Clinical Pharmacology
in Drug Development
2022, 11(7) 878–888

DOI: 10.1002/cpdd.1107

# Intravenous Perampanel as an Interchangeable Alternative to Oral Perampanel: A Randomized, Crossover, Phase I Pharmacokinetic and Safety Study

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## Abstract

Intravenous (IV) drug administration enables treatment of epilepsy when oral administration is temporarily not feasible. Perampanel is a once-daily antiseizure medication currently available as oral formulations. Study 050 (NCT03376997) was an open-label, randomized, single-dose, crossover study to evaluate the interchangeability of oral and IV perampanel in healthy subjects (N = 48). Bioequivalence of single 12-mg doses of IV (30-, 60-, or 90-minute infusion) and oral perampanel, ≥6 weeks apart, was assessed. Analyses indicated bioequivalence of area under the plasma concentration–time curve extrapolated to infinity for 30- and 60-minute IV infusions and oral perampanel doses (geometric mean ratio [90% confidence interval], 0.93 [0.84–1.02] and 1.03 [0.97–1.09], respectively); however, IV maximum observed drug concentration ($C_{max}$) values were 1.35- to 1.61-fold higher than $C_{max}$. Simulated plasma concentration–time profiles using pooled pharmacokinetic data further supported oral and IV perampanel interchangeability in two scenarios: 12-mg per day IV dosing during a temporary 7-day switch from oral steady-state maintenance therapy, and treatment initiation with 2-mg perampanel. Thirty-four (70.8%) subjects experienced treatment-related adverse events. The IV perampanel safety profile was similar to that of oral perampanel without new safety concerns. Perampanel IV infusions may be a suitable temporary alternative to oral perampanel for treatment maintenance and/or initiation.



## Keywords

antiseizure medication, bioavailability/bioequivalence, epilepsy, intravenous, perampanel


Antiseizure medications (ASMs) are considered to be the primary option for the treatment of epilepsy, and with appropriate ASM use, seizure control could be possible in up to 70% of the estimated 50 million patients with epilepsy worldwide.[1,2] Considering the potential dangers associated with epileptic seizures, such as risk of injury and sudden unexpected death in epilepsy,[3–5] it is crucial that seizure control is maintained in patients. However, seizure control may be difficult in situations where the patient is unable to receive their ASM treatment orally. Nonoral formulations of ASMs, including intravenous (IV) formulations, can be used in clinical emergencies, such as when the patient is unconscious or experiencing acute seizure clusters or status epilepticus.[6–9] Nonoral formulations are also beneficial for maintaining therapy to control seizures when oral dosing is not feasible, such as when patients are undergoing surgical procedures or have difficulty swallowing.[6,7,9] Among nonoral ASM formulations, IV formulations of ASMs including phenytoin, brivaracetam, levetiracetam, and lacosamide are available,[10–14] and IV benzodiazepines can be used for treating acute seizures and status epilepticus[15]; for example, IV diazepam can stop seizures in about 75% of patients with status epilepticus.[15] Being able to administer the same ASM via oral and nonoral routes offers flexibility for

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Submitted for publication 5 November 2021; accepted 29 March 2022.

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a variety of clinical situations.[7] Furthermore, formulations that can be administered at the same dose orally and intravenously, thus removing the need for any dose conversion, would be advantageous.

Perampanel, a selective, noncompetitive $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is a once-daily oral ASM for focal-onset seizures (previously known as partial-onset seizures) and generalized tonic-clonic seizures (previously known as primary generalized tonic-clonic seizures).[16–19] Perampanel has been shown to potently inhibit AMPA–induced increases in intracellular free $Ca^{2+}$ concentrations ($[Ca^{2+}]i$) in cultured rat cortical neurons but not N-methyl-D-aspartate (NMDA)-induced $[Ca^{2+}]i$ changes, suggesting that perampanel does not have strong affinity for the NMDA receptor for glutamate.[16] Thus, perampanel may help avoid the psychoactive effects associated with NMDA receptor inhibitors, such as phencyclidine or ketamine.[16,20] Currently, perampanel is clinically available as 2-, 4-, 6-, 8-, 10-, and 12-mg oral tablets, as well as an oral suspension (0.5 mg/mL) and fine granules (1%), and is rapidly absorbed after oral administration, with a median time to peak concentration of 0.5 to 2.5 hours under fasted conditions.[21–23] Plasma concentrations of perampanel have been shown to increase in direct proportion to administered doses over the clinically relevant dose range of up to 12 mg per day.[23] Perampanel metabolism via primary oxidation and sequential glucuronidation occurs predominantly in the liver, primarily via cytochrome P450 (CYP) 3A (CYP3A4 and/or CYP3A5) and to a lesser degree by CYP1A2 and CYP2B6.[23,24] The rate of perampanel metabolism is slow, with a mean elimination half-life of $\approx$105 hours in healthy subjects.[23] Pharmacokinetic (PK) studies have revealed that perampanel is sensitive to interactions with strong and moderate inducers of CYP3A (eg, carbamazepine, phenytoin, and oxcarbazepine), which increase perampanel clearance and reduce perampanel plasma and serum concentrations.[23,25] Short-term coadministration of ketoconazole, a strong CYP3A inhibitor, does not substantially increase perampanel exposure; however, an increase may be expected with chronic exposure to other strong CYP3A inhibitors, such as stiripentol.[25,26] Because patients with refractory epilepsy are often treated with multiple ASMs,[27] perampanel has also been studied with regard to its effect on the clearance of other ASMs. In patients with focal-onset seizures, adjunctive perampanel treatment does not exhibit a significant effect on the clearance of ASMs, including clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, and zonisamide, and was noted to have a small but not clinically relevant effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid.[28] The clinical development of perampanel included multiple phase III randomized, double-blind, placebo-controlled studies, in which oral perampanel (up to 12 mg/day) demonstrated clinical efficacy and favorable tolerability.[17–19,29]

There is a clinical need for an IV formulation of perampanel that can be used interchangeably with the approved oral formulations (tablet and suspension; a fine granule formulation is also approved in Japan) to enable initiation or maintenance of perampanel therapy in situations where oral administration is temporarily not feasible. As such, an open-label, randomized, crossover study was designed to evaluate the PK, safety, and tolerability of perampanel when administered as a single 12-mg dose IV infusion, relative to a single 12-mg dose as oral tablet. Bioavailability was investigated for IV infusion durations of 30, 60, and 90 minutes, which were selected on the basis of prior modeling analyses that identified IV regimens with perampanel maximum observed drug concentration ($C_{max}$) and area under the plasma concentration–time curve (AUC) comparable to that following oral administration. The results of this study are presented in this report. Modeling and simulation analysis was also carried out to further support the interchangeability of oral and IV formulations of perampanel in two treatment scenarios: steady-state maintenance therapy and treatment initiation.

