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Efficacy and safety of adjunctive perampanel in adolescent patients with epilepsy: Post hoc analysis of six randomized studies

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ABSTRACT

Objective: This post hoc analysis of six randomized, double-blind, Phase II and III studies evaluated efficacy and safety of adjunctive perampanel (2–12 mg/day) in adolescent patients (aged ≥12 to ≤17 years) with uncontrolled partial-onset seizures, with or without secondarily generalized (SG) seizures, or primary generalized tonic–clonic (PGTC) seizures.

Methods: Adolescent patients from Studies 304 (NCT00699972), 305 (NCT00699582), 306 (NCT00700310), 335 (NCT01618695), 235 (NCT01161524), and 332 (NCT01393743) were included. Efficacy assessments (split by seizure type) included median percent change in seizure frequency per 28 days from baseline and seizure-freedom rates. Safety assessments (all seizure types combined) included monitoring of treatment-emergent adverse events (TEAEs).

Results: The Safety Analysis Set included 372 adolescent patients (placebo, n = 114; perampanel, n = 258); the Full Analysis Set included 346 patients with partial-onset seizures (placebo, n = 103; perampanel, n = 243), of whom 125 experienced SG seizures during baseline (placebo, n = 37; perampanel, n = 88), and 22 with PGTC seizures (placebo, n = 9; perampanel, n = 13). Compared with placebo, perampanel 8 and 12 mg/day conferred greater median percent reductions in seizure frequency per 28 days for partial-onset seizures (18.0% vs 35.9% and 53.8% [both $P < 0.01$]) and SG seizures (24.4% vs 72.8% [$P < 0.001$] and 57.8% [$P < 0.01$]), and greater seizure-freedom rates (partial-onset: 7.8% vs 13.2% and 11.8% [not statistically significant]; SG: 8.1% vs 40.7% [$P < 0.001$] and 41.7% [$P < 0.01$]). For PGTC seizures, and compared with placebo, perampanel 8 mg/day was also associated with greater median percent reductions in seizure frequency per 28 days (29.8% vs 88.0%) and greater seizure-freedom rates (11.1% vs 23.1%). Treatment-emergent adverse events were reported in 76 (66.7%) placebo- and 192 (74.4%) perampanel-treated patients (most common: dizziness, somnolence, headache, and nasopharyngitis). Serious TEAEs occurred in 5 (4.4%) placebo- and 11 (4.3%) perampanel-treated patients.

Conclusions: Adjunctive perampanel was efficacious and generally well tolerated in adolescent patients with partial-onset, SG, or PGTC seizures and represents a potentially beneficial treatment option for adolescents with uncontrolled epilepsy.

Abbreviations: AE, adverse event; ADHD, attention-deficit hyperactivity disorder; AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EIAED, enzyme-inducing antiepileptic drug; inad. ther. effect, inadequate therapeutic effect; max, maximum; MedDRA, Medical Dictionary for Regulatory Activities; min, minimum; PGTC, primary generalized tonic–clonic; PK, pharmacokinetic; SD, standard deviation; SG, secondarily generalized; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.

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1. Introduction

The management of epilepsy can be difficult due to its complex nature and the fact that the incidence of epilepsy varies as a function of age [1,2]. Many seizure types and syndromes have a specific age of onset and, given that some antiepileptic drugs (AEDs) are more effective against certain seizure types, some AEDs will be more appropriate for certain age groups than other AEDs [1]. Therefore, physicians must consider both the patient's age and seizure type(s) when selecting the most appropriate AEDs. Treatment of adolescent patients with epilepsy can pose additional challenges, not least because adolescence can be a difficult period of life even without the complications of living with a chronic disease [2]. It has been reported that approximately 40–50% of children with epilepsy will continue to have epilepsy well into adulthood [3]; therefore, effective and comprehensive transition of care from pediatric to adult care services is required during adolescence, which can further complicate treatment management in this age group. In addition, AEDs can have a detrimental impact upon cognitive outcomes in patients with epilepsy [4–6], as well as leading to behavioral and emotional side effects, which may be particularly important for children and adolescents [7–9]. Therefore, the neuropsychological profiles of AEDs also need to be carefully considered when selecting which AED(s) to prescribe to adolescent patients.

Adherence to AEDs is important for preventing or minimizing seizures and is correlated with clinical outcome in patients with epilepsy [10]. However, adherence can be problematic, particularly in adolescent patients, since it is not unusual for patients in this age group to forget to take their AEDs or to self-initiate trials off medication [1,2,11,12]. It has been suggested that nonadherence can be associated with the complexity of the drug regimen, with greater adherence reported among patients receiving drugs requiring fewer daily intakes compared with those receiving drugs requiring multiple daily intakes [2,13–17]. Thus, an AED requiring fewer daily intakes may help to improve adherence in patients with epilepsy and, in particular, adolescent patients [2,17].

