age of 6, which limits the ability to make dosing decisions in this younger patient cohort. However, as noted above, the PK data generated from this study were sufficient to include in a separate PopPK model and analysis to inform the dosing regimen for use in clinical studies including patients 4 years of age.

5. Conclusions

This study prospectively examined the PK of an investigational ASM, carisbamate, in pediatric patients with LGS as part of early-phase development. The drug's pharmacokinetics appear linear and predictable across a broad age range, simplifying dose selection, and the safety profile observed in this small, short-term study suggests that carisbamate may be administered to LGS patients with acceptable tolerability. These findings have directly informed the design of a larger, ongoing phase 3 clinical trial in LGS (NCT05219617), in which efficacy and longer-term safety of carisbamate will be assessed.

CRediT authorship contribution statement

Vijay Vashi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Janice Kearns:** Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **Mark Kamin:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. **David G, Vossler:** Investigation, Writing – original draft, Writing – review & editing.

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Data availability

The data for the analyses described in this paper are available by request from SK Life Science, Inc, the company sponsoring the clinical development of carisbamate.

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