## Methods

### Clinical Study

*Study Design.* Study 050 was an open-label, randomized, single-dose, crossover, phase I study (protocol E2007-A001-050; ClinicalTrials.gov identifier: NCT03376997) in healthy subjects conducted between November 8, 2017, and February 16, 2018, at a single site in the United States.

The study was performed in accordance with the Declaration of Helsinki, International Council for Harmonization E6 Guideline CPMP/ICH/135/95, and the US Code of Federal Regulations Title 21. The trial protocol, amendments, and informed consent were reviewed by the institutional review board (Austin, Texas). Before trial participation, all subjects gave written informed consent. The study was carried out at Anaheim Clinical Trials, LLC (Anaheim, California).

The primary objective was to evaluate the bioavailability of a single 12-mg dose of perampanel IV infusion relative to a single 12-mg oral tablet of perampanel. The safety and tolerability of perampanel (12 mg) following a single IV infusion (30-, 60-, or 90-minute) or a single administration of perampanel oral tablet was evaluated as a secondary objective.

**Table 1.** Demographics at Study Screening (Safety Analysis Set)

| | Arm 1 30-min IV infusion (n = 20) | Arm 2 60-min IV infusion (n = 20) | Arm 3 90-min IV infusion (n = 8) | Overall (N = 48) |
|---|---|---|---|---|
| Mean age, y (SD) | 37.0 (10.6) | 39.4 (9.0) | 43.1 (5.7) | 39.0 (9.4) |
| Sex, n (%) | | | | |
| Male | 9 (45.0) | 11 (55.0) | 5 (62.5) | 25 (52.1) |
| Female | 11 (55.0) | 9 (45.0) | 3 (37.5) | 23 (47.9) |
| Race, n (%) | | | | |
| White | 10 (50.0) | 5 (25.0) | 0 (0.0) | 15 (31.3) |
| Black or African American | 4 (20.0) | 7 (35.0) | 3 (37.5) | 14 (29.2) |
| Asian | 6 (30.0) | 8 (40.0) | 5 (62.5) | 19 (39.6) |
| Mean BMI, kg/m$^2$ (SD) | 25.0 (3.3) | 26.3 (3.8) | 23.4 (3.5) | 25.3 (3.6) |

BMI, body mass index; IV, intravenous; SD, standard deviation.

*Subjects.* Healthy subjects were eligible to participate if they were 20 to 55 years of age at the time of informed consent, with a body mass index of 18–32 kg/m$^2$. Key exclusion criteria included: pregnancy, clinically significant illness requiring medical treatment within 8 weeks of dosing, clinically significant infection (requiring medical treatment) or disease (eg, psychiatric, gastrointestinal, renal, hepatic, cardiac, respiratory, endocrine, or hematologic) that may influence the outcome of the study within 4 weeks of dosing, history of gastrointestinal surgery that may affect PK profiles of perampanel, any clinically abnormal symptom found at screening via medical history or physical examination, and drug or alcohol dependence within the previous 2 years.

Overall, 48 subjects were allocated into the three perampanel IV infusion arms and were included in the safety analysis and PK analysis sets (30-minute infusion, n = 20; 60-minute infusion, n = 20; 90-minute infusion, n = 8; Figure S1). Four subjects discontinued the study for reasons of being lost to follow-up (n = 2), adverse event (AE; n = 1; onset 42 days after dosing and therefore not considered to be treatment emergent), and withdrawal of consent (n = 1). Subject demographics were generally similar across IV infusion arms (Table 1). Overall, 52.1% of the healthy subjects were men, 39.6% were Asian, mean age was 39.0 years, and mean body mass index was 25.3 kg/m$^2$ (Table 1).

*Study Procedures.* The study consisted of a pretreatment phase (days –28 to –1) and a treatment phase (Figure 1). The pretreatment phase comprised the screening period (days –28 to –2) and the baseline period (day –1). The treatment phase comprised two treatment periods; subjects were randomized on day 1 of treatment period 1 (days 1 to 22) to receive either a single 12-mg dose of perampanel IV infusion (administered as a 30-, 60-, or 90-minute infusion) or a single 12-mg oral tablet, administered after an overnight fast (≥10 hours); no food was permitted for at least 4 hours after dosing. The alternative treatment (IV or oral perampanel) was received on day 43 of treatment period 2 (days 42 to 64), following baseline period 2 on day 42. The two treatment periods were separated by a ≥6-week washout period. Within each IV infusion arm (30, 60, or 90 minutes), subjects were randomly allocated (1:1) to one of two treatment sequences (oral followed by IV perampanel, or IV followed by oral perampanel) according to a computer-generated randomization schedule. Subjects resided at the research site from days –1 to 4 of treatment period 1 and days 42 to 46 of treatment period 2. Outpatient assessments occurred on days 6, 8, 15, and 22 of treatment period 1 and days 48, 50, 57, and 64 of treatment period 2.

