FULL-LENGTH ORIGINAL RESEARCH

Intravenous carbamazepine as short-term replacement therapy for oral carbamazepine in adults with epilepsy: Pooled tolerability results from two open-label trials

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Summary

Objective: To report tolerability findings and maintenance of seizure control from a pooled analysis of phase I open-label trial OV-1015 (NCT01079351) and phase III study 13181A (NCT01128959).

Methods: Patients receiving a stable oral dosage of carbamazepine were switched to an intravenous (IV) carbamazepine formulation solubilized in a cyclodextrin matrix (at a 70% dosage conversion) for either a 15- or a 30-min infusion every 6 h for up to 7 days and then switched back. A subset of patients who tolerated 15-min infusions also received 2- to 5-min (rapid) infusions. Assessments included physical and laboratory evaluations, electrocardiography (ECG) studies, as well as adverse event (AE) monitoring for tolerability. Convulsion/seizure AE terms and data from seizure diaries were used as proxies for the assessment of consistency of seizure control between formulations.

Results: Of the 203 patients exposed to IV carbamazepine (30 min, n = 43; 15 min, n = 160), 113 received 149 rapid infusions. During infusion, the most commonly reported AEs (≥5%) were dizziness (19%), somnolence (6%), headache (6%), and blurred vision (5%). IV carbamazepine was not associated with clinically relevant cardiac AEs. The tolerability profile appeared similar between patients who received <1,600 mg/day (n = 174) and ≥1,600 mg/day (n = 29) carbamazepine. Cyclodextrin exposure was not associated with clinically relevant changes in AEs or renal biomarkers. Seizure control was maintained as patients transitioned between oral and IV carbamazepine.

Significance: IV carbamazepine administered as multiple 30- or 15-min infusions every 6 h, and as a single rapid infusion, was well tolerated as a short-term replacement in adults with epilepsy receiving stable dosages of oral carbamazepine. Infusion site reactions, which were generally mild, were the only unique AEs identified; seizure control was generally unchanged when patients were switching between formulations.

KEY WORDS: Intravenous carbamazepine, Cyclodextrin, Epilepsy, Tolerability.

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Oral carbamazepine is a well-established antiepileptic drug (AED) that is approved worldwide for the treatment of complex partial and generalized tonic–clonic seizures. Orally administered carbamazepine is metabolized primarily via the cytochrome P450 (CYP) isozyme CYP3A4, resulting in the active metabolite carbamazepine-10,11-

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epoxide.[1–3] Because carbamazepine is a known inducer of CYP3A4 and CYP1A2, and a substrate of these isozymes, it is considered an auto-inducer.[4] Auto-induction of carbamazepine metabolism is concentration- and time-dependent, but the degree of auto-induction can vary widely among patients, influencing both the optimal carbamazepine dosage and the time to achieve steady-state plasma concentrations.[5]

Fluctuations in AED therapy may put patients at risk for breakthrough and potentially life-threatening seizures. Although continuity of care with an existing AED therapy is preferable, when patients whose seizures are controlled with oral carbamazepine (either as monotherapy or polytherapy) are unable to take the drug by mouth (e.g., due to postoperative recovery, or gastrointestinal illness) the only current alternatives are rectal administration or switch to an alternative AED. Using the suspension formulation, rectal carbamazepine is slowly and erratically absorbed, and due to its high osmolality, induces a strong defecatory urge.[6] For these reasons, administration of carbamazepine rectally is not a practical option. Switching to another AED raises the possibility of decreased seizure control and/or the potential for adverse events (AEs).[7]

Carbamazepine has limited aqueous solubility and, to date, no commercial intravenous (IV) replacement formulation is available. To address this treatment gap, an IV formulation of carbamazepine solubilized in a cyclodextrin matrix (sulfobutylether-β-cyclodextrin [SBECD]) has been developed, which would allow for AED dosing continuity while transitioning patients who are well-controlled on oral carbamazepine to IV treatment and back.[8] SBECD is used in U.S. Food and Drug Administration (FDA)–approved IV formulations of voriconazole,[9] ziprasidone mesylate,[10] aripiprazole,[11] amiodarone HCl,[12] and carfilzomib.[13] SBECD is renally excreted, and a study evaluating IV voriconazole in renally impaired participants showed that a linear correlation between SBECD clearance and creatinine clearance in participants with moderate renal impairment and elevated SBECD levels did not correlate with increased serum creatinine levels.[14] No tolerability concerns have been raised in relation to SBECD in the limited trial data available or postmarketing surveillance for the IV formulations of other SBECD-containing drugs. However, because of the limited data, no definitive statements can be made in this regard.

A previously conducted bioequivalence study (OV-1015) showed that this IV carbamazepine formulation provides exposure that is comparable to that of oral carbamazepine when adult patients with epilepsy are administered IV carbamazepine (15- or 30-min infusions every 6 h) at a 70% dosage conversion from their oral dosages.[15] Two open-label studies (OV-1015[15] and 13181A[16]) evaluated tolerability of this IV carbamazepine formulation as 15- or 30-min infusions or as 2–5-min infusions. Pooled data describing tolerability findings from these two open-label studies following a switch between oral and IV carbamazepine formulations are reported here.

