Received: 8 August 2022 | Revised: 13 September 2022 | Accepted: 13 September 2022

DOI: 10.1111/epi.17411

Epilepsia®

RESEARCH ARTICLE

Time to exceed pre-randomization monthly seizure count for perampanel in participants with primary generalized tonic–clonic seizures: A potential clinical end point

Wesley T. Kerr[1] | **Christian Brandt**[2] | **Leock Y. Ngo**[3] | **Anna Patten**[4] | **Jocelyn Y. Cheng**[3] | **Lynn Kramer**[3] | **Jacqueline A. French**[5]

[1]Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA

[2]Bethel Epilepsy Center, University Hospital for Epileptology, Bielefeld, Germany

[3]Department of Neurology, Eisai Inc., Nutley, New Jersey, USA

[4]Department of Biostatistics, Eisai, Hatfield, UK

[5]Comprehensive Epilepsy Center, New York University, New York City, New York, USA

Correspondence
Wesley T. Kerr, F2597 University Hospital South, 1500 E Medical Center Dr, Ann Arbor, MI 48109-5223, USA.
Email: kerrwe@med.umich.edu

Funding information
American Epilepsy Society; National Institute of Neurological Disorders and Stroke, Grant/Award Number: R25 NS089450 and U24 NS107158

Abstract

Objective: To evaluate the exploratory time to exceed pre-randomization seizure count (T-PSC) in the determination of efficacy of adjunctive perampanel in participants with primary generalized tonic–clonic (PGTC) seizures in generalized-onset epilepsy.

Methods: In this multicenter, double-blind study (ClinicalTrials.gov identifier: NCT01393743), participants ≥12 years of age with treatment-resistant idiopathic generalized epilepsy were randomized to receive placebo or adjunctive perampanel (≤8 mg/day) across a 17-week double-blind treatment phase (4-week titration; 13-week maintenance). We evaluated the pre-planned exploratory end point of the T-PSC using a Kaplan–Meier analysis. We also re-evaluated the correspondence of the primary end points of median percent seizure frequency change (MPC) and 50% responder rate (50RR) calculated at T-PSC and at the end of the trial.

Results: The exploratory end point of median T-PSC on placebo was 43 days and >120 days on perampanel (log-rank $p < .001$). The primary end points calculated at T-PSC did not differ significantly from the end points at the end of the trial (MPC −31% vs −42% at T-PSC; 50RR 32% vs 51% at T-PSC). After T-PSC was reached, participants had a median (interquartile range) of 5 (3–13) additional seizures on placebo and 5 (2–10) on perampanel.

Significance: The exploratory end point of T-PSC demonstrated the effectiveness of perampanel despite a shorter duration of monitoring. The seizures that occurred after T-PSC did not influence the conclusions of the trial; therefore, T-PSC may be a viable alternative to traditional trial end points that reduces the risk to participants.

KEYWORDS

clinical trials, epilepsy, genetic generalized epilepsy, perampanel, primary generalized tonic–clonic seizures, time to event

1 | INTRODUCTION

Trials for regulatory approval of antiseizure medicines (ASMs) typically use a placebo comparator arm. Because epilepsy is considered a potentially life-threatening condition, trials are performed as add-on. Nonetheless, participants randomized to placebo, or an ineffective therapy, will continue to experience potentially life-threatening seizures. In a meta-analysis of prior randomized trials, participants who were randomized to placebo had a 6.1-fold increased risk for sudden unexpected death in epilepsy (SUDEP).[1] This risk of SUDEP is particularly important for participants with generalized tonic–clonic seizures, which is a separate risk factor for SUDEP.[2,3]

As a result, new methodologies have been explored to reduce placebo exposure.[4–10] One of these proposed methodologies is "time to event," which could maintain or improve statistical power while reducing participant risk.[8,11–13] This end point proposes that participants can be observed on investigative treatment for a pre-specified number of seizures instead of a pre-specified number of weeks.[7] With this methodology, participants need only remain in a study until the arm they have been randomized to (either active or placebo) proves ineffective. If they do not reach the pre-determined end point, they remain in the study for the full pre-specified maintenance period.

Because time-to-event trials have the same maximum duration as a standard parallel trial, the outcome can be calculated as a secondary or post hoc analysis. A post hoc analysis explored time to "pre-randomization seizure count" in trials of perampanel for focal epilepsy.[8] In this trial design, subjects exit when they experience 1 month's worth of seizures, as measured during a prospective baseline. These and other post hoc analyses have concluded that time to pre-randomization seizure count was able to demonstrate efficacy similar to standard end points of median percent change in seizure frequency (MPC) and at least 50% responder rate (50RR).[7,8,14,15] Although the Phase 3 trial for lacosamide in primary generalized tonic–clonic (PGTC) seizures used a time to second seizure as an end point,[16] time to exceed pre-randomization seizure count (T-PSC) has not been analyzed in a trial of PGTC in generalized-onset epilepsy.

In this work, we evaluate the exploratory end point of T-PSC for the randomized placebo-controlled trial of perampanel for PGTC seizures. We compared this T-PSC end point both to the traditional primary end points of MPC and 50RR, as well as the time to first and second PGTC seizure. To illustrate that enough information was available to determine efficacy after pre-randomization seizure count, we also evaluate the correspondence of MPC and 50RR calculated at the end of the maintenance period with these end points calculated at T-PSC, after first PGTC seizure, and after second PGTC seizure. To demonstrate reduction in participant risk, we also report the number of seizures and adverse effects that occurred after T-PSC. By further characterizing the T-PSC design, this work aims to provide evidence for the use of this exploratory endpoint as a primary end point in future trials.