Perampanel, a selective, noncompetitive, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is a once-daily oral AED for partial-onset seizures and primary generalized tonic–clonic (PGTC) seizures [18,19]. Perampanel is approved in the United States for the treatment of partial-onset seizures (adjunctive and monotherapy) in patients 4 years of age and above, and as adjunctive treatment of PGTC seizures in patients 12 years of age and above [19]. Adjunctive perampanel has previously demonstrated efficacy and safety in a number of Phase II and Phase III, randomized double-blind, placebo-controlled trials in adolescent and adult patients with uncontrolled partial-onset seizures, with or without secondarily generalized (SG) seizures [20–24], or idiopathic generalized epilepsy and PGTC seizures [25]. In addition, in a Phase II cognition study and its open-label extension phase in adolescent patients with partial-onset seizures, with or without SG seizures, adjunctive perampanel treatment was not associated with any short- or long-term effects on the global cognition score [24,26].

Perampanel is metabolized via oxidation and sequential glucuronidation, primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5) [19,27,28]. Previous population pharmacokinetic (PK) analyses have shown that CYP3A4 enzyme-inducing AEDs (EIAEDs), including carbamazepine, oxcarbazepine, and phenytoin, significantly increase perampanel apparent oral clearance [19,29]. As such, patients receiving perampanel concomitantly with EIAEDs may require a higher perampanel dose and/or more frequent uptitration schedule to achieve similar efficacy to patients receiving non-EIAEDs [29,30]. Therefore, it is important to assess perampanel efficacy both with and without EIAEDs.

Here, we report a post hoc analysis of data from six double-blind studies to characterize the efficacy and safety of adjunctive perampanel (2–12 mg/day) in adolescent patients (aged ≥12 to ≤17 years) with uncontrolled partial-onset seizures, with or without SG seizures, or PGTC seizures. A subanalysis was also included to assess efficacy outcomes in adolescent patients who were receiving EIAEDs during baseline compared with those who were receiving only non-EIAEDs. The data reported here build on a previous post hoc analysis of efficacy and safety outcomes with adjunctive perampanel in adolescent patients with partial-onset seizures [9] by including a larger patient population to consider a range of seizure types.

2. Methods

2.1. Study designs

The designs of Studies 304 (NCT00699972), 305 (NCT00699582), 306 (NCT00700310), 335 (NCT01618695), 235 (NCT01161524), and 332 (NCT01393743) have been previously reported in detail [20–25]. In brief, patients aged ≥12 years with uncontrolled partial-onset seizures, with or without SG seizures, or PGTC seizures were randomized to receive once-daily placebo or adjunctive perampanel 2–12 mg/day across a double-blind treatment phase. The majority of studies used 1:1 randomization for placebo vs perampanel; however, Study 235 used 1:2 randomization [20–25]. During the double-blind studies, patients could receive treatment with 1–3 concomitant AEDs, only one of which was permitted to be an EIAED. All studies were performed in accordance with the Declaration of Helsinki and Good Clinical Practice ICH-E6 Guideline CPMP/ICH/135/95, and all patients provided written informed consent to participate. Further details on the designs of these six studies are provided in Supplementary Table S1.

2.2. Post hoc analysis

This post hoc analysis included efficacy and safety data from adolescent patients (aged ≥12 to ≤17 years) with partial-onset seizures, with or without SG seizures, or PGTC seizures who participated in Studies 304, 305, 306, 335, 235, or 332. A subanalysis was also performed for adolescent patients with partial-onset seizures who experienced SG seizures during the baseline periods of Studies 304, 305, 306, 335, or 235. For patients with partial-onset seizures, analyses were performed for placebo vs perampanel 2, 4, 8, and 12 mg/day and placebo vs perampanel 4–12 mg/day combined. For patients with PGTC seizures, analyses were performed for placebo vs perampanel 8 mg/day.

Efficacy and safety were also assessed in adult patients aged ≥18 years with partial-onset seizures, with or without SG seizures, or PGTC seizures from Studies 304, 305, 306, 335, and 332. Outcomes in adult patients were compared with the equivalent outcomes in adolescent patients as part of this post hoc analysis.

2.3. Efficacy assessments

Efficacy assessments were based on the Full Analysis Set, which consisted of all randomized patients who received ≥1 dose of study drug and had any postbaseline seizure frequency data available. The Full Analysis Set was split by seizure type at baseline (partial-onset seizures [with or without SG seizures], SG seizures, or PGTC seizures). Efficacy assessments included the following: median percent change in seizure frequency per 28 days (baseline vs double-blind treatment phase); 50% and 75% responder rates (defined as the proportion of patients with a ≥50% or ≥75% reduction in seizure frequency between baseline and the maintenance phase; last observation carried forward); and seizure-freedom rates (defined as the proportion of patients who were study completers and free from seizures during the maintenance phase). Efficacy outcomes were also stratified by baseline EIAED use for adolescent patients with partial-onset seizures and the subgroup of patients who experienced SG seizures during baseline; because of the low patient numbers, efficacy outcomes stratified by EIAED use are not reported here for adolescent patients with PGTC seizures. For these analyses, EIAEDs were defined as carbamazepine, oxcarbazepine, phenytoin, and eslicarbazepine.