Methods

The primary objective of this pooled analysis was to determine the tolerability of the IV carbamazepine/SBECD formulation. The secondary objective included an assessment of renal safety using exploratory biomarkers to assess possible effects of SBECD. Although not an efficacy study, an analysis of seizure control using seizure diaries and AEs was conducted.

Data for this pooled analysis were obtained from trials OV-1015 (NCT01079351)[15] and 13181A (NCT01128959).[16] Trial OV-1015 was a phase I, open-label study evaluating the tolerability and pharmacokinetics of IV carbamazepine relative to oral carbamazepine. The pharmacokinetic data for study OV-1015 are presented in a separate report.[15] Study 13181A was a phase III, open-label trial that assessed the tolerability of IV carbamazepine relative to oral carbamazepine. Both studies were similarly designed (Fig. 1) and are summarized below.

Study design

In both studies, eligible patients received a stable regimen of oral carbamazepine prior to the switch to IV carbamazepine. In each study, the IV formulation was infused at approximately 70% of the total daily oral carbamazepine dosage and was administered in divided doses every 6 h.

Both studies were divided into three periods (Fig. 1): a 28-day lead-in (27-day for 13181A) where patients were treated with oral carbamazepine, a 9-day confinement period (7-day for 13181A) during which IV administration occurred, and a 30-day (28-day for 13181A) follow-up where oral carbamazepine was resumed. In study OV-1015, patients were assigned to one of two cohorts based on infusion duration (15 min or 30 min). The infusion period (time from start of first infusion to first oral dose following infusion) for the 30- and 15-min cohorts included 28 planned infusions over 7 days. A subset of patients in the 15-min cohort had the option to participate in four 2- to 5-min infusions occurring on study day 8 after seven consecutive days of 15-min infusions. In study 13181A, the infusion period included 12 planned 15-min infusions over 4 days followed by one rapid 5-min infusion (Fig. 1). For both studies, the patients resumed their oral regimen 6 h following the final IV dose.

Patients

Both trials had similar patient inclusion and exclusion criteria. All patients were adults (≥18 years) diagnosed with epilepsy consistent with carbamazepine approval (e.g., complex partial, generalized tonic–clinic, or mixed

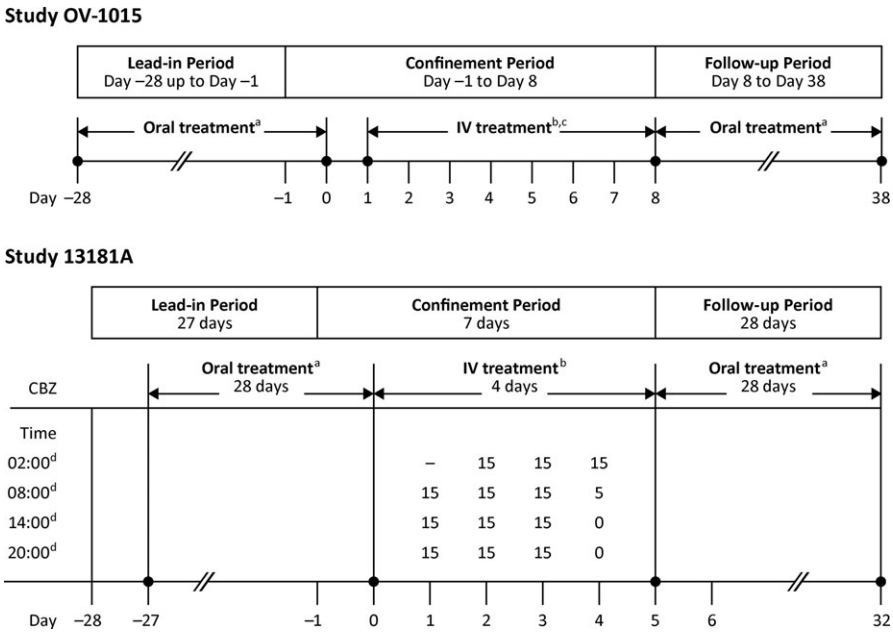

Figure 1.

Study designs. CBZ, carbamazepine; 15, 15-min infusion of IV carbamazepine; 5, 5-min infusion of IV carbamazepine; o, oral carbamazepine.

[a]The oral carbamazepine dosage and frequency were identical to the prescribed dosage and frequency at the screening visit (day −28).

[b]Seventy percent of the daily oral carbamazepine dosage.

[c]Patients received either 30- or 15-min infusions from day 1 to 7, every 6 h. Patients from the 15-min infusion had the option of receiving four 2- to 5-min infusions on day 8.

