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# Efficacy and safety of perampanel in patients with drug-resistant partial seizures after conversion from double-blind placebo to open-label perampanel

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ABSTRACT

*Objective:* To evaluate the efficacy and safety of perampanel in patients with drug-resistant partial seizures after the conversion from double-blind placebo in three phase III studies to open-label perampanel, and to assess the impact of perampanel titration rates through a comparison of weekly vs biweekly dose increases.

*Methods:* Patients who completed the three multinational, double-blind, placebo-controlled, phase III core studies (studies 304, 305, or 306) were eligible to enroll in the extension study (study 307). Patients completing the double-blind treatment (6-week titration, 13-week maintenance) with placebo (DB-PBO) or perampanel (DB-PER) began the extension study with a 16-week blinded conversion period, during which DB-PBO patients were switched to perampanel. Doses were titrated in 2-mg increments (biweekly) to an individualized maximum tolerated dose of perampanel (up to 12 mg/day). Patients then entered a planned, open-label treatment period.

*Results:* Perampanel treatment during the extension study reduced total seizure frequency/28 days relative to the double-blind prerandomization baseline regardless of prior perampanel or placebo treatment in the core studies. In the DB-PBO patients, median percent reductions in seizure frequency at the end of the double-blind period, at the end of the conversion period, and at Weeks 40–52 in the open-label maintenance period were 18.6%, 44.3%, and 55.0%, respectively. Seizure control was also improved in the DB-PER patients during the extension period compared to the end of the double-blind period. Responder rates were similar between the 2 patient groups at the end of the conversion period. Perampanel was well tolerated, with the most common treatment-emergent adverse events being dizziness, somnolence, weight increase, irritability, fatigue, and headache. For those patients randomized to the 12 mg group (DB-PER 12 mg), 78.4% reached the daily dose of 10 or 12 mg by the end of the 6-week titration period of the double-blind phase. By the end of the 16-week conversion period of the extension study, 64.0% of DB-PBO patients reached the daily dose of 10 or 12 mg. Seizure frequency reduction was greater after the first 13-week maintenance period of the extension study in the DB-PBO group compared to patients assigned to DB-PER 12 mg during the 13-week maintenance period of the double-blind study.

*Abbreviations:* AE, adverse event; AED, antiepileptic drug; BMI, body mass index; CP, complex partial seizure; DB, double blind; EMA, European Medicines Agency; FDA, US Food and Drug Administration; ITT, intent to treat; MTD, maximum tolerated dose; PBO, placebo; PER, perampanel; SAE, serious adverse event; SG, secondarily generalized seizure; SP, simple partial seizure.

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*Conclusion:* Patients who received placebo in the phase III core DB studies and transitioned to perampanel in the open-label extension study (DB-PBO) achieved seizure control at the end of the conversion period similar to that of patients who had been previously exposed to perampanel (DB-PER) as well as comparable safety outcomes. Patients who received perampanel during the core studies and continued with treatment during the extension study (DB-PER) also showed sustained improvements in seizure control with long-term exposure to perampanel.



## Introduction

Despite the availability of more than 20 approved agents for the treatment of epilepsy, 30% of patients remain drug resistant (Brodie, 2010; Krauss et al., 2013). Therefore, new antiepileptic drugs (AEDs), particularly those with novel mechanisms of action, may benefit patients with uncontrolled epilepsy (Brodie, 2010). The AMPA receptors are the principal receptors involved in glutamate-mediated fast excitatory postsynaptic neurotransmission, and they play a critical role in the generation and spread of epileptic activity (Rogawski, 2011). Compounds that are AMPA-receptor antagonists may act via a novel mechanism of action to reduce excessive excitatory activity and modulate seizure activity in drug-resistant patients. Moreover, noncompetitive AMPA-receptor antagonists have the ability to inhibit receptor activity, even in the presence of high glutamate concentrations, and may also have a sustained effect in hyperexcitatory states (Rektor, 2013). Perampanel (PER), the first in a novel class of AEDs, is an orally active, noncompetitive, selective AMPA-receptor antagonist (Rektor, 2013). PER is approved in more than 40 countries for use as an adjunctive therapy for the treatment of partial seizures, with or without secondarily generalized seizures, by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in patients with epilepsy aged 12 years and older, and by Health Canada in patients aged 18 years and older with epilepsy that is not satisfactorily controlled with conventional therapy (FYCOMPA SPC 2012; FYCOMPA Product Monograph 2013; FYCOMPA US Prescribing Information 2014).

The efficacy of PER as an adjunctive therapy was demonstrated in three multicenter, double-blind (DB), randomized, parallel group, placebo-controlled phase III studies—studies 304, 305, and 306 ("core DB studies")—each of which enrolled patients with drug-resistant partial seizures. Data from these studies, which were published previously, indicated that once-daily PER, at doses up to 12 mg/day, significantly reduced seizure frequency and increased responder rates in patients with drug-resistant partial seizures (French et al., 2012,2013; Krauss et al., 2012; Steinhoff et al., 2013). Patients who completed the three core DB studies were eligible to enroll in an extension study (study 307). Interim results from the extension study during the 1–2-year monitoring period were previously published and demonstrated that PER had a favorable safety and tolerability profile in patients with drug-resistant partial seizures over the long term, which was consistent with the pivotal phase III studies (Krauss et al., 2013). Furthermore, the decrease in seizure frequency was consistent and maintained in patients through 1–2 years of PER exposure (Krauss et al., 2013).

Here we report a post hoc analysis of the data from the three core DB studies and the extension study. The focus of this analysis is to evaluate the efficacy and safety of PER in patients who received placebo (PBO) in the phase III core DB studies and transitioned to PER in the extension study. We further report on the impact of PER titration rates through a comparison of weekly vs biweekly titration (core DB studies and extension study, respectively).