*Sample Size Calculation.* The study planned to enroll a total of 48 subjects, with 20 planned for each of the 30- and 60-minute IV infusion arms and 8 subjects planned for the 90-minute IV infusion arm. Sample size determination for 30- and 60-minute infusions was based on within-subject standard deviation (SD) values for perampanel $C_{max}$ (log scale) of 0.181 and 0.26 derived from two previous PK studies (NCT02279485 [fasted arm] and NCT01396590, respectively). With a natural log scale SD of 0.22 and a sample size of 18 subjects, two-sided 90% confidence intervals (CIs) for the ratio for $C_{max}$ would extend 0.121 from the observed mean difference equating to –11.4% and +12.9% for $C_{max}$ of the observed ratio on the original scale. To conclude bioequivalence for either 30- or 60-minute infusions, assuming a true ratio of 1 and a within-subject SD (log scale) for $C_{max}$ of 0.22, a sample size of 18 was anticipated to provide ≈80% power. For the 90-minute infusion (n = 6; exploratory), two-sided 90%CIs for the ratio for $C_{max}$ would extend 0.209 from the observed mean difference equating to –18.9% and +23.2% for $C_{max}$ of the observed ratio on the original scale.

*PK and Statistical Calculations.* The PK analysis was performed using the PK analysis set (all subjects with sufficient data to derive at least 1 PK

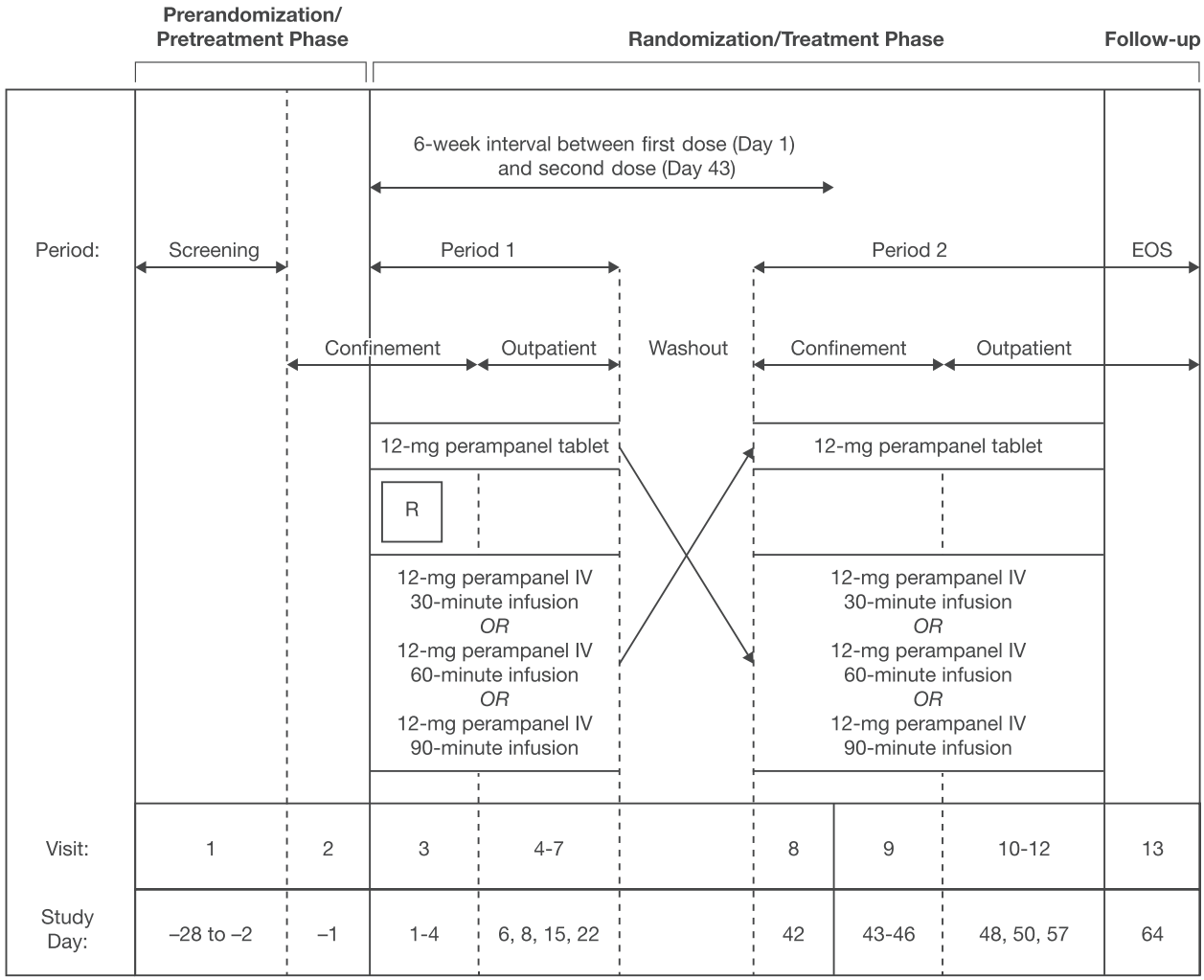


**Figure 1.** Clinical study design. EOS, end of study; IV, intravenous; R, randomization.

parameter). Blood samples for PK assessment (6 mL) were collected before and after dosing on days 1 to 4, 6, 8, 15, and 22 during treatment period 1 and on days 43 to 46, 48, 50, 57, and 64 during treatment period 2. Post-dose samples were collected at the following time points: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, and 12 hours on all dosing days. The following additional post-dose samples were collected on specific days: 24 and 36 hours (days 2 and 44), 48 hours (days 3 and 45), 72 hours (days 4 and 46), 120 hours (days 6 and 48), 168 hours (days 8 and 50), 336 hours (days 15 and 57), and 504 hours (days 22 and 64). For the treatment period with the IV infusion, blood samples for PK assessment at the 0.5, 1, and 1.5 hours post-dose time points were collected ≈2 minutes after the end of the 30-, 60-, and 90-minute infusions, respectively, and from the opposite arm.