[d]Recommended infusion times, actual times could vary.

patterns of both seizure types). Patients in OV-1015 were receiving a stable oral carbamazepine dosage of 400–2,000 mg/day, and patients in 13181A were receiving a stable oral carbamazepine dosage of 1,200–2,000 mg/day. Patients were required to be on their respective dosage of carbamazepine for at least 14 days prior to the lead-in period and on a stable regimen of concomitant medications for OV-1015 (28 days for 13181A) throughout the study period. In trial OV-1015, patients with a creatinine clearance (CL_{cr}) of <30 ml/min (corresponding to severe renal impairment in accordance with FDA guidelines at the time the study was conducted) were excluded. In trial 13181A, patients with a CL_{cr} of <50 ml/min (corresponding to moderate and severe renal impairment in accordance with FDA guidelines at the time the study was conducted) were excluded, as were patients with a corrected QT interval by Fridericia's correction formula (QTcF) >450 msec. Trial and consent forms were approved by an institutional review board at each investigative site (see Table S1 for a complete listing), and all patients provided informed written consent.

Intravenous carbamazepine

Preparation of the IV carbamazepine solution has been described in a separate paper.[15] To summarize, the concentrated IV carbamazepine solution was supplied as 10 mg/ml carbamazepine solubilized with 250 mg/ml SBECD sodium salt (Captisol; Ligand Pharmaceuticals, Inc., La Jolla, CA, U.S.A.) in water, which was sealed in 20 ml single-use vials. The IV infusion was prepared by dilution with 5% dextrose in water.

Assessments

Patients underwent assessments of the following: (1) laboratory parameters (hematology, clinical chemistry, and urinalysis); (2) neurologic function (evaluation of coordination, cranial nerves, gait mental status, motor system, reflexes, sensory system, and station); (3) physical examinations (abdomen, cardiovascular system, ears, eyes, head, lung/chest, lymphatic, musculoskeletal assessment, nose and throat, and skin); and (4) vital signs (e.g., blood pressure; respiratory rate, heart rate, and temperature). Twelve-lead electrocardiography (ECG) studies were interpreted either by a central reader (OV-1015) or local cardiologists (13181A). Because SBECD is renally excreted, CL_{cr} was measured, as well as exploratory biomarkers of renal function (urinary *N*-acetyl-β-D-glucosaminidase [NAG] and β2-microglobulin).[17,18]

Tolerability was assessed during the outpatient portion (oral carbamazepine) and the inpatient portion of both studies by asking patients open-ended, nonleading questions, and the investigator assessed the intensity and relationship

of each AE to study drug. The severity of each AE was evaluated as (1) mild: the AE was transient and easily tolerated by the patient; (2) moderate: the AE caused the patient discomfort and interrupted the patient's usual activities; or (3) severe: the AE caused considerable interference with the patient's usual activities and may have been incapacitating or life threatening. Findings based on analyses of AEs and laboratory parameters were considered clinically relevant if they led to discontinuation, did not resolve, required treatment, or resulted in sequelae.

During the outpatient periods, seizure diary data were collected. Investigation-site personnel documented seizure activity that occurred during confinement periods. Consistency of seizure control was estimated using descriptive statistics of data from seizure diaries and an analysis of convulsion/seizure AE terms (Table S2) in the overall pool.

Statistical analyses

Patients who were treated with at least one dose of IV carbamazepine from both studies comprised the all-patients-treated set (APTS), which was used for all assessments, including AEs. Results were summarized using descriptive statistics for the infusion period, as well as the study period preceding the first infusion of carbamazepine (preinfusion), and for the study period following the last infusion (postinfusion). The infusion period was defined as the time of first infusion until just before treatment change. For example, the 15-min infusion period was defined as the time of the first 15-min infusion administration until the time immediately preceding the first 2- to 5-min infusion administration, or until the patient was placed back on oral medication. Given minor differences in study design (noted above), the preinfusion, during-infusion period, and postinfusion period durations varied slightly across studies. Tolerability findings were also summarized by dosage group based on total prescribed daily oral carbamazepine dose (<1,600 mg/day or ≥1,600 mg/day). AEs were also summarized by severity (mild, moderate, or severe) and onset (preinfusion, during infusion, or postinfusion period). AE data from both studies were evaluated by their relationship to a mixture of Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 high-level terms (HLTs) and preferred terms of special interest that were categorized as cardiovascular-, convulsion-, infusion-site reaction–, or renal-related (Table S2).

For ECG results, potential effects were assessed by descriptive statistics for the observed data at each time point and for change pre- and post-IV dose for QRS complex, PR and RR intervals, QTcF, QTcB, and heart rate. For evaluation of infusion-site reactions, tolerability data from both studies were evaluated through a review of both investigator-identified infusion reactions and AE data.