Key points

- Efficacy of investigational treatments for epilepsy in trials can be determined earlier.
- Time to exceed pre-randomization monthly seizure count (T-PSC) can reduce exposure to ineffective therapy.
- After T-PSC, there was minimal change in primary efficacy end points.
- In contrast, the efficacy of perampanel was underestimated after the first or second seizure.
- T-PSC reduced exposure to placebo and may increase patient safety.

2 | METHODS

2.1 | Trial protocol information

This was a pre-planned exploratory analysis of a previously published multicenter, double-blinded, randomized placebo-controlled trial (Eisai Inc. protocol: E2007-G000-332; ClinicalTrials.gov identifier: NCT01393743). This trial was performed in accordance with the Declaration of Helsinki, Good Clinical Practice ICH-E6 Guideline CPMP/ICH/135/95, European Good Clinical Practice Directive 2005/28/EC, Clinical Trial Directive 2001/20/EC, and US Code of Federal Regulations Part 21. Before participation, all participants gave written informed consent. We describe the details of the trial in brief here. For additional details regarding the trial, please refer to the original publication of the primary efficacy end points.[17]

This trial was conducted at 78 sites in 16 countries and included participants 12 years of age or older diagnosed with PGTC seizures from generalized-onset epilepsy according to the 1981 International League Against Epilepsy (ILAE) classification of epileptic seizures and the 1989 ILAE classification of epilepsies and epileptic syndromes. This corresponds to generalized tonic–clonic motor seizures in the setting of generalized-onset epilepsy based on the 2017 ILAE classification of seizures. For consistency with the original trials, the 1981 and 1989 ILAE classification

terminology is utilized here. Participants were required to have at least three PGTC seizures during pre-randomization baseline and be taking stable doses of one to three approved ASMs. The pre-randomization phase comprised screening (≤4 weeks) and baseline (4–8 weeks, depending on the accuracy of diary-documented seizures during screening). Eligible participants were randomized (1:1) to receive placebo or oral perampanel, stratified by country. The subsequent randomization phase comprised titration (weeks 1–4), maintenance (weeks 5–17), and follow-up (weeks 18–21; only participants not entering an extension phase). During randomization, participants and all personnel—including investigators, site personnel, and sponsor staff—were blinded to treatment.

During titration, participants in the perampanel group received an initial daily dose of 2 mg, before uptitration in weekly 2-mg increments to the targeted daily dose of 8 mg or the highest tolerated dose (whichever was lower). Participants entered the maintenance period at the last dose achieved during titration. Dose adjustment during the maintenance period was not recommended; however, according to the investigator's clinical judgment, participants with inadequate seizure control could have their dose increased by one 2-mg increment (up to a maximum daily dose of 8 mg) and participants who experienced intolerable adverse events (AEs) could have their dose decreased by one 2-mg increment.

2.2 | Exploratory end point assessment

In this work, we evaluate the pre-planned exploratory end point of the time to exceed the pre-randomization monthly seizure count (or T-PSC). The pre-randomization monthly seizure count, n, was calculated as the number of seizures during screening and baseline divided by the duration of screening plus baseline multiplied by 28 days. Post-randomization, T-PSC was the days from the first dose to the day of the $(n+1)$th seizure plus 1 day. These data were analyzed using a Kaplan–Meier analysis with censoring, and log-rank tests were performed to estimate the median and 95% confidence intervals (CIs) of T-PSC. Data from participants who did not experience $(n+1)$ seizures were censored at the days between first dose and last dose plus one. The Brookmeyer and Crowley method was used to calculate 95% CIs of the median T-PSC. This end point was similar to the end point described by French and colleagues in studies 304 (ClinicalTrials.gov identifier NCT00699972), 305 (NCT00699582), and 306 (NCT00700310) for focal-onset seizures treated by perampanel,[8] and also evaluated in other trials.[7,14,15]

To further evaluate this exploratory end point, we performed additional sensitivity analyses. (1) We analyzed the time to the first PGTC seizure using a Kaplan–Meier analysis with censoring. (2) We also analyzed the time to the second PGTC seizure using Kaplan–Meier analysis with censoring, to compare to the recent analysis of lacosamide for PGTC seizures.[16] (3) We analyzed efficacy at T-PSC based on the start of the titration period as compared to the start of the maintenance period.

For each of these time to seizure events, we also recalculated the primary efficacy end points based on the seizures experienced up to each seizure event (first, second, $[n+1]$th) and the end of the trial. The first primary efficacy end point was defined according to the requirements of the US Food and Drug Administration (FDA) and was the median percent change in PGTC seizure frequency post-randomization (titration plus maintenance until the event) vs pre-randomization baseline (MPC). The key secondary efficacy end point was defined by the European Medicines Agency and was 50% PGTC seizure responder rate (50RR, percentage of participants achieving MPC at least −50% during maintenance; last observation carried forward).

For statistical analysis of MPC and 50RR, the methods matched that of the full-length trial. Analysis of covariance was conducted on the rank transformed MPC, with pooled countries as factors and ranked baseline PGTC seizure frequency as covariate. Treatment difference was estimated using the Hodges-Lehmann estimator and associated 95% CIs. Correspondence of the rank MPC at each time to seizure event compared to the end of the trial was calculated using Spearman's rho. Treatment differences for 50RR were analyzed using Cochran–Mantel–Haenszel test, stratified by pooled country. We also compared the correspondence of 50RR at each time-to-seizure event to the end of the trial using Cohen's kappa and report the false-positive and false-negative rates for at least −50% MPC.

3 | RESULTS

The participants included in this exploratory analysis matched the participants who were included in the primary analysis of this trial. Of 164 randomized participants, 162 were included in this analysis (placebo $n = 81$, perampanel $n = 81$). Of these 162, a total of 157 (97%) completed the titration phase and entered the maintenance phase (placebo $n = 78$, perampanel $n = 79$). The demographic and clinical information of participants is summarized in Table 1.