Perampanel plasma concentrations were quantified via liquid chromatography coupled with tandem mass spectrometry. Perampanel was extracted from human plasma (treated with sodium heparin) by protein precipitation using methanol. A perampanel-associated analog substance was used as the internal standard. Reversed-phase high-performance liquid chromatography separation was achieved with a Unison UK-C8 column (50 × 4.6 mm, 3$\mu$m; Imtakt, Portland, Oregon). Tandem mass spectrometry detection was set at mass transitions of $m/z$ 350.0→219.1 for perampanel and $m/z$ 359.0→323.1 for the internal standard in turbo ion spray–positive mode. Precision (percent coefficient of variation) for intraday was <6.5% and interday was <5.6%. Accuracy (percent nominal) for intraday and interday ranged from 91.8% to 100.4% and 94.6% to 98.0%. The lower limit of quantitation was 1 ng/mL in human plasma. PK parameters were derived via noncompartmental analysis using Phoenix WinNonlin version 6.3 (Certara, Princeton, New Jersey), and included $C_{max}$, AUC extrapolated to infinity ($AUC_{0\text{-inf}}$), AUC to the last quantifiable concentration ($AUC_{(0\text{-t})}$), AUC to 72 hours after dosing, time of maximum concentration

($t_{max}$), terminal elimination half-life ($t_{1/2}$), apparent total body clearance (CL), and apparent volume of distribution ($V_d$; calculated by the area method).

*Analysis of Bioequivalence (BE).* Primary perampanel PK parameters ($C_{max}$ and $AUC_{0\text{-inf}}$) were compared between single doses of each of the 12-mg IV infusion durations and 12-mg oral tablet separately, using a mixed linear model of logarithmically transformed values, with fixed effects for treatment and period, and a random effect of subject. Two-sided 90%CIs for the geometric mean ratio of primary PK parameters for IV vs oral perampanel were estimated; if each of the two-sided 90%CIs fell within 80% to 125%, it was concluded that the 12-mg IV infusion and 12-mg tablet were bioequivalent. Absolute oral bioavailability (F) was calculated in a post hoc analysis, and was defined as $AUC_{0\text{-inf,oral}}/AUC_{0\text{-inf,IV}}$.

*Modeling and Simulation Analysis.* To improve the estimate of intersubject variability, PK data from the current study were pooled with PK data from healthy subjects who received a single oral dose of 12-mg perampanel under fasted conditions in an open-label, two-arm, single-dose, randomized, crossover, phase I study (protocol E2007-A001-048; NCT02279485).[30] A total of 2754 PK observations were included from 97 subjects. A three-compartment disposition model was fitted to the pooled PK data and used to simulate PK profiles using NONMEM version 7.3 (ICON plc, Dublin, Ireland). Two treatment scenarios were evaluated: scenario 1, switch between oral and IV dosing during steady-state maintenance therapy; and scenario 2, treatment initiation with IV dosing. For scenario 1 (steady-state switch), simulations involved 20 replicates of 50 subjects each treated with 12-mg tablets for 28 days before switching to a 12-mg 30-, 60-, or 90-minute IV infusion for 7 days (days 29 to 35) and then back to oral dosing at the same dose (day 36). Parameters derived following steady-state oral tablet administration on day 28 were used as the reference to represent subjects maintained on an oral dose. $C_{max}$ at steady state ($C_{ss,max}$), minimum observed drug concentration at steady state ($C_{ss,min}$) and AUC at steady state ($AUC_{ss}$) for the first and seventh IV infusions (days 29 and 35, respectively), as well as following the switch back to oral tablets, were compared with those on reference day 28. In scenario 2 (treatment initiation), simulations included a total of 200 subjects, comprising 50 subjects for each of the following treatments: a single 2-mg oral dose, a single 2-mg 30-minute IV infusion, a single 2-mg 60-minute IV infusion, or a single 2-mg 90-minute IV infusion. $C_{max}$ was compared for treatment initiation with IV vs oral perampanel.

*Clinical Safety Assessments.* Clinical safety assessments were based on the safety analysis set, which included subjects who received at least 1 dose of perampanel and had at least 1 post-dose safety assessment. Safety assessments included: monitoring and recording of AEs and serious AEs; laboratory evaluations for hematology (hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential); blood chemistry (including electrolytes, liver function markers [alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin]; and renal function markers [blood urea/blood urea nitrogen, creatinine]), urinalysis (bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells); and periodic measurement of vital signs (blood pressure, pulse, respiratory rate, and body temperature), body weight, electrocardiograms, and physical examinations.

## Results

### Clinical Study

*PK and BE Outcomes.* The mean plasma concentration–time profiles of perampanel over 4 and 72 hours after a single dose of the IV and oral formulations are shown in Figure 2. Plasma perampanel PK parameters for both IV and oral dosing are summarized in Table 2 for each of the three treatment groups. Following a single IV 12-mg dose, perampanel plasma concentrations peaked at the end of the infusion period with a median $t_{max}$ of ≈0.5, 1.0, and 1.5 hours after dosing for the 30-, 60-, and 90-minute IV infusions, respectively; following oral 12-mg dosing, $t_{max}$ was 0.9 to 1.3 hours (Table 2). Mean $t_{1/2}$ for the 30-, 60-, and 90-minute IV infusions (133, 116, and 97.8 hours, respectively) was comparable to that for oral dosing (129, 124, and 111 hours, respectively). For IV dosing, CL ranged from 0.524 to 0.633 L/h, and apparent volume of distribution ranged from 69.5 to 95.2 L. Mean bioavailability of perampanel was calculated to be 1.1, 1.0, and 1.0, based on the 30-, 60-, and 90-minute IV infusions, respectively.

Following single-dose administration, 90%CIs for the geometric mean ratio of $AUC_{0\text{-inf}}$ for the 30- and 60-minute IV infusions vs the oral tablet were each within the BE criteria of 80% to 125%, indicating BE for this parameter (Table 3). For the 90-minute infusion, the 90%CI for the geometric mean ratio of $AUC_{0\text{-inf}}$ for the IV infusion vs the oral tablet was outside of the BE criteria, though the planned smaller sample size in this arm should be noted here. Overall, mean $C_{max}$ values for the 30-, 60-, and 90-minute IV infusions were 1.61-, 1.35-, and 1.06-fold higher than those observed for the oral tablet, and the corresponding 90%CIs fell outside of the BE bounds (Table 3).