Pooled tolerability data were evaluated for differences among patient groups based on renal function. Although the renal function of patients in studies OV-1015 and 13181A were categorized using previous FDA CL_{cr} classifications for inclusion (described earlier), for this pooled analysis, renal function categories were defined using current FDA CL_{cr} classifications (normal renal function: CL_{cr} ≥90 ml/min; mild renal impairment: CL_{cr} ≥60 to 90 ml/min; and moderate renal impairment: CL_{cr} ≥30 to 60 ml/min).[19]

Descriptive statistics of seizure control data are provided. No statement about the power of this analysis can be made, as both studies were not designed to evaluate seizure control.

Results

Demographic and patient characteristics

Patients in the 30- or 15-min infusion groups were similar with respect to demographic and baseline characteristics (Table 1). Approximately half of the patients were female (53%), and the majority were white (77%), with a mean age of 43 years. The most frequently reported recent and concomitant AED therapies (≥10% of pooled population) were levetiracetam (24%), topiramate (14%), and lamotrigine (12%). Among the 203 patients, most (161) had normal renal function (CL_{cr} ≥90 ml/min); 39 patients were classified as having mild renal impairment (CL_{cr} ≥60 to 90 ml/min), and three patients had moderate renal impairment (CL_{cr} ≥30 to 60 ml/min).

Table 1. Demographics and baseline characteristics (all-patients-treated set)

	Patient group by infusion period[b]			
Dose group[a]	2–5 min n = 113	15 min n = 160	30 min n = 43	Total N = 203
Age, years				
Mean (SD)	40.8 (10.6)	42.4 (11.5)	44.3 (12.0)	42.8 (11.6)
Range	18.0, 65.0	18.0, 76.0	19.0, 68.0	18.0, 76.0
Male, n (%)	57 (50.4)	79 (49.4)	16 (37.2)	95 (46.8)
Weight, kg				
Mean (SD)	85.7 (20.7)	86.3 (21.6)	85.4 (23.4)	86.1 (21.9)
Range	45.4, 150.1	45.4, 168.7	58.7, 149.2	45.4, 168.7
Concomitant AED class, n (%)				
Barbiturates	5 (4.4)	6 (3.8)	2 (4.7)	8 (3.9)
Benzodiazepines	16 (14)	20 (12.5)	0	22 (10.8)
Oxcarbazepine	1 (0.9)	1 (0.6)	0	1 (0.5)
Valproate, valproic acid	9 (8)	14 (8.8)	0	14 (6.9)
Phenytoin, fosphenytoin	11 (9.7)	15 (9.4)	5 (11.6)	20 (9.9)
Lamotrigine	11 (9.7)	18 (11.3)	6 (14.0)	24 (11.8)
Levetiracetam	30 (26.5)	39 (24.4)	10 (23.3)	49 (24.1)
Topiramate	18 (15.9)	22 (13.8)	7 (16.3)	29 (14.3)

[a]Based on the total daily prescribed oral carbamazepine, the overall patient population was split into two dose groups (<1,600 mg, ≥1,600 mg).
[b]Patients in the 2- to 5-min infusion cohort received 15-min infusions prior to 2- to 5-min infusions in both studies; therefore, they were counted in both the 2- to 5-min and 15-min infusion cohorts. The total column only counted them once.

Table 2. Study treatment exposure (all-patients-treated set)

	Patient group by infusion period[a]			
Overall	2–5 min n = 113	15 min n = 160	30 min n = 43	Total N = 203
Total daily dose carbamazepine injection (mg)				
Mean (SD)	900.0 (185.92)	823.2 (251.34)	643.4 (194.83)	785.1 (251.08)
Median	840.0	840.0	630.1	840.0
Min, max	280.0, 1,400.0	64.0, 1,400.0	350.0, 1,050.0	64.0, 1,400.0
Duration of exposure to carbamazepine injection (days)				
Mean (SD)	4.5 (1.47)	5.3 (1.96)	7.7 (0.57)	5.8 (2.02)
Median	4.0	4.0	7.8	4.0
Min, max	3.7, 8.8	1.0, 8.8	4.0, 7.8	1.0, 8.8

[a]Patients in the 2- to 5-min infusion cohort received 15-min infusions prior to 2- to 5-min infusions in both studies; therefore, they were counted in both the 2- to 5-min and 15-min infusion cohorts. The total column only counted them once.

Exposure and disposition

A total of 203 patients in the two studies were exposed to IV carbamazepine (98 from OV-1015 and 105 from 13181A). Among the 203 patients, 43 in the 30-min infusion group received a total of 1,189 infusions, and 160 in the 15-min infusion group received a total of 2,750 infusions. A total of 149 2- to 5-min infusions were completed for 113 patients following a 15-min infusion. The mean (SD), minimum, and maximum doses for carbamazepine injection (mg) are presented for the APTS by infusion time group in Table 2.

The majority of patients (96%) completed the studies. In the 15-min infusion group, three patients discontinued due to AEs, three patients withdrew consent, and one patient was lost to follow-up. In the 30-min infusion group, only one patient (2%) discontinued (because of an AE).