## Methods

### *Patients and study design*

Patients who were eligible for the core studies were aged 12 years or older with a diagnosis of partial seizures [simple partial seizure (SP) with motor signs, complex partial seizure (CP), or CP with secondary generalization] according to the 1981 International League Against Epilepsy Classification of Epileptic Seizures (ILAE, 1981). Patients must have had uncontrolled partial seizures, had ≥2 AED failures in the previous 2 years, and had been taking a stable type and dose regimen of 1–3 AEDs. During the 6-week prerandomization phase, eligible patients must have had ≥5 partial seizures (with 2 or more partial seizures per each 3-week period) (French et al., 2012,2013; Krauss et al., 2012).

### *Core DB studies*

The core DB studies were conducted in 3 phases: the prerandomization phase (baseline), the DB treatment phase (6-week titration period, 13-week maintenance period), and a follow-up phase of 4 weeks for patients who withdrew prematurely or who did not elect to enter the extension study (French et al., 2012,2013; Krauss et al., 2012). Patients were randomized to once-daily DB treatment with PBO, PER 8 mg, or PER 12 mg in studies 304 (NCT00699972) and 305 (NCT00699582). In study 306 (NCT00700310), patients were randomized to PBO, PER 2 mg, PER 4 mg, or PER 8 mg. Patients continued to receive a stable treatment regimen of 1–3 concomitant AEDs throughout the study (French et al., 2012,2013; Krauss et al., 2012). During the titration period, PER doses were increased by 2 mg per week to the randomized dose, and dose reductions were permitted for intolerability. Patients treated with PER continued treatment with the dose achieved during titration throughout the maintenance period. Patients who completed one of these phase III studies of adjunctive PER were eligible to continue in the extension study (Montouris et al., 2012).

### *Extension study*

The extension study (307; NCT00735397) was comprised of a 16-week blinded conversion period, a planned 256-week maintenance period, and a 4-week follow-up phase (Krauss et al., 2013,2014). In the 16-week blinded conversion period, patients randomized to receive PBO in the core studies (DB-PBO) were given PER 2 mg/day and titrated upward in 2-mg increments every 2 weeks (in contrast to weekly titration in the core DB studies). Titration continued to the patient's individualized maximum tolerated dose (MTD), up to 12 mg/day. Patients receiving PER during the core studies (DB-PER) continued to receive PER on a blinded basis. Those DB-PER patients not already receiving 12 mg/day were titrated upward in 2-mg increments every 2 weeks to their individualized MTD (up to 12 mg/day) (Krauss et al., 2013,2014). All doses were given once daily at bedtime with food (Krauss et al., 2013).

The open-label maintenance period of the extension study began upon completion of the blinded conversion/titration period. Patients remained on the MTD achieved at the end of the

conversion period unless further dose adjustment for tolerability and/or efficacy was necessary (Krauss et al., 2013,2014). Patients remained on the same 1–3 concomitant AEDs given during the core DB studies; however, during the extension study, concomitant AEDs could be discontinued or changed at the investigator's discretion (Krauss et al., 2013,2014). Patients began entering the extension study in October of 2008; the end date for the analysis was October 2011 (Krauss et al., 2014). Patients who could not tolerate at least 2 mg/day PER withdrew from the study. Study visits were scheduled every 4 weeks during the conversion period and increased to every 3 months thereafter (Krauss et al., 2013,2014).

The core DB studies and extension study were performed in accordance with the International Conference on Harmonisation/Good Clinical Practice guidelines and the Declaration of Helsinki (French et al., 2012,2013; Krauss et al., 2012,2013,2014). The study protocols, amendments, and informed consents were reviewed by national regulatory authorities in each country and by independent ethics committees or institutional review boards for each site. All patients provided informed consent prior to participating in the studies (Krauss et al., 2013,2014).

### *Efficacy end points*

Patients with partial seizures recorded seizure frequency and type in daily diaries (SP with or without motor signs, CP, and partial seizures with secondary generalization [SG]) (Steinhoff et al., 2013). The primary efficacy end points were the median percent reduction in total seizure frequency (all partial seizures) per 28 days of treatment relative to the DB prerandomization phase baseline, and the percentage of patients who experienced a ≥50% reduction from baseline in seizure frequency per 28 days of treatment (responder rate) (Krauss et al., 2013; Montouris et al., 2012; Steinhoff et al., 2013). Secondary efficacy end points included percent change in CP plus SG (CP + SG) frequency per 28 days during treatment relative to baseline. Other exploratory efficacy variables included percent change in the frequency per 28 days of SG during treatment relative to baseline, and responder rate based on CP + SG and SG. Additional analysis of the DB-PBO group was conducted using the 13-week maintenance period seizure frequency of the core DB studies as baseline.

### *Safety assessments*

Adverse events (AEs) were recorded throughout the studies. Safety assessments included examinations of the incidence rates of AEs, serious adverse events (SAEs), and withdrawals due to AEs (Montouris et al., 2012). AEs were considered to be "treatment-emergent" if they started on or after the first PER dose date (core phase III or extension study) and prior to 30 days after the last dose, or if they were present prior to treatment but worsened in severity during the study (Krauss et al., 2013).

### *Statistical analyses*

All seizure-related analyses for the extension study were performed on the intent-to-treat (ITT) analysis set, which was defined as all patients who provided informed consent for the extension study, received at least 1 dose of PER in the extension study, and had valid seizure data during the PER treatment duration (DB and/or extension) (Krauss et al., 2013,2014). The ITT population for the core DB studies consisted of the group of subjects who were randomized to and received at least 1 dose of the study drug and had any seizure data during the DB phase.

The safety analysis set was defined as all patients who received at least 1 dose of PER in the extension study and had at least 1 postdose safety assessment during this period (Krauss et al., 2013). Safety data are presented by predefined ranges of maximum daily dose and include data from the entire PER treatment duration. For AE analyses, PER treatment duration was defined as all exposure to PER in the DB and extension studies (Krauss et al., 2013).

## Results

### *Patient disposition and characteristics*

A total of 1218 eligible patients (96.4% of DB completers) provided informed consent and were enrolled in the extension study (Fig. 1), which included 311 patients from study 304 (105 DB-PBO, 206 DB-PER), 312 patients from study 305 (118 DB-PBO, 194 DB-PER), and 595 patients from study 306 (157 DB-PBO, 438 DB-PER). Of the 1218 patients, 380 were previously randomized to PBO and 838 were randomized to PER in the core DB studies (Krauss et al., 2014).