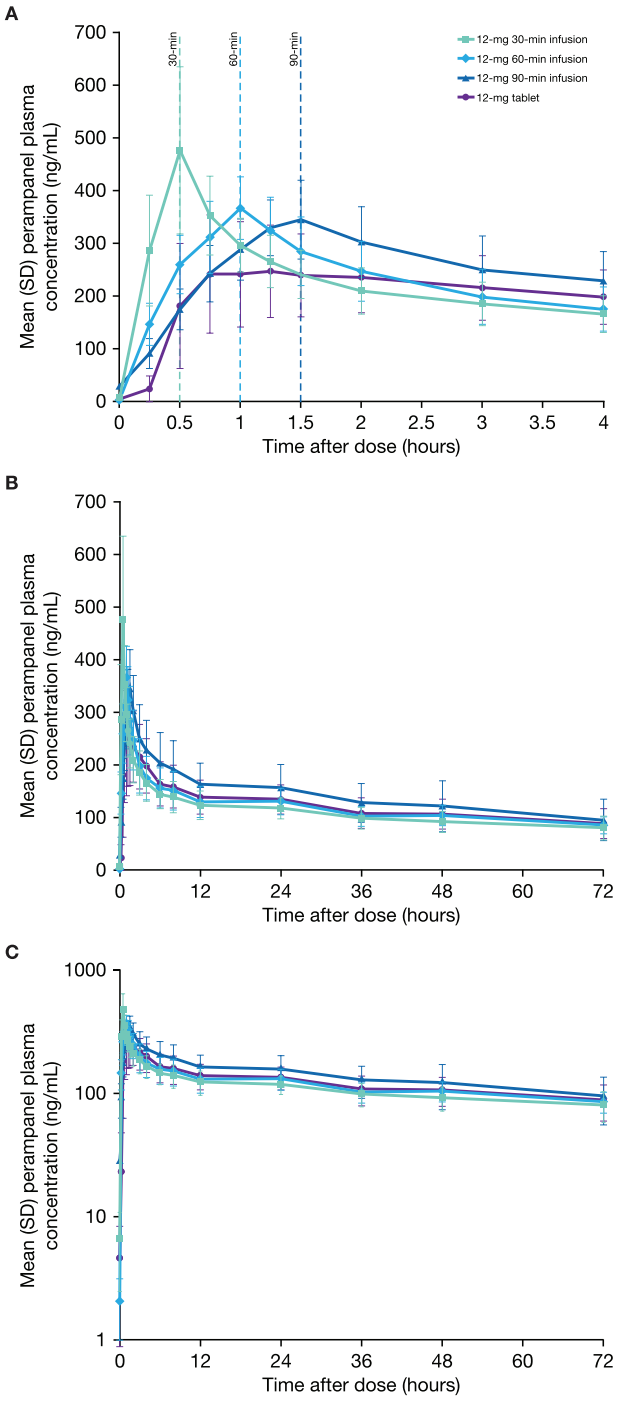


**Figure 2.** Mean (SD) plasma concentration–time profiles of perampanel following single 12-mg IV infusions (30, 60, and 90 minutes) and 12-mg oral tablet administration over (A) 4 hours and (B, C) 72 hours after initiation of dosing. IV, intravenous; SD, standard deviation.

## Modeling and Simulation

*Scenario 1: Switch From Steady-State Oral Dosing to IV Dosing of Perampanel.* Simulated perampanel plasma concentration–time profiles for the first and seventh IV infusions (days 29 and 35) compared with steady-state oral dosing (day 28), and for restarted oral tablet dosing on day 36 vs steady-state oral dosing (day 28) are shown in Figure 3. Forest plots of $C_{ss,max}$ geometric means and associated two-sided 90%CIs are presented in Figure S2, and show that for the 60- and 90-minute infusions, all replicates were within the 0.8 to 1.25 BE bounds. For the 30-minute infusion, 19 of 20, 11 of 20, and 20 of 20 replicates had 90%CIs within the 0.8 to 1.25 BE bounds for days 29, 35, and 36, respectively. $C_{ss,min}$ and $AUC_{ss}$ 90%CIs for 30-, 60-, and 90-minute infusions demonstrated BE to day 28 for all 20 replicates in each simulation on days 29, 35, and 36 (data not shown).

*Scenario 2: Treatment Initiation With IV Dosing of Perampanel.* Treatment initiation simulations with single 2-mg IV infusions or a 2-mg oral dose of perampanel were performed to evaluate treatment initiation with either IV or oral formulations using this recommended starting dose. The simulations showed 1.7-, 1.3-, and 1.2-fold higher geometric mean $C_{max}$ values following IV infusions of 30-, 60-, and 90-minutes, respectively, compared with the oral tablet (geometric mean $C_{max}$ [95%CI] of 86.1 [55.9–119.1], 68.6 [42.9–96.9], and 63.6 [39.7–89.8] vs 51.0 [14.1–95.3] ng/mL, respectively). Predicted concentration–time profiles for 2-mg IV infusions vs the 2-mg single oral dose are shown in Figure S3.

*Clinical Safety Outcomes.* A total of 37 (77.1%) subjects reported treatment-emergent AEs (TEAEs) and 34 (70.8%) reported treatment-related TEAEs (Table 4). All treatment-related TEAEs were mild (n = 34) or moderate (n = 2: lethargy and somnolence in subjects receiving the 60-minute IV infusion), and there were no deaths or serious TEAEs. Furthermore, no subjects discontinued the study due to a TEAE. Incidences of TEAEs were similar across all durations of IV infusion and oral tablet administration (Table 4). The most common TEAEs were dizziness (n = 29 [60.4%]) and lethargy (n = 11 [22.9%]) (Table 4). No treatment-related infusion-site reactions were reported.

No clinically significant changes over time in mean vital signs (blood pressure, pulse, respiratory rate, and body temperature) or electrocardiogram parameters were reported with any administration of perampanel. Mean change from baseline for systolic blood pressure, diastolic blood pressure, and pulse at 30, 60, 90, and 120 minutes and 4 days after dosing are shown in Figure S4, and indicate minimal changes in these parameters. Likewise, there were no changes of clinical importance in mean laboratory values over time, including the hepatic function markers, alanine aminotransferase and alkaline phosphatase, and the renal function marker, creatinine (Table S1).