Adverse events

Table 3 summarizes the most commonly reported AEs (≥5%) with onset occurring in the pre-, during-, and postinfusion periods. The most commonly reported AEs (≥5%) during the infusion period (the time from the first IV infusion until just before the first oral dose) in the pooled population were dizziness (19%), somnolence (6%), headache (6%), and blurred vision (5%). The AEs reported during the infusion period that were possibly or probably related to treatment (incidence ≥5%) were dizziness (18%), somnolence (6%), and blurred vision (5%). Of the 330 AEs reported, 258 (78%) were mild, 52 (16%) were moderate, and 20 (6%) were severe in intensity; none of the severe AEs occurred in >1 patient. In addition, no clinically relevant findings in terms of physical examination and laboratory parameters were observed (data not shown).

Because the maximum approved dosage for oral carbamazepine is 1,600 mg/day, to evaluate potential dose-related tolerability concerns, pooled data were also grouped by total prescribed oral carbamazepine daily dose (<1,600 mg or ≥1,600 mg). AEs reported during the IV dosing period by ≥5% of patients receiving a daily oral dose of <1,600 mg or ≥1,600 mg are summarized in Table 4.

Table 3. Adverse events reported by ≥5% and at least two patients in any infusion time cohort with onset pre-, during, and postinfusion (all-patients-treated set)

	No. (%) of patients			
	Patient group by infusion period[a]			
System organ class preferred term	2–5 min n = 113	15 min n = 160	30 min n = 43	Total[b] N = 203
Preinfusion				
At least 1 AE	44 (38.9)	56 (35.0)	10 (23.3)	66 (32.5)
Headache	5 (4.4)	8 (5.0)	2 (4.7)	10 (4.9)
During infusion				
At least 1 AE	22 (19.5)	84 (52.5)	28 (65.1)	118 (58.1)
Anemia	1 (0.9)	0	3 (7.0)	4 (2.0)
Blurred vision	2 (1.8)	7 (4.4)	2 (4.7)	11 (5.4)
Dizziness	13 (11.5)	28 (17.5)	4 (9.3)	38 (18.7)
Headache	0	12 (7.5)	1 (2.3)	13 (6.4)
Somnolence	1 (0.9)	10 (6.3)	2 (4.7)	13 (6.4)
Postinfusion[c]				
At least 1 AE	28 (24.8)	33 (20.6)	8 (18.6)	41 (20.2)

[a]Patients in the 2- to 5-min infusion cohort received 15-min infusions prior to 2- to 5-min infusions in both studies; therefore, they were counted in both the 2- to 5-min and 15-min infusion cohorts. The total column only counted them once.

[b]Patients in the 2- to 5-min infusion cohort were a subset of patients receiving 15-min infusion. AEs with onset time during 15-min infusions were reported in the 15-min infusion cohort, and AEs with onset time during 2- to 5-min infusions were reported in the 2- to 5-min infusion cohort. However, the total within a given system organ class or preferred term reflects the sum of all three infusion periods.

[c]No AEs reported during the postinfusion period occurred at an incidence of ≥5% in at least two patients in any infusion time cohort.

Serious adverse events

No serious adverse events (SAEs) were reported prior to the infusion period (preinfusion period). During the infusion period, three patients (2%) reported an SAE (two in the 15-min group [cerebral hemorrhage and convulsion] and one in the 30-min group [bacteremia]), none of which were considered to be related to study drug. Postinfusion, 5 (3%)

Table 4. Adverse events reported ≥5% of patients during the infusion period by dose groups based on prescribed daily oral doses of carbamazepine (<1,600 mg or ≥1,600 mg; all-patients–treated set)

	Daily oral dose of carbamazepineNumber (%) of patients	
Preferred term	<1,600 mg/day (n = 174)	≥1,600 mg/day (n = 29)
At least 1 AE	99 (56.9)	19 (65.5)
Dizziness	30 (17.2)	8 (27.6)
Headache	10 (5.7)	3 (10.3)
Blurred vision	8 (4.6)	3 (10.3)
Diplopia	5 (2.9)	3 (10.3)
Infusion-site pain	2 (1.1)	3 (10.3)
Dysarthria	0	3 (10.3)
Somnolence	11 (6.3)	2 (6.9)
Fatigue	1 (0.6)	2 (6.9)
Dermatitis contact	1 (0.6)	2 (6.9)

patients (one in the 15-min group and four in the 2–5-min infusion group) reported an SAE. One patient in study 13181A fell and experienced three SAEs (fall, cervical spinal cord injury, and cervical myelopathy). The patient was hospitalized for decompressive laminectomy and developed postoperative complications. These complications resulted in significant spinal cord dysfunction requiring intubation and intensive care unit (ICU) admission. The patient experienced additional SAEs of pyrexia (of unknown origin) and subsequent pneumonia, autonomic nervous system imbalance, pneumothorax, pulmonary embolism, respiratory failure, and hypotension.