During pre-randomization, the median (range) PGTC seizure frequency per 28 days was 2.5 (1.0–11.7) for placebo and 2.6 (1.4–18.5) for perampanel.

TABLE 1 Baseline demographics, inclusion, and epilepsy-specific medical history

	Placebo	Perampanel
Demographics; full analysis set		
Randomized participants (*n*)	81	81
Completed titration (*n*)	78	79
Completed before Titration + Maintenance T-PSC (*n*)	2	5
Completed before Maintenance only T-PSC (*n*)	4	8
Mean age, years (SD)	29.5 (12.2)	27.3 (10.5)
Female, *n* (%)	45 (56)	46 (57)
Race, *n* (%)		
White	43 (53)	44 (54)
Black or African American	2 (4)	1 (1)
Japanese	6 (7)	5 (6)
Chinese	18 (22)	18 (22)
Other Asian	10 (12)	11 (14)
Other	1 (1)	2 (3)
Epilepsy-specific medical history; safety analysis set		
Randomized participants (*n*)	82	81
Mean time since diagnosis, years (SD)	18 (13)	16 (11)
Seizure type, *n* (%)		
Tonic–clonic	82 (100)	81 (100)
Myoclonic	33 (40)	32 (40)
Absence	41 (50)	42 (52)
Clonic	1 (1)	0 (0)
Tonic	2 (2)	0 (0)
Atonic	1 (1)	0 (0)
No. of background ASMs at baseline, *n* (%)		
1	29 (35)	26 (32)
2	36 (44)	39 (48)
3	16 (20)	16 (20)
4	1 (1)	0 (0)
Pre-randomization PGTC Seizure Frequency per 28 days, median (range)	2.5 (1.0–11.7)	2.6 (1.4–18.5)
PGTC Seizure count after Titration + Maintenance T-PSC, median (range, max)	5 (3–13, 170)	5 (2–10; 78)

Abbreviations: %, percent; *n*, sample size; PGTC, primary generalized tonic–clonic; SD, standard deviation; T-PSC, time to pre-randomization seizure count; y, years.

3.1 | Time-to-event analyses

The time-to-event results are summarized in Figure 1 and Table S1. The median (95% CI) time from the start of the titration period to exceed the pre-randomization seizure count (or T-PSC) was 43 days (34–51) for placebo and >120 days (70 to >120) for perampanel ($p < .0001$). A similar proportion of participants receiving perampanel and placebo discontinued the study before T-PSC or completing the study (placebo 2.5%, perampanel 6.2%, Fisher's exact $p = .44$).

The median (interquartile range; maximum) of number of seizures after the T-PSC was 5 (3–13; 170) for 63 participants on placebo and 5 (2–10; 78) for 38 participants on perampanel. The 63 and 38 participants on placebo and perampanel, respectively, reflect the number of participants whose T-PSC was shorter than the duration of titration plus maintenance.

The median (95% CI) time from the start of the titration period to the first and second PGTC seizure was 12 days (6–15) and 23 days (15–32) for placebo and 19 days (8–40) and 54 days (30–95) for perampanel, respectively (first