The safety analysis set included 1216 patients, of which 92.3% of patients received a maximum daily dose of PER 10 or 12 mg/day in the extension study. The mean ± standard deviation dose of PER in the safety analysis set across the entire open-label maintenance period was 10.6 ± 2.3 mg (Krauss et al., 2014).

The demographic characteristics and baseline seizure history of patients were comparable between DB-PBO and DB-PER treatment groups and are summarized in Table 1.

### *Efficacy*

All efficacy results in this study used the ITT analysis data set. The percent reduction in total seizure frequency per 28 days during the extension study (conversion and Weeks 1–52 of the maintenance period) relative to DB prerandomization baseline is summarized in Fig. 2 by previous DB treatment (DB-PBO or DB-PER). At the time of entry into the extension study, the median percent reduction in total seizure frequency per 28 days relative to baseline was 18.6% for patients in the DB-PBO group and 31.7% for patients in the DB-PER group. Relative to the prerandomization phase of the core studies, use of PER in the extension study, regardless of prior PBO or PER administration, decreased total seizure frequency. By the end of the 16-week conversion period during the extension study, patients in the DB-PBO group achieved reductions in seizure frequency similar to those in the DB-PER group: 44.3% for DB-PBO and 41.4% for DB-PER (Fig. 2A). The decrease in seizure frequency was maintained through the first 52 weeks of the open-label maintenance period (Weeks 1–52), with reductions of 55.0% in the DB-PBO group ($n = 209$) and 53.9% in the DB-PER group ($n = 485$) at Weeks 40–52.

Additionally, by the end of the extension conversion period, seizure frequency reductions of CP + SG or SG in the DB-PBO group were similar to those in the DB-PER group (Fig. 2B and C). These improvements were generally maintained through the first 52 weeks of the open-label maintenance period of the extension study, although reduction in SG seizure frequency was greater in DB-PER during Weeks 40–52.

Similarly, relative to the prerandomization baseline of the core DB studies, use of PER in the extension study increased the responder rate (Fig. 3). At the time of entry into the extension study, the responder rate for patients in the DB-PBO group was 20.3%; it increased to 44.3% by the end of the 16-week blinded conversion period. For patients in the DB-PER group, the responder rate increased from 34.0% at the time of entry into the extension study to 43.4% by the end of the 16-week blinded conversion period of the

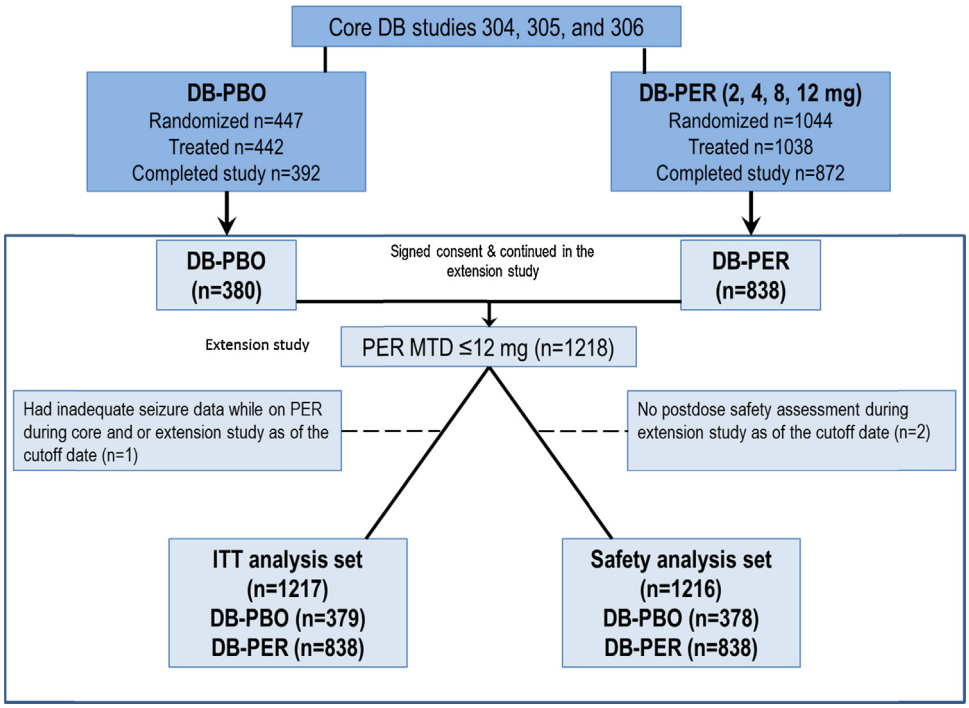


**Figure 1.** Patient disposition in studies 304, 305, and 306 and the extension study.[a] Sources: French et al., 2012,2013; Krauss et al., 2012,2013; Montouris et al., 2012). DB, double blind; ITT, intent to treat; PBO, placebo; PER, perampanel; MTD, maximum tolerated dose.[a]DB-PBO = patients who received placebo in the phase III core DB studies and transitioned to perampanel in the open-label extension study; DB-PER = patients who received perampanel during the core studies and continued with perampanel treatment during the extension study.

extension study. The responder rates were also maintained in both groups through the first 52 weeks of the open-label maintenance period, with similar responder rates at Weeks 40–52 (Fig. 3A). Additionally, the responder rates in the DB-PBO group for CP + SG and SG increased to a level similar to the responder rates in the DB-PER group at the end of the 16-week blinded conversion period (Fig. 3B and C), which was maintained throughout the first 52 weeks of the open-label maintenance period.