In addition, hemiparesis, postictal psychosis, status epilepticus (SE), and subclavian vein thrombosis were each experienced by one patient. The event of SE occurred on day 16 (during the post-IV infusion period) after the patient did not take their oral carbamazepine dose that morning, and the event of subclavian vein thrombosis occurred in a patient with a peripherally inserted central catheter. With the exception of hemiparesis, all postinfusion SAEs were deemed unrelated to study drug by the investigator. The SAE of hemiparesis was reported by a patient who also had experienced a previous, nonserious event of panic attack. A workup including magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), carotid duplex, and two-dimensional (2D) echocardiography imaging, and all laboratory results were normal. The event resolved within several hours without sequelae. One death in the patient with cerebral hemorrhage (above), occurred in study 13181A, but was related to underlying uncontrolled hypertension; this event was deemed unrelated to study drug by the investigator.

Cardiovascular-related adverse events

AEs identified as cardiovascular-related were reported for 42 patients (21%) during the infusion period (29 patients [18%] who received 15-min infusions, seven patients [16%] who received 30-min infusions, and 13 patients [12%] who received 2- to 5-min infusions). Dizziness was the most common AE identified in this analysis (19%). Three patients in study 13181A reported mild transient dysarthria; however, the study drug was continued and all events resolved without recurrence. As noted in the SAE section above, one patient in study 13181A experienced a severe, fatal cerebral hemorrhage that was deemed by the investigator to be unrelated to study drug. In study 13181A, another patient experienced transient mild electrocardiographic T-wave inversion that was not serious. Mild arrhythmia (consisting of two episodes of 2-s cardiac pauses), atrial tachycardia, palpitations, and ventricular extrasystoles were observed in one patient each in OV-1015; all events were deemed nonserious by the investigator and resolved.

With respect to ECG findings, there were no instances of a QTcF value exceeding 500 msec in OV-1015. Overall, the number of QTcF values exceeding 450 msec and 480 msec were 39 and 3, respectively, out of 3,325 measurements. Similarly, no patients in study 13181A had postbaseline ECG values for heart rate, QT interval, or QTcF interval that were identified by the investigator as clinically relevant and reported as AEs (data not shown).

CNS-related adverse events

AEs reported under the higher order term "Nervous System Disorders" were most common during the infusion period. Approximately 30% of the patients in the APTS reported a central nervous system (CNS)–related AE at any time during the study compared with 9% and 7% in the pre- and postinfusion periods, respectively. During the infusion period, the most common CNS-related AEs were dizziness, headache, and somnolence (Table 3). A total of 30% and 21% of patients in the 15- or 30-min infusion group (respectively) reported a CNS-related AE during the infusion period, and 13% of patients in the 2- to 5-min subgroup experienced CNS-related AEs.

Infusion-site reactions

Investigator-identified infusion-site reactions were noted for 25 patients (12%) in the APTS. Nineteen patients (12%) experienced an infusion-site reaction during the 15-min infusion, and six patients (14%) experienced a reaction during the 30-min infusion. Overall, the most commonly reported infusion reactions were infusion-site erythema, infusion-site extravasation, infusion-site pain, and cellulitis (2% each). Similarly, using a preselected list of HLTs and preferred terms, the most frequently reported AEs overall were infusion-site extravasation and infusion-site pain (3% each).

Adverse events leading to study withdrawal

A total of five patients (four receiving 15-min infusions, and one receiving 30-min infusions) reported an AE during

the infusion period that resulted in study withdrawal. Two of the five patients discontinuing due to an AE were from study OV-1015 (one patient in the 30-min group due to bacteremia [considered to be related to IV procedures] and one in the 15-min group discontinuing due to an infusion-site AE). In study 13181A, three patients experienced AEs leading to withdrawal; all occurred during the 15-min IV dosing period and included: a severe convulsion was deemed unrelated to study drug as the patient had been experiencing increased seizure activity 2 weeks prior to study enrollment, an infusion site reaction, and a fatal cerebral hemorrhage (as mentioned in the SAEs section above).

Renal biomarkers and renal-related adverse events

The tolerability profile of the IV carbamazepine/SBECD formulation appeared similar between patients who received a daily oral dose of <1,600 mg (174 patients) and ≥1,600 mg (29 patients; Table 4) in that no unique tolerability concerns were identified. Only eight patients received carbamazepine doses >1,600 mg/day. The greatest SBECD concentration measured in plasma was 1,898 μg/mL in one patient with normal renal function following a single rapid infusion (carbamazepine/SBECD doses of 1,400/35,000 mg/day). A total of 83 (40.9%) patients in both trials had elevated NAG values during infusion compared with preinfusion values, which returned to preinfusion levels at follow-up visits. However, other established renal biomarker values such as CL_{cr} remained within the reference ranges for most patients. No clinically meaningful changes were observed in other exploratory renal biomarkers during IV carbamazepine infusion in trials OV-1015 and 13181A.