**Table 2.** Summary of Plasma PK Parameters of Perampanel after Single 12-mg Oral and 12-mg IV Dosing in Healthy Subjects (PK Analysis Set)

| | $C_{max}$, ng/mL | $t_{max}$, h | $AUC_{0-inf,}$ ng • h/mL | $t_{1/2}$, h | CL, L/h | $V_d$, L | F |
|---|---|---|---|---|---|---|---|
| *Single oral dose vs 30-min infusion* | | | | | | | |
| Oral (n = 20) | 296 (99.9) | 1.00 (0.53–4.00) | 24 900 (10 100)[a] | 129 (52.4)[a] | … | … | 1.1 (0.2)[a] |
| 30-min IV infusion (n = 19) | 477 (158) | 0.53 (0.53–0.75) | 24 500 (10 300)[b] | 133 (56.0)[b] | 0.605 (0.4)[b] | 95.2 (29.4)[b] | |
| *Single oral dose vs 60-min infusion* | | | | | | | |
| Oral (n = 19) | 281 (70.3) | 1.25 (0.50–3.00) | 24 900 (7800)[c] | 124 (46.3)[c] | … | … | 1.0 (0.1)[h] |
| 60-min IV infusion (n = 19) | 368 (57.6) | 1.03 (0.75–1.03) | 25 300 (7940)[d] | 116 (46.6)[d] | 0.524 (0.2)[d] | 78.5 (18.6)[d] | |
| *Single oral dose vs 90-min infusion* | | | | | | | |
| Oral (n = 8) | 330 (84.7) | 0.88 (0.50-2.02) | 21 800 (12 300)[e] | 111 (65.2)[e] | … | … | 1.0 (0.2)[i] |
| 90-min IV infusion (n = 6) | 354 (71.7) | 1.53 (1.25-1.53) | 23 400 (13 900)[f] | 97.8 (68.6)[f] | 0.633 (0.3)[f] | 69.5 (15.2)[f] | |

$AUC_{0-inf}$, area under the plasma concentration–time curve extrapolated to infinity; CL, apparent total body clearance; $C_{max}$, maximum observed drug concentration; F, absolute oral bioavailability; IV, intravenous; PK, pharmacokinetic; $t_{max}$, time of maximum concentration; $t_{1/2}$, terminal elimination half-life; $V_d$, apparent volume of distribution.

All values are arithmetic mean (standard deviation) except for $t_{max}$, which is shown as median (range). $AUC_{0-inf}$, $t_{1/2}$, CL, and $V_d$ values were not reported where the terminal elimination rate constant could not be estimated.

[a]n = 15; [b]n = 15; [c]n = 17; [d]n = 18; [e]n = 6; [f]n = 5; [g]n = 14; [h]n = 17; [i]n = 4.

**Table 3.** Statistical Analysis Comparing Perampanel Administered as Single 12-mg IV Infusions Over 30, 60, or 90 minutes with a Single 12-mg Oral Tablet (PK Analysis Set)

| Infusion duration (min) | PK parameter | Geometric LS mean | | | | GMR | 90%CI of GMR |
|---|---|---|---|---|---|---|---|
| | | Tablet | | Infusion | | | |
| 30 | $C_{max}$ (ng/mL) | 281 | n = 20 | 452 | n = 19 | 1.61 | 1.37–1.90 |
| | $AUC_{0-inf}$ (ng • h/mL) | 23 320 | n = 15 | 21 570 | n = 15 | 0.93 | 0.84–1.02 |
| 60 | $C_{max}$ (ng/mL) | 271 | n = 19 | 366 | n = 19 | 1.35 | 1.23–1.49 |
| | $AUC_{0-inf}$ (ng • h/mL) | 23 452 | n = 17 | 24 117 | n = 18 | 1.03 | 0.97–1.09 |
| 90 | $C_{max}$ (ng/mL) | 321 | n = 8 | 342 | n = 6 | 1.06 | 0.88–1.29 |
| | $AUC_{0-inf}$ (ng • h/mL) | 21 008 | n = 6 | 22 122 | n = 5 | 1.05 | 0.77–1.43 |

$AUC_{0-inf}$, area under the plasma concentration–time curve extrapolated to infinity; CI, confidence interval; $C_{max}$, maximum observed drug concentration; GMR, geometric mean ratio; IV, intravenous; LS, least squares; PK, pharmacokinetic.

## Discussion

The clinical study reported here was designed to compare the relative bioavailability of a single 12-mg IV dose of perampanel (as a 30-, 60-, or 90-minute infusion) vs a single 12-mg oral dose in healthy subjects. Following single-dose administration, BE between the 30- and 60-minute IV infusions and the oral tablet was demonstrated for $AUC_{0-inf}$, indicating that the two formulations provide equivalent perampanel exposures when administered at the same dose during maintenance treatment. Whilst the observed mean $AUC_{0-inf}$ following the 90-minute IV infusion was comparable to that after administration of the oral tablet (geometric mean ratio of $AUC_{0-inf}$, 1.05), the 90%CI of geometric mean ratio did not meet the prespecified BE criteria of 80% to 125%. This discrepancy may be due to the small number of subjects enrolled in this arm. On the other hand, BE of IV and oral formulations for $C_{max}$ was not demonstrated given that the observed 90%CIs fell outside the 0.8 to 1.25 acceptance bounds, with $C_{max}$ values 61%, 35%, and 6% higher than the oral tablet for 30-, 60-, and 90-minute infusions, respectively. Mean F was close to or equal to 1 based on all three IV infusion durations.

