Epilepsy & Behavior 48 (2015) 45–52

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Perampanel in the treatment of partial seizures: Time to onset and duration of most common adverse events from pooled Phase III and extension studies

David Ko [a,*], Haichen Yang [b], Betsy Williams [c], Dongyuan Xing [d], Antonio Laurenza [b]

[a] Keck Medical Center of USC, 1520 San Pablo Street, Los Angeles, CA 90033, USA
[b] Eisai Neuroscience and General Medicine PCU, Eisai Inc., 155 Tice Blvd., Woodcliff Lake, NJ 07677, USA
[c] Eisai Medical and Scientific Affairs, Eisai Inc., 100 Tice Blvd., Woodcliff Lake, NJ 07677, USA
[d] Formerly Eisai Medical and Scientific Affairs, Eisai Inc., 100 Tice Blvd., Woodcliff Lake, NJ 07677, USA

ARTICLE INFO

Article history:
Received 25 February 2015
Revised 11 May 2015
Accepted 12 May 2015
Available online 4 June 2015

Keywords:
Antiepileptic drugs
Epilepsy
Adverse events

ABSTRACT

Perampanel (PER) is a novel noncompetitive AMPA-receptor antagonist approved in over 40 countries for treatment of partial seizures. The safety and tolerability of PER have been well-documented in three double-blind, randomized, placebo (PBO)-controlled Phase III studies and an open-label extension (OLE). This post hoc analysis evaluated the occurrence and characteristics of the most common treatment-emergent adverse events (TEAEs) associated with PER. Results from the Phase III studies were pooled; post hoc analyses on the double-blind phase and up to 1 year of the OLE were performed on the four most common TEAEs for which incidence was higher for PER than PBO. The four most common TEAEs were dizziness, somnolence, fatigue, and irritability. For most subjects in the Phase III double-blind studies, these TEAEs were observed during 6-week titration and were mild or moderate in severity. For severe AEs, no dose–response relationship was observed. Patients in the PBO group during Phase III (who therefore received their first PER treatment during OLE) experienced these TEAEs with incidence and timing similar to that of PER-treated patients in Phase III. The first onset of these TEAEs occurred during the early weeks of PER conversion in the OLE. After 6 months and up to 1 year of PER treatment, low to no incidence of the first onset of the four TEAEs was observed. Post hoc analyses of data from pooled Phase III studies provide greater insight into occurrence/duration of TEAEs. Phase III double-blind and OLE data showed that dizziness, somnolence, fatigue, and irritability were the most common TEAEs reported by patients taking PER. Additionally, these results suggest consistency between studies in patient responses to onset of these TEAEs. Although concomitant antiepileptic drugs (AEDs) might be predicted to affect development of TEAEs in patients taking PER, an effect was not observed in this analysis. The low incidence of TEAEs in these studies provides additional support for long-term PER treatment.

1. Introduction

Perampanel (PER) is approved in the United States for the adjunctive treatment of partial seizures, with or without secondarily generalized seizures, in patients 12 years of age or older with epilepsy [1]. It is approved in the European Union, in Canada (for patients 18 years of age or older), and, to date, has been approved in more than 40 countries worldwide [2–4]. Perampanel has a novel mechanism of action, being a selective, noncompetitive AMPA receptor antagonist. There were three randomized, double-blind, placebo (PBO)-controlled Phase III studies that demonstrated significant decreases in seizure frequency with PER at 4-, 8-, and 12-mg daily doses compared to PBO [5–7].

All antiepileptic drugs (AEDs) are associated with risk for adverse events (AEs); thus, minimizing AEs is an important consideration in their successful use [8,9]. The nature, distribution, and severity of these AEs vary widely by drug, by patient characteristics, and by interactions with other drugs, among other factors [8,9].

This article describes the post hoc analyses of the occurrence and nature of AEs associated with PER therapy in patients with partial seizures observed in the double-blind phase of three Phase III studies and during the first 52 weeks of an open-label extension (OLE). Analysis of the pooled Phase III data focused on the frequency, severity, time to the first onset, and duration of the four most common treatment-emergent adverse

Abbreviations: AED, antiepileptic drug; DB, double blind; MedDRA, Medical Dictionary for Regulatory Activities; MTD, maximum tolerated dose; OLE, open-label extension; PBO, placebo; PER, perampanel; TEAE, treatment-emergent adverse event.

* Corresponding author. Tel.: +1 323 442 5710.
E-mail addresses: dko@usc.edu (D. Ko), haichen_yang@eisai.com (H. Yang), betsy_williams@eisai.com (B. Williams), dyxing2010@gmail.com (D. Xing), antonio_laurenza@eisai.com (A. Laurenza).

http://dx.doi.org/10.1016/j.yebeh.2015.05.020

events (TEAEs) observed. The relationship of these TEAEs to dosing during titration and maintenance in the three Phase III studies was also determined. Analysis of OLE data focused on the time to the first onset of the TEAEs over the course of up to 52 weeks of PER treatment.

2. Methods

2.1. Phase III studies

All three Phase III studies [5–7] included subjects 12 years of age or older with refractory partial seizures despite treatment with one to three AEDs. The use of concomitant AEDs at baseline for PER and PBO treatment groups is summarized in Table 1. The studies were multinational, multicenter, randomized, double-blind, and PBO-controlled. They all included an initial 6-week baseline period. This was followed by a 19-week, double-blind phase (6 weeks of titration and 13 weeks of maintenance). In two of the three studies, subjects were randomized in equal proportion to once daily PER 8 mg, PER 12 mg, or PBO, while in the third study, subjects were equally randomized to once daily PER 2 mg, 4 mg, or 8 mg, or PBO. After completing the double-blind phase, subjects were eligible to immediately enter the open-label extension study, or proceed into a 4-week follow-up period in which no PER treatment was provided. In all three studies, regardless of patients' baseline AEDs, PER dosing was initiated at 2 mg daily and increased at a rate of 2 mg per week during titration until the randomized target dose was reached. If a patient experienced tolerability issues, the investigator had the authority to reduce the dose by 2 mg, but more than a single 2-mg dose reduction was discouraged. Subsequent uptitration was permitted if tolerability issues resolved [5–7].