When renal status was evaluated, the profile of IV carbamazepine appeared similar between patients with normal renal function (161 patients), mild renal impairment (39 patients), and moderate renal impairment (three patients). No notable differences were observed between the 15- and 30-min infusion groups among patients with normal renal function or impaired renal function for the overall incidence of SAEs prior to, during, or postinfusion in the pooled studies. Furthermore, at all dosages studied with this formulation, patient exposure to SBECD (in patients with normal renal function or mild renal impairment) was not associated with a clinically relevant pattern of change in renal function. Renal-related AEs were reported for six patients (4%) who received 15-min infusions: three patients experienced hyponatremia, (all of which were asymptomatic requiring no specific intervention or interruption to study drug). One patient experienced decreased creatinine renal clearance [day 4; this patient had an increase in serum creatinine concentration that returned to baseline values during the post-IV infusion period], one experienced proteinuria [day 2], and one experienced increased urine protein/creatinine ratio [day 4]); no patients who received 30-min infusions experienced renal-related AEs.

Table 5. Weekly seizure rates by treatment period (studies OV-1015 and 13181A)

Study and infusion duration	Preinfusion	During infusion	Postinfusion
OV-1015			
15-min infusion	n = 55	n = 55	n = 53
Mean (SD)	1.4 (5.4)	1.1 (2.7)	1.1 (3.8)
Range	0–34.1	0–16.0	0–24.3
30-min infusion	n = 43	n = 43	n = 41
Mean (SD)	1.0 (2.4)	0.4 (1.0)	0.6 (1.5)
Range	0–13.5	0–4.0	0–7.9
13181A			
15 + 5 min infusion	n = 105	n = 105	n = 102
Mean (SD)	1.7 (4.09)	2.5 (8.68)	1.4 (3.73)
Range	0–35	0–65	0–32

Consistency of seizure control

The extrapolated weekly seizure rates for 15- and 30-min infusion groups (where the 15-min group data accounts for subset receiving 2- to 5-min infusions) pre-, during, and postinfusion from studies OV-1015 and 13181A are presented in Table 5. Evaluation of seizure frequencies and AEs of convulsion did not indicate a loss of seizure control during the infusion period.

Discussion

In this pooled analysis of two open-label studies, the tolerability profile of IV carbamazepine was similar among the different infusion durations (2- to 5-, 15-, or 30-min), and no clinically relevant concerns were identified.

In general, the types of AEs reported during the infusion period were consistent with those in the AE profile for oral carbamazepine (also noted by the AEs reported prior to the infusion period).[20] Infusion-site reactions, which were generally mild and transient, were the only AEs unique to IV carbamazepine administration. In both studies, the average duration for AE collection was approximately 1 month during the postinfusion periods. Therefore, AEs reported during the postinfusion period were most likely related to oral carbamazepine, but the duration of each AE could not be determined in this analysis. Patients in these studies could be receiving concomitant medications, including other AEDs (e.g., approximately one fourth of patients in the APTS were also receiving levetiracetam), but our analyses did not distinguish AEs due to individual AED combinations. Interpretation of these tolerability data may be limited by the following: (1) differences in how patients interpreted open-ended questions to evaluate AEs in the outpatient vs. inpatient setting, (2) the observation that patients may experience improved seizure frequency in an inpatient setting, and (3) the absence of a placebo control for comparison. Although data were obtained in patients with epilepsy on a stable dosage of oral carbamazepine, the open-label study designs with no controls further limits interpretability.

Significant cardiovascular-related AEs have been associated with oral carbamazepine.[21,22] Therefore, AEs specifically associated with cardiovascular disorders were evaluated from the tolerability data collected during studies OV-1015 and 13181A. Overall, there were no clinically relevant mean changes from baseline in ECG values, and no treatment-related trends were observed in the ECG data. IV carbamazepine was not associated with any clinically relevant cardiac AEs in this pooled analysis.[23] In addition, no obvious trends emerged among infusion groups for CNS-related AEs, although these AEs were more common during the infusion period (30%) compared with pre- or postinfusion (9% and 7%, respectively). These pooled cardiac- and CNS-related AE findings are in agreement with those from OV-1015.[23,24]

The most frequently reported AEs during the IV dosing period (≥5% of all patients) were dizziness, somnolence, headache, and blurred vision, regardless of dosing group (≥1,600 mg/day vs. <1,600 mg/day [greatest labeled dosage for oral carbamazepine]). A greater incidence of dizziness, blurred vision, diplopia, and infusion-site pain was reported in the ≥1,600-mg/day group compared to the <1,600-mg/day group. However, the small sample size and numerical imbalance between the <1,600-mg/day (n = 174) and ≥1,600-mg/day (n = 29) groups makes it difficult to interpret observed differences in the percentage of patients reporting AEs as dosage related. Furthermore, although the lack of serum carbamazepine concentrations for all patients in this analysis limits data interpretability, a comparison of pharmacokinetic and tolerability data for patients in bioequivalence trial OV-1015 is available.[15] Data from the bioequivalence trial show that postinfusion plasma concentrations of carbamazepine were similar to that of oral carbamazepine on day 0, and that dizziness was the only AE that increased with more rapid IV carbamazepine infusions, but not temporally with transient maximum plasma concentrations.