The modeling and simulation analyses were designed to provide further insight into the interchangeability of oral and IV formulations of perampanel in two clinical scenarios. The first scenario examined a temporary switch from steady-state 12-mg oral dosing to 12-mg IV dosing for a defined period of time (7 days) before reverting to oral dosing. This scenario represents a situation where a patient maintained well on oral perampanel treatment needs to temporarily discontinue oral intake, for example, to undergo surgery. On the first day of IV perampanel administration (day 29), the simulated $AUC_{ss}$ and $C_{ss,min}$ was

**Table 4.** Overview of TEAEs and Most Common TEAEs (Occurring in ≥5% of Subjects in Any Treatment Arm) Following a Single 12-mg Oral or IV Dose of Perampanel (Safety Analysis Set)

| | | IV infusion | | | |
|---|---|---|---|---|---|
| | Oral tablet (n = 47) | 30 min (n = 19) | 60 min (n = 19) | 90 min (n = 7) | Overall[a] (N = 48) |
| Any TEAEs, n (%) | 28 (59.6) | 10 (52.6) | 11 (57.9) | 4 (57.1) | 37 (77.1) |
| Any treatment-related TEAEs, n (%) | 25 (53.2) | 10 (52.6) | 11 (57.9) | 3 (42.9) | 34 (70.8) |
| Most common (≥5% subjects in any treatment arm) TEAEs, n (%) | | | | | |
| Dizziness | 20 (42.6) | 7 (36.8) | 8 (42.1) | 3 (42.9) | 29 (60.4) |
| Lethargy | 2 (4.3) | 5 (26.3) | 3 (15.8) | 1 (14.3) | 11 (22.9) |
| Nausea | 3 (6.4) | 2 (10.5) | 1 (5.3) | 0 (0.0) | 4 (8.3) |
| Constipation | 2 (4.3) | 2 (10.5) | 0 (0.0) | 0 (0.0) | 4 (8.3) |
| Headache | 3 (6.4) | 0 (0.0) | 1 (5.3) | 2 (28.6) | 4 (8.3) |
| Dry mouth | 2 (4.3) | 0 (0.0) | 1 (5.3) | 0 (0.0) | 3 (6.3) |
| Diarrhea | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) | 1 (2.1) |
| Hypoesthesia | 0 (0.0) | 1 (5.3) | 0 (0.0) | 0 (0.0) | 1 (2.1) |
| Somnolence | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) | 1 (2.1) |
| Upper respiratory tract infection | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) | 1 (2.1) |
| Vomiting | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) | 1 (2.1) |

IV, intravenous; TEAE, treatment-emergent adverse event.
[a] Overall refers to both Treatment Periods (oral and IV) combined.

found to be bioequivalent to steady-state oral dosing on day 28 for all 3 infusion durations. The $C_{ss,max}$ values on day 29 were within the BE bounds for the 60- and 90-minute infusions, and for 19 of 20 replicates of the 30-minute infusion (the upper 90% confidence limit for one replicate was slightly above the BE bounds). These findings suggest that perampanel exposure would remain steady immediately following switch from oral to IV dosing, despite the change in administration method. Following 7 days of IV administration (day 35), the simulated $AUC_{ss}$ and $C_{ss,min}$ remained bioequivalent to oral steady-state dosing on day 28 for all three infusion durations, with no evidence of perampanel accumulation during this time. $C_{ss,max}$ was also within BE bounds for the 60- and 90-minute infusions following 7 days of IV dosing, though the 30-minute infusion led to $C_{ss,max}$ having the upper 90% confidence limit slightly above the BE bounds in 9 of 20 replicates. However, the clinical benefits of being able to switch from oral to IV maintenance therapy with perampanel, namely, maintaining therapeutic perampanel concentrations with the same perampanel dose and avoiding the need to discontinue oral perampanel and initiate IV treatment with an alternative ASM, will likely outweigh the potential risk of intolerability associated with marginally increased peak perampanel concentrations. If required, longer infusion durations could offer an alternative for patients who do not tolerate an increased concentration as the mean $C_{max}$ following the 90-minute IV infusion was found to be comparable to that after oral dosing in this study (geometric main ratio, 1.06). Thus, these simulations support that 12-mg IV dosing can be used interchangeably with 12-mg oral dosing during steady-state maintenance therapy.

The second simulation scenario reflects perampanel treatment initiation with IV perampanel rather than the standard oral perampanel formulation, which may be required if, for example, a patient is unable to receive oral tablets due to being unconscious. Treatment initiation with 2-mg perampanel showed that perampanel $C_{max}$ was up to ≈70% higher following an initial 2-mg IV infusion compared with the 2-mg oral tablet. However, the 2-mg starting dose is subtherapeutic, with exposures 6- to 20-fold lower than those observed for steady-state therapeutic doses of 4 to 12 mg. Additionally, the clinical administration of the 12-mg IV infusions resulted in AE profiles consistent with that of the 12-mg oral tablet (discussed below). These factors, taken together with the proposal that treatment initiation with IV administration of perampanel would be only for temporary use under close medical supervision, suggest that the simulated ≈70% increase in $C_{max}$ associated with a 2-mg starting dose administered as an IV infusion would be unlikely to lead to any clinically relevant consequences; however, as noted in the steady-state scenario, the longer-duration infusions may offer an alternative for patients where there are concerns about increased $C_{max}$ following IV administration of perampanel.

The perampanel IV infusions had a safety profile similar to that of the oral tablet. The most commonly reported TEAE in healthy subjects following both IV