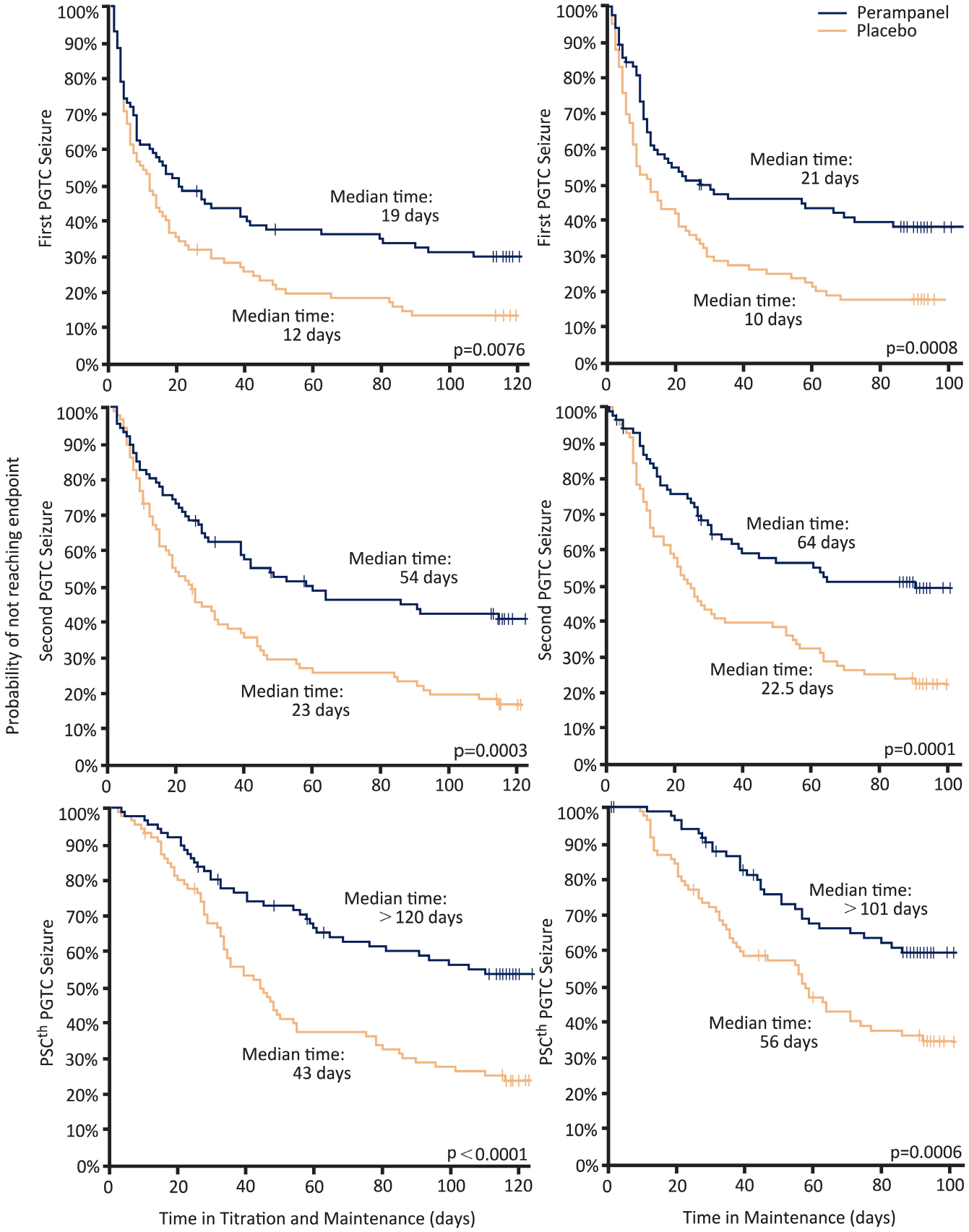

FIGURE 1 Kaplan–Meier time to end point curves with censoring starting with titration or maintenance for the time to first, second, or exceeding pre-randomization monthly seizure count (PSC). + represents a censored observation. Abbreviation: PGTC, primary generalized tonic–clonic

seizure $p = .0076$, second seizure $p = .003$; Figure 1). The median (95% CI) time from the start of the maintenance period to the first and second PGTC was 10 days (7–19) and 22.5 days (14–31) for placebo and 21 days (12–64) and 64 days (34 to more than 101) for perampanel, respectively (first seizure $p = .0008$, second seizure $p = .0001$; Figure 1).

The median (95% CI) time from the start of the maintenance period to exceed the pre-randomization seizure count (T-PSC) was 56 days (35–70) for placebo and >101 days (74 to >101) for perampanel (Figure 1, $p = .0006$). A similar proportion of participants receiving perampanel and placebo discontinued the study before T-PSC or completing the study (placebo 5.1%, perampanel 10.1%, Fisher's exact $p = .37$).

3.2 | Correspondence with primary efficacy outcomes

When calculated traditionally, the MPC from the start of treatment was 38% vs 76% for placebo vs perampanel, respectively (median difference 31%, 95% CI 15%–46%, $p < .0001$); and the 50RR during the maintenance period was 40% vs 64% for placebo vs perampanel, respectively (odds ratio [OR] = 2.7, 95% CI 1.4–5.1, $p < .0001$). The MPC and 50RR when calculated the first, second, and PSCth PGTC seizure, and at the end of the trial are illustrated in Figure 2. The degree of correspondence between the MPC and 50RR at each time to event compared to the traditional trial is illustrated in Figure 3. These values are summarized below and specific results by treatment group are listed in Tables S2–S4.

3.2.1 | Primary efficacy outcomes calculated at PSC

When calculated from the start of the titration period to T-PSC or the end of the trial, whichever occurred first, the MPC was 20% vs 76% for placebo vs perampanel, respectively (median difference 42%, 95% CI 19%–64%, $p < .0001$). The Spearman's rho between MPC at T-PSC and the end of the trial was 94% (95% CI 92%–96%).

When calculated from the start of the maintenance period to T-PSC or the end of the trial, whichever occurred first, the 50RR was 36% vs 66% for placebo vs perampanel, respectively (OR = 3.3, 95% CI 1.7–6.3, $p = .0002$). Based on seizures that occurred after T-PSC, 5% (4/74) of participants who were 50RR responders became nonresponders (false positives). Based on