In study 304, an unusually high placebo responder rate was observed among patients in the Central and South America region (CA/SA) compared to North American sites (French et al., 2012). To ensure that this high placebo response did not impact the

**Table 1**
Demographic and baseline characteristics of patients in the extension study by previous DB treatment assignment: ITT set.[a]

| Category | DB-PBO (*N* = 379) | DB-PER 2 mg (*N* = 147) | DB-PER 4 mg (*N* = 154) | DB-PER 8 mg (*N* = 356) | DB-PER 12 mg (*N* = 181) | DB-PER overall (*N* = 838) |
|---|---|---|---|---|---|---|
| Median age, years (range)[b] | 33 (12–76) | 31 (13–65) | 32 (12–68) | 34 (12–72) | 32 (12–66) | 33 (12–72) |
| Sex, *n* (%) | | | | | | |
| Male | 200 (52.8) | 66 (44.9) | 79 (51.3) | 177 (49.7) | 89 (49.2) | 411 (49.0) |
| Race, *n* (%) | | | | | | |
| White | 294 (77.6) | 92 (62.6) | 93 (60.4) | 282 (79.2) | 150 (82.9) | 617 (73.6) |
| Black or African American | 9 (2.4) | 0 | 0 | 7 (2.0) | 7 (3.9) | 14 (1.7) |
| Asian | 41 (10.8) | 32 (21.8) | 33 (21.4) | 33 (9.3) | 16 (8.8) | 114 (13.6) |
| Chinese | 26 (6.9) | 22 (15.0) | 27 (17.5) | 21 (5.9) | 0 | 70 (8.4) |
| American Indian or Alaska Native | 0 | 0 | 0 | 4 (1.1) | 1 (<1.0) | 5 (<1.0) |
| Other | 9 (2.4) | 1 (<1.0) | 1 (<1.0) | 9 (2.5) | 7 (3.9) | 18 (2.1) |
| Ethnicity, *n* (%) | | | | | | |
| Hispanic or Latino | 67 (17.7) | 7 (4.8) | 8 (5.2) | 66 (18.5) | 48 (26.5) | 129 (15.4) |
| Median BMI, kg/m$^2$ (range)[b] | 23.88 (14.0–50.5) | 23.41 (16.4–41.7) | 23.82 (12.1–38.4) | 24.93 (15.1–45.3) | 24.58 (15.9–43.9) | 24.44 (12.1–45.3) |
| Seizure type, *n* (%)[c] | | | | | | |
| Simple partial without motor signs | 133 (35.1) | 42 (28.6) | 43 (27.9) | 121 (34.0) | 53 (29.3) | 259 (30.9) |
| Simple partial with motor signs | 112 (29.6) | 43 (29.3) | 50 (32.5) | 110 (30.9) | 54 (29.8) | 257 (30.7) |
| Complex partial | 326 (86.0) | 125 (85.0) | 129 (83.8) | 305 (85.7) | 156 (86.2) | 715 (85.3) |
| Complex partial with secondary generalization | 274 (72.3) | 97 (66.0) | 107 (69.5) | 249 (69.9) | 134 (74.0) | 587 (70.0) |

[a] DB-PBO = patients who received placebo in the phase III core DB studies and transitioned to perampanel in the open-label extension study; DB-PER = patients who received perampanel during the core studies and continued with perampanel treatment during the extension study.
[b] Age at informed consent for the preceding DB study.
[c] BMI and seizure type are at baseline in the preceding DB study.
BMI, body mass index; DB, double blind; ITT, intent to treat; PBO, placebo; PER, perampanel.