Assessment of safety and tolerability included recording of AEs, previous and concomitant medication use, discontinuations, clinical laboratory parameters, vital signs, electrocardiography studies, physical and neurologic examinations, and administration of both photosensitivity and withdrawal questionnaires. Treatment-emergent adverse events were recorded for each subject at every study visit, regardless of possible relationship to the study drug [5–7].

2.2. Open-label extension

Enrollment in the OLE was available exclusively to subjects who had completed the double-blind phase of a Phase III study. The ongoing OLE is comprised of three stages: (1) a 16-week, blinded conversion period; (2) a 256-week, open-label maintenance period; and (3) a 4-week follow-up period [10]. Data presented herein represent results from up to the first 52 weeks of PER treatment.

Table 1
Use of concomitant antiepileptic drugs at baseline, from pooled Phase III study data.

Antiepileptic drug	Placebo group (N = 442) n (%)	Total perampanel group (N = 1038) n (%)
Carbamazepine	143 (32.4)	348 (33.5)
Lamotrigine	125 (28.3)	333 (32.1)
Levetiracetam	125 (28.3)	310 (29.9)
Oxcarbazepine	88 (19.9)	182 (17.5)
Topiramate	90 (20.4)	204 (19.7)
Valproic acid	140 (31.7)	338 (32.6)
CYP enzyme inducing (EIAEDs)	255 (57.7)	610 (58.8)
1 AED	27 (6.1)	66 (6.4)
2 AEDs	131 (29.6)	313 (30.2)
3 AEDs	97 (21.9)	231 (22.3)
Non-EIAEDs	187 (42.3)	427 (41.1)
1 AED	33 (7.5)	80 (7.7)
2 AEDs	87 (19.7)	220 (21.2)
3 AEDs	67 (15.2)	127 (12.2)
Total		
1 AED	60 (13.6)	146 (14.1)
2 AEDs	218 (49.3)	533 (51.3)
3 AEDs	164 (37.1)	358 (34.5)

All subjects who had attained a once daily, 12-mg dose of PER during their Phase III study remained on that dose upon entry into the OLE. Subjects who previously received PBO or whose dose of PER was <12 mg/day remained blinded to their Phase III dose, which was uptitrated during the conversion period in 2-mg increments every 2 weeks to an individualized maximum tolerated dose (MTD) of ≤12 mg/day; this titration rate was half as fast as the 2-mg/week titration of the Phase III studies. Subjects remained on their MTD of PER unless the investigator determined that additional dose titration was needed to address tolerability or efficacy issues. Discontinuation, also at the investigator's discretion, was automatic for subjects unable to tolerate a 2-mg daily dose. Concomitant AED regimens from the Phase III studies were maintained at entry into the OLE but could be adjusted at the investigator's discretion. Safety evaluations in the OLE were similar to those in the Phase III studies [10].

The study subjects were divided into two groups for this post hoc analysis: those who received PER during both the double-blind Phase III studies and the OLE (DB-PER, includes the 19 weeks of double-blind Phase III studies), and those who received PBO during Phase III and converted to PER during the OLE (DB-PBO, starts with the 16 weeks of conversion in the OLE). Results from the OLE are reported here as "time to first onset" for TEAEs, and were analyzed over a period of up to 52 weeks of PER treatment.

2.3. Statistical methods

A TEAE was defined as an adverse event that began either on or after the first dose date and up to 30 days after the last dose date of study drug, or that began before the first dose date and increased in severity during the treatment period. In the analysis of overall frequency, a subject who had two or more AEs with the same Medical Dictionary for Regulatory Activities (MedDRA) preferred term was counted only once. Adverse event frequency was also stratified by AE severity. In the computation of duration, if AE outcome was unrecovered, recovering, or unknown, the AE ending date was imputed with the last dose date plus 30 days. The analysis on duration of AEs was limited to the first AE if the subject had more than one AE.

Analysis by dose level was based on the dose groups at the end of the study. Four subjects who did not receive PER at the end of the study were not shown in figures and tables due to small n values, but were included in the total PER group. Because this was a post hoc analysis, *p* values are not provided.

3. Results

Safety results from all three Phase III studies were pooled, resulting in a safety population of 1480 study subjects (PER, n = 1038; PBO, n = 442). Of the 1264 study subjects who completed the double-blind Phase III studies, 1218 (96.4%) elected to enter the OLE. Of these, 380 were DB-PBO subjects, and 838 were DB-PER subjects. The safety population for the OLE was comprised of 1186 study subjects [10].

3.1. Pooled Phase III study data

Table 2 illustrates TEAEs occurring in ≥5% of subjects in the safety analysis set who received PER during the double-blind Phase III studies and has been reported previously [11,12]. Very common TEAEs were defined as those occurring in ≥10% of patients in any treatment group and included dizziness, somnolence, headache, fatigue, irritability, and fall. Of these, the four TEAEs occurring with greater frequency in the total PER group than in the PBO group were dizziness (28.1% vs 9.0%), somnolence (14.5% vs 7.2%), fatigue (8.5% vs 4.8%), and irritability (7.0% vs 2.9%). Headache, the third most very common TEAE in the PER group, occurred with approximately the same frequency in the PER and PBO groups (11.4% and 11.3%, respectively). As shown in Fig. 1, severity of the four TEAEs was mild or moderate in most cases.