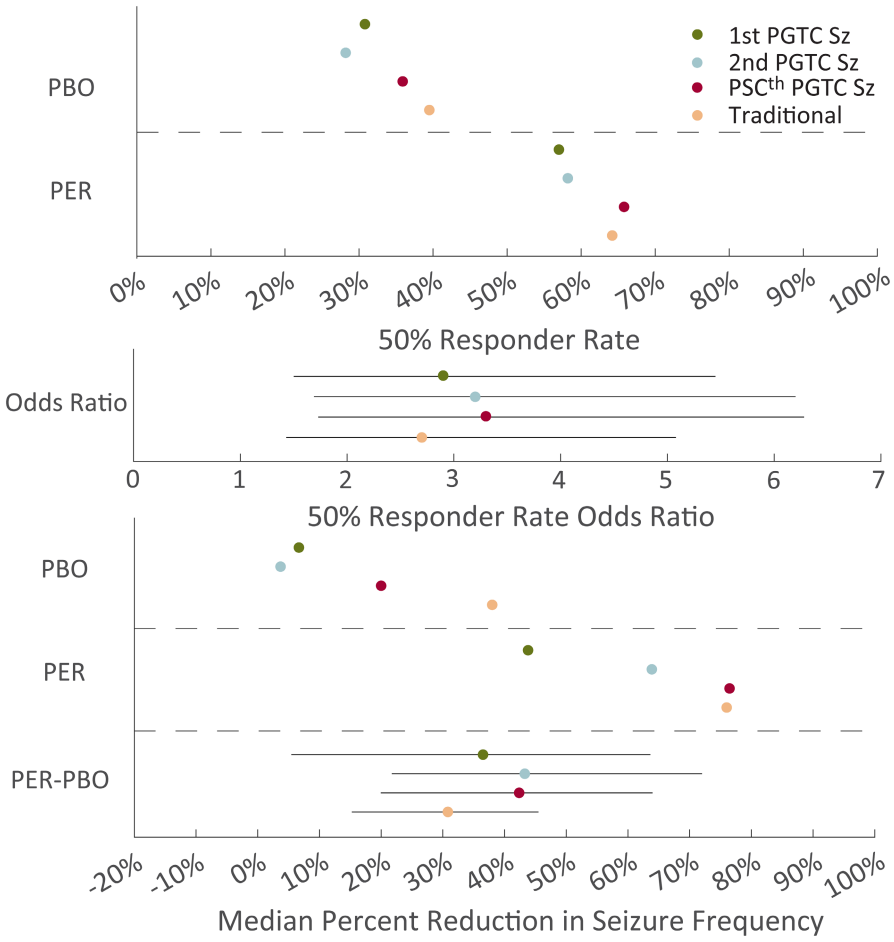

FIGURE 2 Primary efficacy outcomes calculated at each of the time-to-event end points. Median percent reduction in seizure frequency (MPC) was calculated during titration and maintenance; 50% responder rate (50RR) was calculated during maintenance only. For MPC and 50RR during both treatment periods, see Figure S1. Error bars reflect 95% confidence intervals. Abbreviations: PBO, placebo; PER, perampanel; PGTC Sz, primary generalized tonic–clonic seizure

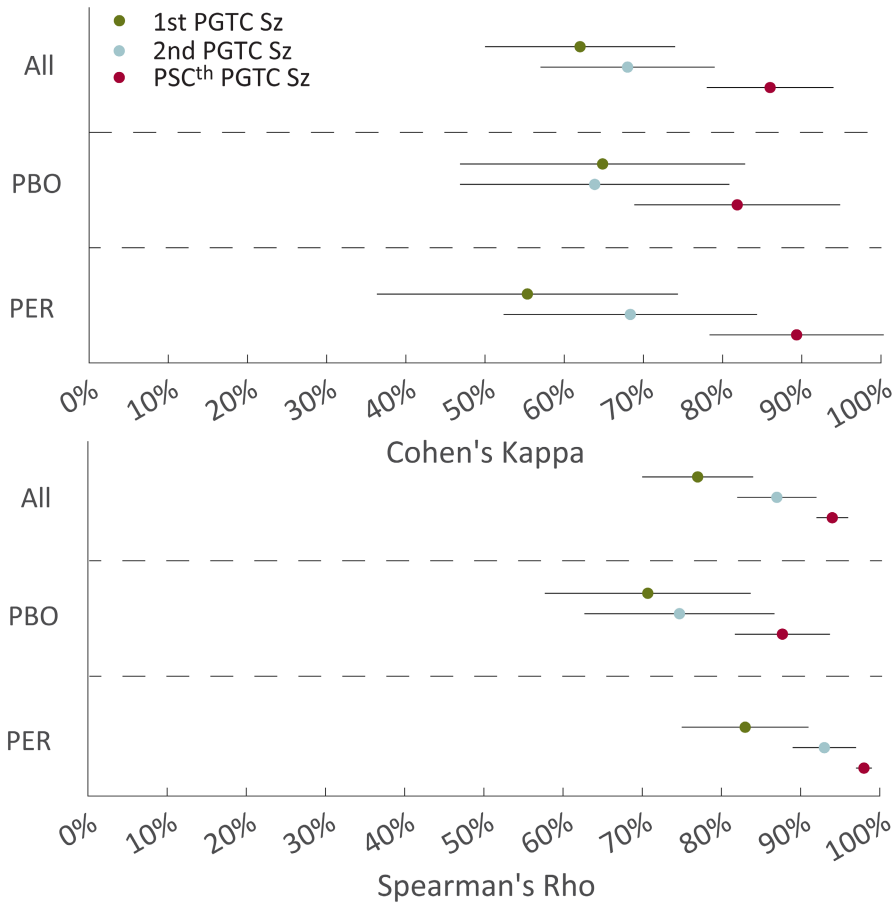

FIGURE 3 Individual level correspondence of 50% responder rate (50RR) using Cohen's kappa and median percent reduction in seizure frequency (MPC) using Spearman's rho when calculated at each of the time-to-event end points compared to the full-length trial. Analogous to Figure S2. Abbreviations: PBO, placebo; PER, perampanel; PGTC Sz, primary generalized tonic–clonic seizure

observation after T-PSC, 8% (7/83) who had <50% seizure frequency reduction at T-PSC eventually had at least 50% seizure frequency reduction at the end of the trial (false negatives). This corresponded to a Cohen's kappa of 86% between 50RR at T-PSC vs the end of the trial (95% CI 78%–94%).

3.2.2 | Primary efficacy outcomes calculated at second PGTC seizure

When calculated from the start of titration to the time to 2nd (T-2nd) PGTC seizure or the end of the trial, whichever occurred first, the MPC was 4% vs 64% for placebo vs perampanel, respectively (median difference 43%, 95% CI 21%–72%, $p < .0001$). The Spearman's rho between MPC at T-2nd PGTC seizure and the end of the trial was 87% (95% CI 82%–90%).

When calculated from the start of maintenance to T-2nd PGTC seizure or the end of the trial, whichever occurred first, the 50RR was 28% vs 58% for placebo vs perampanel, respectively (OR = 3.2, 95% CI 1.6–6.2, $p = .0002$). Based on seizures that occurred after T-PSC, 7% (5/74) who were 50RR responders became nonresponders (false positives). Based on observation after T-2nd PGTC seizure, 24% (20/83) of participants who had <50% seizure frequency reduction at T-PSC eventually had at least 50% seizure frequency reduction at the end of the trial (false negatives). This corresponded to a Cohen's kappa of 68% between 50RR at T-2nd PGTC seizure vs the end of the trial (95% CI 57%–80%).

3.2.3 | Primary efficacy outcomes calculated at first PGTC seizure

When calculated from the start of titration to the time to 1st (T-1st) PGTC seizure or the end of the trial, whichever occurred first, the MPC was 7% vs 44% for placebo vs perampanel, respectively (median difference 37%, 95% CI 5%–64%, $p < .0001$). The Spearman's rho between MPC at T-1st PGTC seizure and the end of the trial was 77% (95% CI 70%–83%).