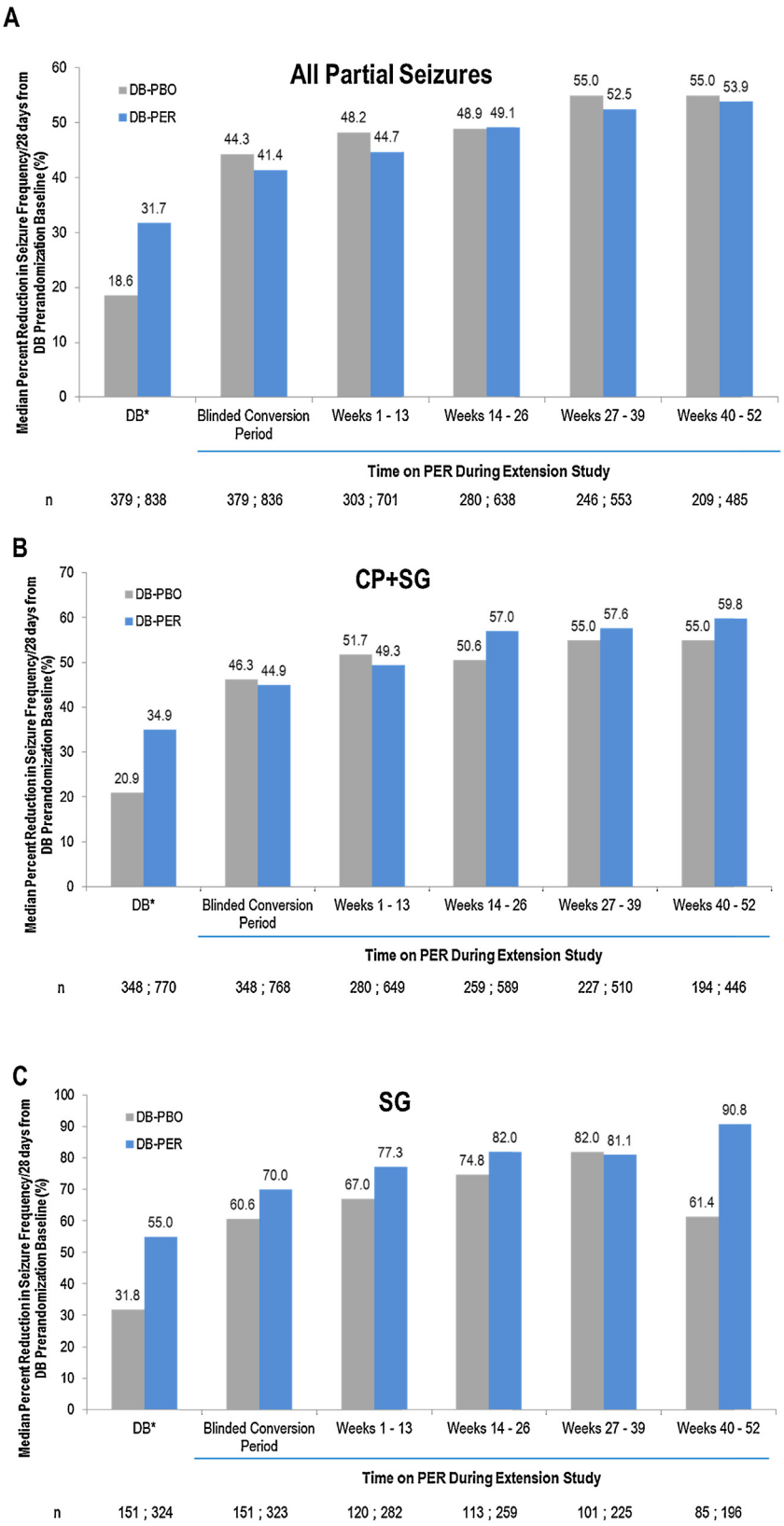


**Figure 2.** Median % reduction in seizure frequency/28 days from the DB prerandomization baseline during treatment duration for all partial seizures (A), CP + SG (B), and only SG (C).[a] *Percent change from prerandomization baseline seizure frequency/28 days during the maintenance period of the core studies (304, 305, and 306). CP, complex partial seizure; PER, perampanel; SG, secondarily generalized seizure.[a]DB-PBO = patients who received placebo in the phase III core DB studies and transitioned to perampanel in the open-label extension study; DB-PER = patients who received perampanel during the core studies and continued with perampanel treatment during the extension study.

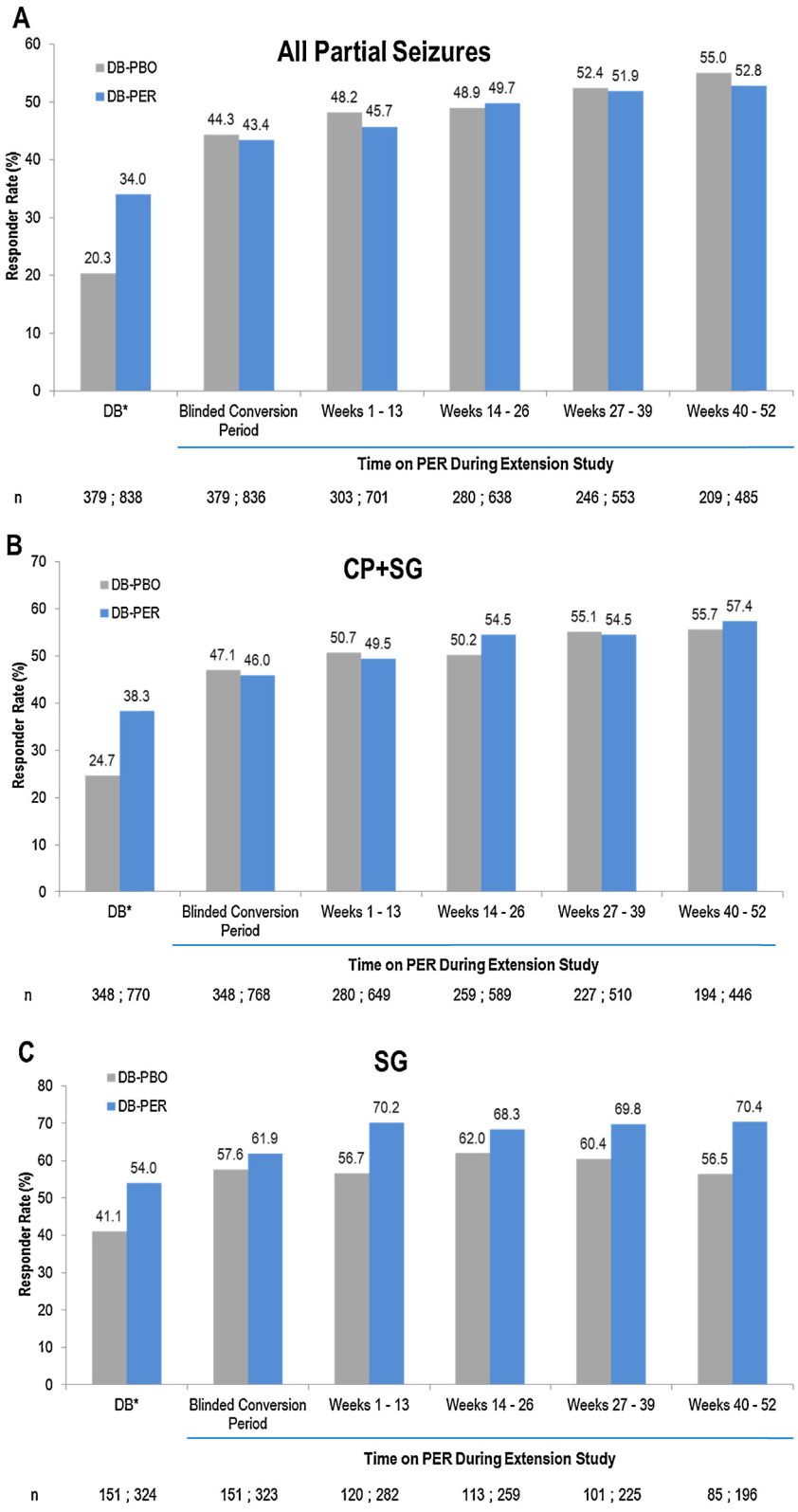


**Figure 3.** Responder rates (% of patients experiencing ≥50% reduction in seizure frequency) from the DB prerandomization period through the indicated treatment duration for all partial seizures (A), CP + SG (B), and only SG (C).[a] *Responder rate during maintenance period of the core studies (304, 305, and 306). CP, complex partial seizure; PER, perampanel; SG, secondarily generalized seizure. [a]DB-PBO = patients who received placebo in the phase III core DB studies and transitioned to perampanel in the open-label extension study; DB-PER = patients who received perampanel during the core studies and continued with perampanel treatment during the extension study.

evaluation of the conversion or the reduction in seizure frequency observed during the extension study with PER, we undertook additional analyses that excluded data from sites in CA/SA (Supplementary Figure 1). At the time of entry into the extension study, the median percent reduction in total seizure frequency per 28 days relative to baseline in the population excluding CA/SA was 15.1% for patients in the DB-PBO group and 31.7% for patients in the DB-PER group (Supplementary Fig. 1A). Except for the median percent