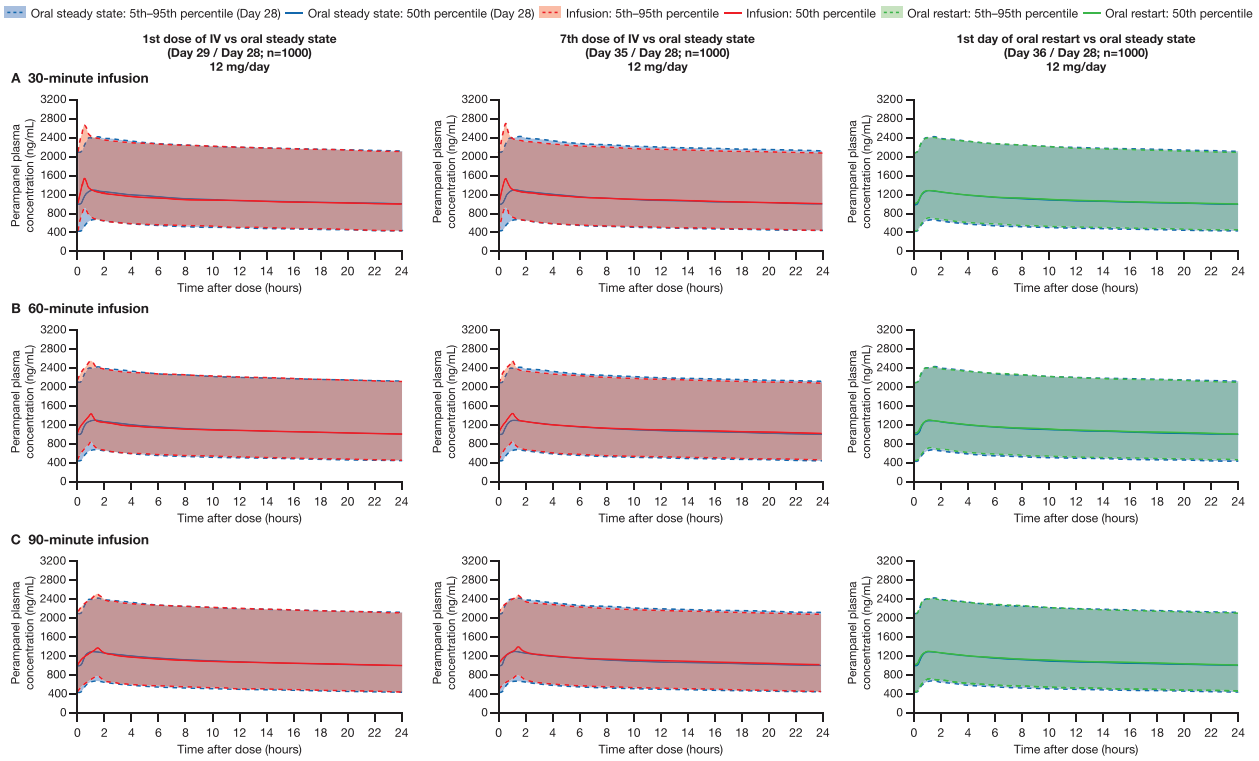


**Figure 3.** Simulated perampanel plasma concentration–time profiles following switching from oral steady state on day 28 to first perampanel 12-mg IV infusion on day 29, seventh perampanel 12-mg IV infusion on day 35, and first day of oral tablet restart on day 36 for (A) 30-minute IV infusions, (B) 60-minute IV infusions, and (C) 90-minute IV infusions, all vs oral tablet at steady state on day 28. IV, intravenous.

and tablet perampanel formulations was dizziness, with lethargy also commonly reported. This is similar to the known safety profile of oral perampanel in patients with epilepsy,[17–19,29,31,32] as well as several other ASMs.[33] In addition, the majority of TEAEs reported here were mild, with no serious TEAEs reported and no clear association between incidence of TEAEs and infusion duration. It has previously been reported that central nervous system AEs may occur more rapidly and with greater severity with IV formulations of ASMs compared with oral formulations.[9] In the current study, no increased incidence of central nervous system AEs, such as headache and dizziness, was observed in healthy subjects who received 30- or 60-minute infusions, compared with the tablet formulation or the 90-minute infusion; however, subject numbers were small and longer-term studies in patients with epilepsy would be required to investigate this aspect further.

Maintaining adequate seizure control is critically important in patients with epilepsy, since seizures may be associated with physical injury[5] and increased risk of sudden unexpected death in epilepsy.[3,4] IV formulations of ASMs may have certain advantages in that they can be administered in clinical emergencies such as in patients rendered unconscious due to status epilepticus. In addition, oral dosing may not always be feasible during maintenance therapy, for example, when a surgical procedure is required or in patients experiencing difficulty swallowing.[9] In these situations, additional IV treatment options are advantageous due to their ease of administration, rapid delivery, and 100% bioavailability.[9] Based on the results presented in the current report, IV perampanel may offer a convenient option for interchangeable administration of the same dose administered orally and intravenously, thus removing the need for dose conversions.

This study does have certain limitations. For example, the study did not assess whether the formulation could be administered over an infusion duration of <30 minutes or as an IV bolus. Additionally, the investigations and simulations reported here were carried out in healthy subjects, although perampanel PK are known to be similar in patients with epilepsy and healthy subjects.[34] The interchangeability of IV and oral perampanel in a treatment maintenance setting has been evaluated in patients who temporarily switched from oral to IV administration of adjunctive perampanel for 4 days and then back to oral perampanel treatment (NCT03754582) and will be reported separately.

## Conclusions

PK data from this study of perampanel in healthy adult subjects, supplemented by modeling and simulation analyses, indicate that perampanel IV and oral formulations are interchangeable at the same dose for steady-state maintenance therapy and treatment initiation, without a need for dose conversion between administration routes. IV infusions also had a similar safety profile to oral tablets. These results support the use of perampanel IV infusions as a suitable alternative to oral perampanel for maintenance and initiation of treatment when oral dosing is temporarily not feasible, including in emergency situations.

## Acknowledgments

The authors thank the study subjects, as well as the study investigators and their teams. The authors also thank Jim Ferry for his role in the study conception and Min-Kun Chang for his role as clinical operations lead for the study. Medical writing support, under the direction of the authors, was provided by Laura George, PhD, on behalf of CMC AFFINITY, McCann Health Medical Communications, funded by Eisai Inc., in accordance with Good Publication Practice (GPP3) guidelines. The data reported in this paper were previously presented at the 71st Annual Meeting of the American Academy of Neurology, Philadelphia, PA, USA, May 4–10, 2019, and the 74th Annual Meeting of the American Epilepsy Society (virtual congress), December 4–8, 2020.

## Conflicts of Interest

Z.H., O.M., and P.B. are employees of Eisai Europe Ltd. J.A., L.Y.N., and L.R. are employees of Eisai Inc. Medical writing support, under the direction of the authors, was provided by Laura George, PhD, on behalf of CMC AFFINITY, McCann Health Medical Communications, funded by Eisai Inc., in accordance with Good Publication Practice (GPP3) guidelines.

## Funding

This study was funded by Eisai Inc.

## Author Contributions

Study conception and/or design: P.B. Data acquisition: J.A., Z.H., and O.M. Data analysis: P.B., O.M., and Z.H. Interpretation of results: J.A., P.B., Z.H., O.M., L.Y.N., and L.R. All authors were involved in the reviewing and approval of the manuscript, and in the decision to submit the article for publication. All authors also confirm accountability for the accuracy and integrity of the work.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.