When calculated from the start of maintenance to T-1st PGTC seizure or the end of the trial, whichever occurred first, the 50RR was 31% vs 57% for placebo vs perampanel, respectively (OR = 2.9, 95% CI 1.5–5.5, $p = .0009$). Based on seizures that occurred after T-PSC, 11% (8/74) participants who were 50RR responders became nonresponders on placebo and perampanel, respectively (false positives). Based on observation after T-1st PGTC seizure, 27% (22/83) of participants who had <50% seizure frequency reduction

at T-PSC eventually had at least 50% seizure frequency reduction at the end of the trial (false negatives). This corresponded to a Cohen's kappa of 62% between 50RR at T-1st PGTC seizure vs the end of the trial (95% CI 50%–74%).

4 | DISCUSSION

The time to exceed the pre-randomization seizure count (or T-PSC) may be a reasonable trial design that shortens trial durations and reduces participants' total seizure burden while having minimal to no impact on the statistical conclusions regarding treatment effectiveness. This builds upon prior clinical trial data supporting this approach from perampanel for focal epilepsy,[8] fenfluramine for Dravet syndrome,[15] lacosamide for pediatric epilepsy and PGTC seizures,[14,16] and levetiracetam for pediatric epilepsy.[14] In addition, simulations of clinical trial data suggest that the T-PSC end point has statistical power similar to that of the primary efficacy outcome of median percent seizure frequency reduction (or MPC) and higher statistical power than the primary efficacy outcome of 50% responder rate (or 50RR).[11] Therefore, T-PSC may be a reasonable pre-specified primary effectiveness end point for future clinical trials of epilepsy.

We performed multiple analyses to characterize the relative benefit and costs of T-PSC compared to other potential exploratory end points. The 50% responder rate and MPC was underestimated at the first or second PGTC seizure, whereas response to perampanel was consistent between T-PSC and the full-length trial. This suggests that the time to first or second PGTC seizure may be susceptible to delayed onset of efficacy, seizure clusters, natural variability in seizure frequency, and transient factors related to the early stages of treatment. Similarly, placebo response also tended to be lower at the first or second PGTC seizure compared to T-PSC and the full-length trial, indicating that the placebo effect may not be uniform across the whole study. Although the efficacy end points at time to first or second PGTC seizure were statistically significant, the efficacy when calculated at T-PSC was more precise, robust, and sustained. This increased similarity in outcomes between T-PSC and the full-length trial may be due to encouraging at least 1 month of monitoring on treatment for at least 70% of participants. Because PSC represents the number of seizures the participant had per month during the baseline, participants would only reach T-PSC before 1 month if their seizure frequency had worsened. This duration of observation allows for potential multi-day cycles in seizure frequency, which can have cycle lengths of around 1 month.[18–22]

To further compare T-PSC to the traditional primary efficacy outcomes, we calculated the correspondence between MPC in PGTC seizure frequency and 50% responder rate calculated at either T-PSC or the end of the maintenance period. Both the effect size and conclusions of these analyses matched when calculated at this early time point. On the individual participant level after T-PSC, a relatively small fraction of participants changed from a >50% response to a <50% response, or vice vera. On a more granular level, the participant ranks of percent reduction in PGTC seizure frequency reduction when calculated at T-PSC was >90% correlated with the full-length trial. Therefore, there was strong correspondence between the results of the trial with observation truncated at T-PSC as compared to the full maintenance period.

In contrast, there was substantially less correspondence between MPC in PGTC seizure frequency and 50% responder rate when calculated after first or second PGTC. Therefore, although the population-level statistics showing efficacy of perampanel to placebo were significant at these time points, individual-level response to treatment was not as stable at these very early time points.

The benefit of T-PSC over the full-length trial and the time to first or second seizure were observed irrespective of whether seizure counting started with the start of titration or after the participant reached their maintenance dose. Starting seizure counting with the first titration dose shortens overall trial duration and thereby further reduces exposure to ineffective treatment. However, there are theoretical concerns about starting seizure counting during titration due to delayed onset of efficacy because of insufficient serum levels, especially when, for participants on placebo, a median of 65% of days before PSC were during titration. Even after titration, it may take 17–21 additional days to achieve steady state because of the 105-hour half-life of perampanel. This may explain why time to first or second seizure underestimated the efficacy of perampanel, especially for time to first seizure during titration and maintenance. Therefore, although starting seizure counting for T-PSC with the first treatment dose was effective statistically, there are both practical and theoretical benefits of starting to count with the first maintenance dose.

In addition to shortened trial duration, the T-PSC trial design reduced participant risk by reducing the number of seizures needed to establish efficacy of treatment. Although the risk of death or disability from each individual seizure may be low, participants in the placebo arm of trials for epilepsy have been shown to have a 6.1-fold increased risk for sudden unexpected death in epilepsy (SUDEP).[1] Truncating participation at T-PSC would allow for a reduced exposure to placebo or ineffective treatment, thus potentially avoiding the median of 5 seizures (maximum 170 seizures) that were observed after T-PSC, which did not change the statistical efficacy conclusion of the trial. Although each individual seizure is unlikely to be fatal, one of the predictors

of SUDEP includes generalized tonic–clonic seizures, for which more seizures conferred more risk[2,3]; therefore, it is critical to minimize exposure to further seizures so participants can explore other potentially effective treatments. Our results suggest that a T-PSC design could accomplish this goal and permit participants to pursue other treatments for their seizures, including but not limited to open-label extension of perampanel.