**Table 2**
Overall incidence of TEAEs: safety analysis set.[a]

| Category | DB-PBO (*N* = 378), *n* (%) | DB-PER (*N* = 838), *n* (%) |
|---|---|---|
| TEAEs | 343 (90.7) | 767 (91.5) |
| Treatment-related TEAEs | 304 (80.4) | 689 (82.2) |
| Severe TEAEs | 69 (18.3) | 151 (18.0) |
| Treatment-emergent SAEs* | 77 (20.4) | 150 (17.9) |
| Deaths | 3 (0.8) | 2 (0.2) |
| Other SAEs | 74 (19.6) | 149 (17.8) |
| Life-threatening | 2 (0.5) | 12 (1.4) |
| Requires or prolongs hospitalization | 71 (18.8) | 135 (16.1) |
| Persistent/significant disability/incapacity | 2 (0.5) | 4 (0.5) |
| Congenital anomaly/birth defect | 0 | 0 |
| Important medical events | 6 (1.6) | 19 (2.3) |
| TEAEs leading to dose adjustments | 208 (55.0) | 401 (47.9) |
| TEAEs leading to study/study drug withdrawal | 75 (19.8) | 120 (14.3) |
| TEAEs leading to dose reduction | 162 (42.9) | 321 (38.3) |
| TEAEs leading to dose interruption | 8 (2.1) | 39 (4.7) |

* One subject had multiple SAEs and is summarized in both Deaths and ther SAEs. Adverse events were summarized across the entire PER exposure.

[a] DB-PBO = patients who received placebo in the phase III core DB studies and transitioned to perampanel in the open-label extension study; DB-PER = patients who received perampanel during the core studies and continued with perampanel treatment during the extension study.

DB, double blind; PBO, placebo; PER, perampanel; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

**Table 3**
Rates of the most common TEAEs with an incidence ≥5% in the DB-PBO group compared with the DB-PER group (safety analysis set).[a]

| TEAEs | DB-PBO (*N* = 378), *n* (%) | DB-PER (*N* = 838), *n* (%) |
|---|---|---|
| Dizziness | 171 (45.2) | 398 (47.5) |
| Somnolence | 70 (18.5) | 188 (22.4) |
| Weight increase | 44 (11.6) | 88 (10.5) |
| Irritability | 41 (10.8) | 99 (11.8) |
| Fatigue | 41 (10.8) | 118 (14.1) |
| Headache | 38 (10.1) | 184 (22.0) |
| Ataxia | 31 (8.2) | 49 (5.8) |
| Fall | 31 (8.2) | 68 (8.1) |
| Nasopharyngitis | 28 (7.4) | 86 (10.3) |
| Gait disturbance | 27 (7.1) | 48 (5.7) |
| Convulsion | 27 (7.1) | 69 (8.2) |
| Depression | 22 (5.8) | 44 (5.3) |
| Head injury | 21 (5.6) | 26 (3.1) |
| Dysarthria | 21 (5.6) | 35 (4.2) |
| Aggression | 21 (5.6) | 41 (4.9) |
| Nausea | 21 (5.6) | 75 (8.9) |

Adverse events were summarized across the entire PER exposure.

[a] DB-PBO = patients who received placebo in the phase III core DB studies and transitioned to perampanel in the open-label extension study; DB-PER = patients who received perampanel during the core studies and continued with perampanel treatment during the extension study.

DB, double blind; PBO, placebo; PER, perampanel; TEAE, treatment-emergent adverse event.

reduction in seizure frequency seen in the DB-PBO group at entry into the extension study, which was lower than that reported in the total population (18.6%, Fig. 2A), results at all other time points during the extension study were comparable between the data set in which CA/SA was excluded and the total population. Similarly, relative to the prerandomization baseline of the core DB studies, use of PER in the extension study increased the responder rate in the population excluding CA/SA (Supplementary Fig. 1B), and this was comparable to the data for the total population (shown in Fig. 3). These results suggest that the high placebo response seen in study 304 (French et al., 2012) did not impact the efficacy of PER in patients who transitioned during the extension study (DB-PBO), as seizure reduction and responder rates were comparable to those seen in DB-PER patients, even when the CA/SA population was excluded, starting from the end of the blinded conversion period and continuing throughout the first 52-week maintenance period during the extension study.

To evaluate the impact of conversion to perampanel, an additional analysis in the DB-PBO group was conducted using the 13-week maintenance period seizure frequency of the core DB studies as baseline. The efficacy results demonstrated an improvement for patients in the DB-PBO group that converted to perampanel during the open-label extension study. At the end of the 16-week blinded conversion, the median percent reduction (relative to the 13-week maintenance period seizure frequency of the core DB studies) was 27.1%, and by Weeks 40–52 of the open-label maintenance period the median percent reduction was 39.6%. Similarly, the responder rate was 28.0% and 40.9% at the end of the blinded conversion period and Weeks 40–52 of the maintenance period in the open-label study, respectively.

### *Safety*

The incidence of treatment-emergent adverse events (TEAEs) in the extension study safety population, based on their prior treatment assignment during the core DB studies, is shown in Table 2. TEAEs during the entire PER exposure (extension period for DB-PBO, and DB and extension period for DB-PER) were similar between DB-PBO patients (90.7%, *n* = 343) and DB-PER patients (91.5%, *n* = 767). Treatment-emergent SAEs occurred in 20.4% (*n* = 77) DB-PBO patients and 17.9% (*n* = 150) DB-PER patients. Study withdrawal rates due to TEAEs during the entire PER exposure were slightly higher for DB-PBO patients (19.8%, *n* = 75) compared to withdrawal rates for DB-PER patients (14.3%, *n* = 120).

Incidence rates of the most common TEAEs (≥5%) for DB-PBO patients were generally similar to those for DB-PER patients during the entire PER exposure (Table 3), although somnolence (18.5% vs 22.4%), fatigue (10.8% vs 14.1%), nasopharyngitis (7.4% vs 10.3%) and nausea (5.6% vs 8.9%) were less frequent in the DB-PBO group. The incidence of headache in the DB-PBO group was approximately half that of the DB-PER group, with rates of 10.1% and 22.0%, respectively, whereas the incidence of ataxia and head injury in the DB-PBO group (8.2% and 5.6%, respectively) was slightly greater than in the DB-PER group (5.8% and 3.1%, respectively) throughout the entire PER exposure.