Given that SBECD is renally eliminated, the effects of IV carbamazepine infusion in patients with renal impairment and on exploratory biomarkers in all patients were analyzed. In the three patients with moderate renal impairment, none had renal-related issues. Although NAG values increased during infusion in a proportion of patients, the increase was transient and did not appear to have clinically relevant effects. The clinical significance of this transient elevation of NAG is uncertain because this biomarker is not well validated and its utility remains exploratory.[17,18] Overall, there was no evidence of consistent alteration in any of the renal biomarkers during the infusion period in patients with normal renal function or renally impaired patients.

Based on studies with voriconazole (a systemic antifungal treatment) solubilized in SBECD, the clearance of SBECD was significantly decreased in patients with moderate-to-severe renal impairment, resulting in substantially greater SBECD exposures in these patients compared with patients with normal renal function.[14] In our pooled analysis, exposure to SBECD at the greatest dosages studied was not associated with a clinically relevant pattern of change in AEs or renal function. Although there were only three patients with moderate renal impairment in this pooled analysis, these patients did not experience notable differences from those with normal renal function or mild renal impairment. One patient with mild renal failure experienced an increase in serum creatinine level, which demonstrated improvement prior to the end of the study.

Based on a review of AE data and seizure monitoring during the confinement period, seizure control was generally unchanged as patients transitioned from a stable oral carbamazepine regimen to IV carbamazepine at a dosage approximately equal to 70% of the patient's prescribed oral total daily dose. This observation suggests that seizure control would not be compromised during a short-term switch to IV carbamazepine when oral administration is not feasible, although more data would be required to confirm this. An IV carbamazepine formulation would fulfill an important treatment need for patients who have achieved seizure control with oral carbamazepine but for whom oral administration is temporarily not feasible.

In conclusion, this pooled analysis of two open-label studies of IV carbamazepine demonstrated a favorable tolerability profile in a limited number of patients. The AE profile among the different infusion duration groups was similar to that for oral carbamazepine with the exception of infusion-site reactions, which were generally mild and transient. It is notable that the solubilizing agent SBECD did not appear to be associated with additional AEs. Seizure control was maintained during the switch between formulations. These pooled tolerability data demonstrate that IV carbamazepine could offer a safe option for those patients who receive oral carbamazepine, but who require short-term replacement with an IV carbamazepine formulation, thereby maintaining the continuity of care. The new drug application (NDA) for this product is currently under review by the FDA.

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Conflict of Interest

This study was funded by Lundbeck LLC (Deerfield, IL). Drs. Lee, Kalu, Peng, Dheerendra, and Tolbert are employees of Lundbeck LLC. Dr. Bekersky was an employee of Lundbeck LLC at the time this study was conducted. Dr. Halford is a paid consultant and has received grant funding from Lundbeck LLC. Dr. Biton is currently a clinical research investigator for Accera, Inc., Eisai Co., Ltd., Forum Pharmaceuticals, Lundbeck LLC, Marinus Pharmaceuticals, Inc., Pfizer, Inc., SK Life Science Inc., Sunovion Pharmaceuticals Inc., UCB Inc., and Upsher-Smith Laboratories, Inc., and

has received consulting/lecture fees from Avigen Inc., Eisai Co., Ltd., GlaxoSmithKline plc, Icagen, Inc., Jazz Pharmaceuticals plc, Lundbeck LLC, Merck & Co., Inc., Ortho-McNeil-Janssen Pharmaceuticals, Inc., Pfizer, Inc., UCB Inc., Upsher-Smith Laboratories, Inc., and Valeant Pharmaceuticals International, Inc. Dr. Cloyd has royalty agreements with Lundbeck LLC (IV carbamazepine), and the University of Minnesota and Ligand Pharmaceuticals, Inc. (IV topiramate), as well as a licensing agreement with the University of Minnesota and Allaysis, LLC (IV baclofen). Dr. Cloyd has received grants from Allaysis, LLC, and has consulting agreements with Upsher Smith Laboratories, Inc., and CURx Pharmaceuticals, Inc. Dr. Klein has participated in clinical trials sponsored by Eisai Co., Ltd., GlaxoSmithKline plc, Lundbeck LLC, SK Life Science Inc., Sunovion Pharmaceuticals Inc., and UCB Inc., and is on the speaker's bureau for Eisai Co., Ltd, Sunovion Pharmaceuticals Inc., and UCB Inc., and has served on advisory boards of Accorda Therapeutics, Eisai Co., Ltd., and Sunovion Pharmaceuticals Inc. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. List of institutional review boards (IRBs).

Table S2. List of MedDRA high-level terms and preferred terms of special interest (cardiovascular-, convulsion-, infusion-site reaction, or renal-related).