These results indicate that T-PSC may have been an appropriate primary end point for this trial; however, there remain some limitations in this approach that may warrant further study. To make a timely decision to end or modify treatment at or after T-PSC, participants would need to either contact study staff at that point or provide daily updates on electronic seizure diary that was accessible to study staff in real time. With the wide availability of smart phone–based seizure diary applications, we do not expect timely reporting of seizure diaries to be a significant barrier to time-to-event design trials. However, this early time-to-event end point resulted in reduction of the duration of observation for adverse effects on placebo, which can be valuable statistically when compared to the rate of similar adverse effects on perampanel.[23] This would place more emphasis on open-label extension studies to evaluate adverse effects without a placebo group, as occurred with cenobamate.[24] However, this is mostly an issue for idiosyncratic adverse effects, since dose-related adverse effects could be assessed over a 1-month duration.[23] Furthermore, it is unclear whether the risk–benefit ratio of continued placebo-controlled observation for adverse effects for participants who did not appear to respond to placebo before T-PSC, and therefore were unlikely to respond at the end of the trial, can be justified (50RR false-negative rate 8% during maintenance). After first or second PGTC seizure, the 50RR false-negative rate was higher (27% for first and 24% for second); therefore, monitoring until PSC likely is warranted. This may reflect the increasing evidence that seizure frequency may have individually variable multi-day cycles that may be longer than the time to first or second seizure, but usually are shorter than T-PSC.[18,22] In addition, seizure clusters or status epilepticus early in treatment may not be an accurate representation of an individual's long-term seizure response and would skew the results of time to first or second seizure. Further analysis of this and other trials would be needed to evaluate the potential impact of these natural sources of variability in seizure frequency.[5,25]

5 | CONCLUSION

The exploratory end point of T-PSC is an effective way to evaluate the efficacy of treatments for epilepsy in future trials, while also reducing participant risk and trial cost. In this analysis, we demonstrated similar conclusions of the trial when using this exploratory end point as compared to the primary efficacy outcomes. In addition, we demonstrated a high degree of correspondence in the primary efficacy outcomes when calculated at T-PSC. Based on similar statistical results, this exploratory end point may reduce participant risk by reducing the total number of seizures experienced in the trial and shortening duration of placebo exposure, as well as reducing the cost of trial conduct by shortened post-randomization observation.[11]

AUTHOR CONTRIBUTIONS

Dr. Kerr drafted the manuscript, created the figures, and designed the statistical comparisons. Dr. Patten and her staff performed the statistical comparisons and provided information for the figures. All authors contributed to the study design, reviewed drafts of the manuscript, and approved the final manuscript.

ACKNOWLEDGMENTS

Dr. Kerr's research time was supported by National Institutes of Health (NIH) R25NS089450 and U24NS107158, and the American Epilepsy Society. Portions of work was previously presented at the 71st annual meeting of American Epilepsy Society in 2017.

CONFLICT OF INTEREST

Dr. Kerr writes review articles for Medlink Neurology and has acted as a consultant for SK Life Science. Dr. Brandt has honoraria as a speaker or for consulting from Arvelle Therapeutics/Angelini Pharma, Desitin, Eisai, Equilibre Biopharmaceuticals, GW Pharmaceuticals, Idorsia, Janssen-Cilag GmbH, Marinus Pharmaceuticals, UCB, Xenon Pharmaceuticals, and Zogenix. Drs. Ngo, Patten, Cheng, and Kramer are employees of Eisai, Inc or Eisai, Ltd. Dr. French receives salary support from the Epilepsy Foundation and for consulting work and/or attending Scientific Advisory Boards on behalf of the Epilepsy Study Consortium for Aeonian/Aeovian, Alterity Therapeutics Limited, Anavex, Arkin Holdings, Angelini Pharma S.p.A, Arvelle Therapeutics, Inc., Athenen Therapeutics/Carnot Pharma, Autifony Therapeutics Limited, Baergic Bio, Biogen, Biohaven Pharmaceuticals, BioMarin Pharmaceutical Inc., BioXcel Therapeutics, Bloom Science Inc., BridgeBio Pharma Inc., Camp4 Therapeutics Corporation, Cerebral Therapeutics, Cerevel, Clinical Education Alliance, Coda Biotherapeutics, Corlieve Therapeutics, Eisai, Eliem Therapeutics, Encoded Therapeutics, Encoded Therapeutics, Engage Therapeutics, Engrail, Epalex, Epihunter, Epiminder, Epitel Inc., Equilibre BioPharmaceuticals, Greenwich Biosciences, Grin Therapeutics, GW Pharma, Janssen Phamaceutica,

Jazz Pharmaceuticals, Knopp Biosciences, Lipocine, LivaNova, Longboard Pharmaceuticals, Lundbeck, Marinus, Mend Neuroscience, Marck, NeuCyte Inc., Neumirna Therapeutics, Neurocrine, Neuroelectives USA Corporation, Neuronetics Inc., Neuropace, NxGen Medicine Inc., Ono Pharmaceutical Co., Otsuka Pharmaceutical Development, Ovid Therapeutics Inc., Paladin Labs, Passage Bio, Pfizer, Praxis, Pure Tech LTY Inc., Rafa Laboratories Ltd, SK Life Sciences, Sofinnova, Stoke, Supernus, Synergia Medical, Takeda, UCB Inc., Ventus Therapeutics, Xenon, Xeris, Zogenix, and Zynerba. Dr. French also has received research support from the Epilepsy Study Consortium (Funded by Andrews Foundation, Eisai, Engage, Lundbeck, Pfizer, SK Life Science, Sunovion, UCB, and Vogelstein Foundation), the Epilepsy Study Consortium/Epilepsy Foundation (Funded by UCB), GW/FACES, and the National Institute of Neurological Disorders and Stroke (NINDS). She is on the editorial board of *Lancet Neurology* and *Neurology Today*. She is Chief Medical/Innovation Officer of the Epilepsy Foundation. She has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Angelini Pharma S.p.A., Clinical Education Alliance, NeuCyte, Inc., Neurocrine, Praxis, and Xenon.