### *Impact of the rate of titration on efficacy and safety*

The impact of a slower titration rate of PER on the safety and efficacy was analyzed by comparing core DB study patients previously assigned to the DB-PER 12-mg treatment group (weekly titration) with patients in the DB-PBO treatment group who switched to PER in the extension study (biweekly titration). At the completion of the 16-week conversion period in the extension study, 64.0% of the DB-PBO group completed the uptitration to a dose level of 10–12 mg; in comparison, 78.4% of the DB-PER 12-mg group completed the 6-week titration DB period to a dose level of 10–12 mg (Table 4). At the end of the first 13-week maintenance period on PER, 71.2% of DB-PBO patients during the extension study and 74.2% of DB-PER 12-mg group during the core DB study were on 10–12 mg/day (Table 4).

Despite the longer exposure to PER, the discontinuation rates due to TEAEs were similar for the DB-PBO group in the 16-week conversion period in the extension study and the DB-PER 12-mg group in the 6-week DB titration period (9.5% vs 9.8%) (Table 4). The discontinuation rates due to TEAEs in the first 13-week maintenance period of PER exposure were 3.3% for the DB-PBO group and 10.0% for the DB-PER 12-mg group (Table 4). During the same period, the rates due to other reasons for discontinuation, which included subject choice and inadequate therapeutic effect, were

**Table 4**
Discontinuation rate and completed doses in DB-PBO compared with DB-PER 12 mg based on last dose (safety analysis set).[a]

| Parameter | Titration period | | Maintenance period | |
|---|---|---|---|---|
| | DB-PBO (*N* = 378) | DB-PER 12 mg (*N* = 255) | DB-PBO (*N* = 306) | DB-PER 12 mg (*N* = 221) |
| | 16-week conversion period (biweekly uptitration) | 6-week titration period (weekly uptitration) | Weeks 1–13 maintenance period (extension study) | 13-week maintenance period (DB study) |
| Discontinuations due to adverse event, *n* (%) | 36 (9.5) | 25 (9.8) | 10 (3.3) | 22 (10.0) |
| Discontinuation due to other reasons, *n* (%) | 36 (9.5) | 9 (3.5) | 15 (4.9) | 6 (2.7) |
| Completed period with last dose of, *n* (%); | | | | |
| 10–12 mg/day | 242 (64.0) | 200 (78.4) | 218 (71.2) | 164 (74.2) |
| ≤8 mg/day | 64 (16.9) | 21 (8.2) | 63 (20.6) | 29 (13.1) |

[a] DB-PBO = patients who received placebo in the phase III core DB studies and transitioned to perampanel in the open-label extension study; DB-PER = patients who received perampanel during the core studies and continued with perampanel treatment during the extension study.
DB, double blind; PBO, placebo; PER, perampanel.

4.9% in the DB-PBO group compared to 2.7% in the DB-PER 12-mg group (Table 4).

The first 13-week maintenance period of PER treatment for the DB-PBO group (Weeks 1–13 in the extension study) and for the DB-PER 12-mg group (13-week maintenance period of the core DB study) were compared for PER efficacy. Median percent reduction in seizure frequency was 48.2% in the DB-PBO group ($n = 303$) compared to 33.4% in the DB-PER 12-mg group ($n = 219$). The corresponding responder rate in the 13-week maintenance period for the DB-PBO group was 48.2%, which was higher than the responder rate of 37.9% for the DB-PER 12-mg group. However, throughout the first 52 weeks of the open-label maintenance period of the extension study, the percent seizure reduction (Fig. 4A) and responder rate (Fig. 4B) were similar between patients in the DB-PBO group and patients previously assigned to DB-PER 12-mg.

## Discussion

This extension study post hoc analysis further highlights the efficacy of PER in patients with drug-resistant partial seizures, specifically in patients who converted from placebo during the core DB phase III studies to PER during the open-label study (DB-PBO). DB-PBO patients who transitioned to PER during the extension study achieved seizure reduction and responder rates comparable to DB-PER patients, starting from the end of the blinded conversion period and maintained throughout the first 52 weeks of the maintenance period of the extension study. In addition, the findings of the extension study show that seizure control was sustained for patients from the core studies who continued PER. PER also reduced CP + SG and SG frequency and improved responder rates in patients from the DB-PBO group, and these results were comparable to those of the DB-PER group. These findings were consistent with results from the previously published three core phase III DB studies (French et al., 2012,2013; Krauss et al., 2012; Steinhoff et al., 2013), further supporting the efficacy of PER. Similar efficacy results were seen when patients from the CA/SA population were excluded in an additional analysis conducted to account for the high placebo response seen in study 304. In addition to presenting efficacy data as "relative to prerandomization baseline seizure frequency," a further analysis using seizure frequency during the maintenance period of the core DB studies as reference was conducted to evaluate the impact of conversion to PER and to provide additional information on the real treatment effect in the DB-PBO group. The results show that, whether using prerandomization seizure frequency or seizure frequency of the last 13 weeks of the DB studies (maintenance period), patients in the DB-PBO group who were taking placebo and 1–3 concomitant AEDs during the core DB studies experienced an improvement in seizure frequency when converted to PER during the open-label extension study.

Because PER is a novel AMPA receptor antagonist that has been approved by the FDA, the EMA, and Health Canada, additional analysis of its long-term safety and tolerability are important. The incidence of TEAEs reported in the DB-PBO and DB-PER groups was similar during the entire PER exposure (extension study for DB-PBO, and DB and extension study for DB-PER). Dizziness, somnolence, weight increase, irritability, fatigue, and headache had the highest incidence rates in both patient groups. The rates of TEAEs leading to withdrawal for both patient groups were in the range reported in the core studies (French et al., 2012,2013; Krauss et al., 2012; Steinhoff et al., 2013). The incidence of SAEs was similar between the 2 groups during the entire PER exposure.

The extension study provided physicians with greater flexibility in dosing and titration rates of PER when compared with the DB studies, as patients were titrated biweekly in the extension study to their individualized MTD—an approach that resembles real-life clinical practice. A slightly higher percentage of patients reached the dose of 10–12 mg/day in the DB-PER 12-mg group at the end of the 6-week titration period in the DB core studies than in the DB-PBO group by the end of the 16-week conversion period in the extension. This difference may have been due in part to the DB design and forced titration over the 6-week period, although dose reductions were permitted for intolerability. Nonetheless, the majority of patients (92.3%) in the safety analysis set of the extension study received a maximum daily dose of PER 10 mg or 12 mg (Krauss et al., 2014). The rate of titration (weekly in the core DB studies vs biweekly in the extension study) did not affect the overall safety profile of PER, as the discontinuation rates due to TEAEs were similar between the DB-PBO group in the conversion period of the extension study and the DB-PER 12-mg group during the DB titration period, despite the longer exposure. These data demonstrate the safety of PER in patients who were not previously exposed to PER. A comparison of efficacy data for the first 13-week maintenance period of PER suggests that a slower titration improves efficacy. Alternatively, the longer PER exposure in the DB-PBO patients (due to 16-week conversion period) compared to DB-PBO 12-mg group (6-week titration) may also explain the difference in efficacy during the first 13-week maintenance period. However, further analysis shows the reduction in seizure frequency was similar between the two groups with exposure to PER throughout the first 52 weeks of the maintenance period of the extension study.

In conclusion, the findings of the post hoc analysis showed that patients who received PBO in the phase III core DB studies and transitioned to PER in the extension study (DB-PBO) achieved similar seizure control at the end of the conversion period, and thereafter efficacy and safety were comparable to patients who had been previously exposed to PER (DB-PER). In addition, seizure control was maintained in patients who received PER during the core studies

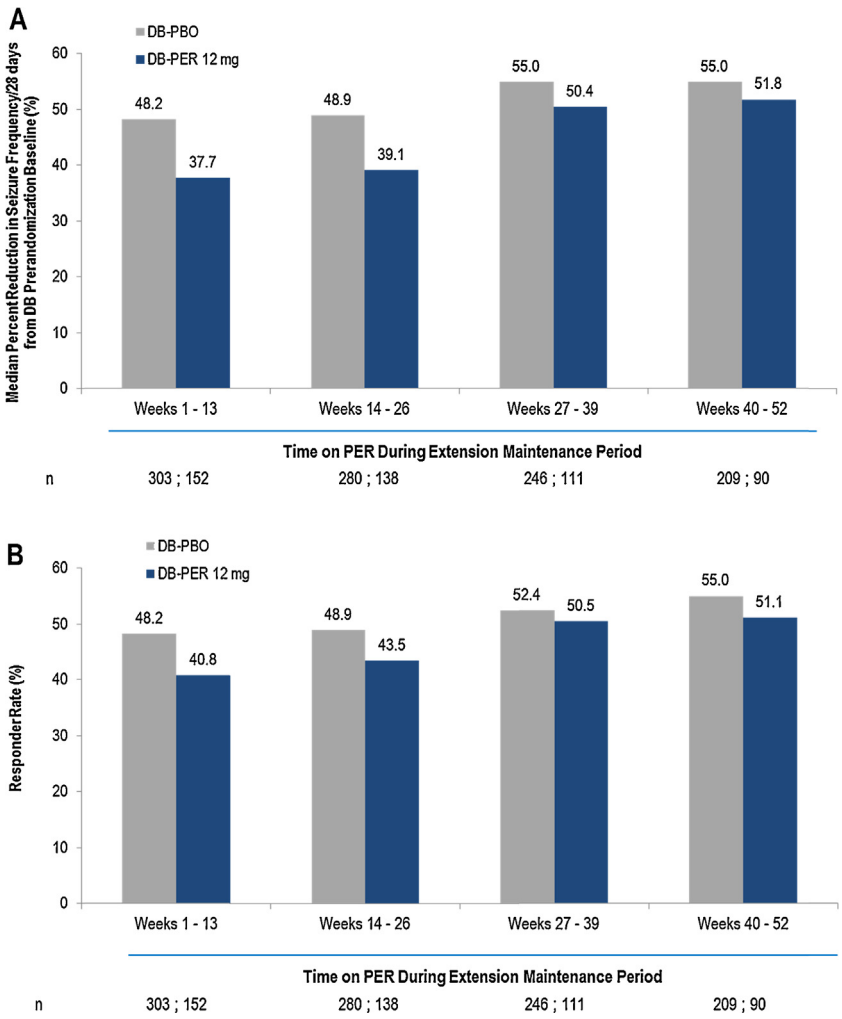


**Figure 4.** Median % reduction in total seizure frequency/28 days (A) and responder rate (B) from the DB prerandomization baseline during the extension open-label maintenance period in DB-PBO and DB-PER 12-mg.[a] DB, double-blind; PBO, placebo; PER, perampanel.[a]DB-PBO = patients who received placebo in the phase III core DB studies and transitioned to perampanel in the open-label extension study; DB-PER 12-mg = patients who were randomized to 12-mg perampanel during the core studies and continued with perampanel treatment during the extension study.

and continued with treatment during the extension study, regardless of titration rate. Taken together, these results demonstrate the long-term efficacy and safety of PER.

## Author contributions

Dr. Montouris: study concept and design, interpretation of data analyses, critical revision of the manuscript for important intellectual content. Dr. Yang: acquisition, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Williams: data analysis and interpretation, and critical revision of the manuscript for important intellectual content. Ms. Zhou: biostatistical data analysis. Dr. Laurenza: acquisition, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Fain: data analysis and interpretation, and critical revision of the manuscript for important intellectual content.

## Disclosures

G. Montouris has served as a consultant within the last year for the following advisory boards: Eisai, Lundbeck, Supernus, Upsher-Smith. H. Yang, B. Williams, S. Zhou, A. Laurenza, and R. Fain are employees of Eisai Inc.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2015.04.011

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