ORCID

Wesley T. Kerr https://orcid.org/0000-0002-5546-5951
Christian Brandt https://orcid.org/0000-0001-8666-1640
Jacqueline A. French https://orcid.org/0000-0003-2242-8027

REFERENCES

1. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol. 2011;10(11):961–8.
2. Verducci C, Hussain F, Donner E, Moseley BD, Buchhalter J, Hesdorffer D, et al. SUDEP in the north American SUDEP registry: the full spectrum of epilepsies. Neurology. 2019;93(3):e227–36.
3. Novak JL, Miller PR, Markovic D, Meymandi SK, DeGiorgio CM. Risk assessment for sudden death in epilepsy: the SUDEP-7 inventory. Front Neurol. 2015;6:252.
4. Romero J, Chiang S, Goldenholz DM. Can machine learning improve randomized clinical trial analysis? Seizure. 2021;91:499–502.
5. Romero J, Larimer P, Chang B, Goldenholz SR, Goldenholz DM. Natural variability in seizure frequency: implications for trials and placebo. Epilepsy Res. 2020;162:106306.
6. Auvin S, Williams B, McMurray R, Kumar D, Perdomo C, Malhotra M. Novel seizure outcomes in patients with Lennox-Gastaut syndrome: post hoc analysis of seizure-free days in rufinamide study 303. Epilepsia Open. 2019;4(2):275–80.
7. Auvin S, French J, Dlugos D, Knupp KG, Perucca E, Arzimanoglou A, et al. Novel study design to assess the efficacy and tolerability of antiseizure medications for focal-onset seizures in infants and young children: a consensus document from the regulatory task force and the pediatric commission of the international league against epilepsy (ILAE), in collaboration with the pediatric epilepsy research consortium (PERC). Epilepsia Open. 2019;4(4):537–43.
8. French JA, Gil-Nagel A, Malerba S, Kramer L, Kumar D, Bagiella E. Time to prerandomization monthly seizure count in perampanel trials: a novel epilepsy endpoint. Neurology. 2015;84(20):2014–20.
9. French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the treatment of epilepsy. Epilepsia. 2010;51(10):1936–43.
10. Pledger GW, Kramer LD. Clinical trials of investigational antiepileptic drugs: monotherapy designs. Epilepsia. 1991;32(5):716–21.
11. Oliveira A, Romero JM, Goldenholz DM. Comparing the efficacy, exposure, and cost of clinical trial analysis methods. Epilepsia. 2019;60(12):e128–32.
12. Leppik IE, Dreifuss FE, Pledger GW, Graves NM, Santilli N, Drury I, et al. Felbamate for partial seizures: results of a controlled clinical trial. Neurology. 1991;41(11):1785–9.
13. Bourgeois B, Leppik IE, Sackellares JC, Laxer K, Lesser R, Messenheimer JA, et al. Felbamate: a double-blind controlled trial in patients undergoing presurgical evaluation of partial seizures. Neurology. 1993;43(4):693–6.
14. Johnson ME, McClung C, Bozorg AM. Analyses of seizure responses supportive of a novel trial design to assess efficacy of antiepileptic drugs in infants and young children with epilepsy: post hoc analyses of pediatric levetiracetam and lacosamide trials. Epilepsia Open. 2021;6(2):359–68.
15. Sullivan J, Specchio N, Devinsky O, Auvin S, Perry MS, Strzelczyk A, et al. Fenfluramine significantly reduces day-to-day seizure burden by increasing number of seizure-free days and time between seizures in patients with Dravet syndrome: a time-to-event analysis. Epilepsia. 2022;63(1):130–8.
16. Vossler DG, Knake S, O'Brien TJ, Watanabe M, Brock M, Steiniger-Brach B, et al. Efficacy and safety of adjunctive lacosamide in the treatment of primary generalised tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial. J Neurol Neurosurg Psychiatry. 2020;91(10):1067–75.
17. French JA, Krauss GL, Wechsler RT, Wang XF, DiVentura B, Brandt C, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy a randomized trial. Neurology. 2015;85(11):950–7.
18. Karoly PJ, Rao VR, Gregg NM, Worrell GA, Bernard C, Cook MJ, et al. Cycles in epilepsy. Nat Rev Neurol. 2021;17(5):267–84.
19. Stirling RE, Cook MJ, Grayden DB, Karoly PJ. Seizure forecasting and cyclic control of seizures. Epilepsia. 2021;62(Suppl 1):S2–14.
20. Karoly PJ, Goldenholz DM, Freestone DR, Moss RE, Grayden DB, Theodore WH, et al. Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. Lancet Neurol. 2018;17(11):977–85.

21. Karoly PJ, Ung H, Grayden DB, Kuhlmann L, Leyde K, Cook MJ, et al. The circadian profile of epilepsy improves seizure forecasting. Brain. 2017;140(8):2169–82.
22. Karoly PJ, Stirling RE, Freestone DR, Nurse ES, Maturana MI, Halliday AJ, et al. Multiday cycles of heart rate are associated with seizure likelihood: an observational cohort study. EBioMedicine. 2021;72:103619.
23. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. Lancet Neurol. 2012;11(9):792–802.
24. Sperling MR, Klein P, Aboumatar S, Gelfand M, Halford JJ, Krauss GL, et al. Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study. Epilepsia. 2020;61(6):1099–108.
25. Goldenholz DM, Goldenholz SR, Moss R, French J, Lowenstein D, Kuzniecky R, et al. Does accounting for seizure frequency variability increase clinical trial power? Epilepsy Res. 2017;137:145–51.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kerr WT, Brandt C, Ngo LY, Patten A, Cheng JY, Kramer L, et al. Time to exceed pre-randomization monthly seizure count for perampanel in participants with primary generalized tonic–clonic seizures: A potential clinical end point. Epilepsia. 2022;63:2994–3004. https://doi.org/10.1111/epi.17411