2.4. Safety assessments

Safety assessments were based on the Safety Analysis Set, which consisted of all patients who received ≥1 dose of study drug and had ≥1 postdose safety assessment. Safety data were combined for all seizure types and included monitoring of treatment-emergent adverse events (TEAEs) using Medical Dictionary for Regulatory Activities (MedDRA) search terms, serious TEAEs, and discontinuation rates.

2.5. Statistical analysis

Changes in seizure frequency were analyzed using rank analysis of covariance with treatment as factors and prerandomization seizure frequency as a covariate. Responder and seizure-freedom rates were analyzed using the Cochran–Mantel–Haenszel test, stratified by country. Outcomes with perampanel were considered to be significantly different from those with placebo when $P < 0.05$. Because of the small number of adolescent patients with PGTC seizures (n = 22), statistical analysis is not reported here for these patients.

3. Results

3.1. Patients

Overall, 375 adolescent patients were randomized during the six double-blind studies. The number of adolescent patients by individual study is provided in Fig. 1A. Of the 375 randomized patients, 372 were treated and included in the Safety Analysis Set (placebo, n = 114; perampanel, n = 258; Fig. 1B). Across studies, 39 adolescent patients discontinued treatment, including 15 (13.2%) placebo-treated patients and 24 (9.3%) perampanel-treated patients (Fig. 1B). In both the placebo and perampanel groups, the most common reasons for discontinuation were patient choice and adverse events (AEs). In the Safety Analysis Set, demographics and clinical characteristics during baseline were generally balanced between treatment groups for all seizure types (Table 1). Overall, 172 (49.1%) patients with partial-onset seizures, 59 (46.5%) patients with SG seizures during baseline, and 3 (13.6%) patients with PGTC seizures were receiving treatment with an EIAED during baseline (Table 1).

The Full Analysis Set included 346 patients with partial-onset seizures (placebo, n = 103; all perampanel dose groups, n = 243) and 22 patients with PGTC seizures (placebo, n = 9; perampanel 8 mg/day, n = 13). Of the 346 patients with partial-onset seizures, 125 patients experienced SG seizures during baseline (placebo, n = 37; all perampanel dose groups, n = 88).

3.2. Efficacy outcomes

Compared with placebo, perampanel 8 and 12 mg/day conferred significantly greater median percent reductions in seizure frequency per 28 days in adolescent patients with partial-onset seizures (18.0% vs 35.9% and 53.8%, respectively [both $P < 0.01$]) and those who had SG seizures during baseline (24.4% vs 72.8% [$P < 0.001$] and 57.8% [$P < 0.01$], respectively). Box and whisker plots showing median and mean percent change in partial-onset and SG seizure frequency per 28 days for adolescent patients in each treatment group are presented in Fig. 2A and B. Responder rates (50% and 75%) were also significantly greater with perampanel 8 and 12 mg/day compared with placebo for partial-onset seizures and SG seizures, except for the 50% responder rate for SG seizures with perampanel 12 mg/day, which did not quite reach statistical significance ($P = 0.0501$; Fig. 3A and B). Partial-onset seizure-freedom rates were 7.8% with placebo vs 13.2% and 11.8% with perampanel 8 and 12 mg/day, respectively; however, these differences were not statistically significant (Fig. 3A). In patients who had SG seizures during baseline, SG seizure-freedom rates were 8.1% with placebo vs 40.7% ($P < 0.001$) and 41.7% ($P < 0.01$) with perampanel 8 and 12 mg/day, respectively (Fig. 3B).

For adolescent patients with PGTC seizures, and compared with placebo, perampanel 8 mg/day was associated with greater median percent reductions in seizure frequency per 28 days (29.8% vs 88.0%, respectively [statistical significance not reported due to the small number of adolescent patients with PGTC seizures]). Box and whisker plots showing median and mean percent change in PGTC seizure frequency per 28 days for adolescent patients receiving placebo or perampanel 8 mg/day are presented in Fig. 2C. Greater 50% and 75% responder rates were also observed with perampanel 8 mg/day compared with placebo (33.3% vs 53.8% and 22.2% vs 53.8%, respectively [statistical significance not reported due to small patient numbers; Fig. 3C]). Primary generalized tonic–clonic seizure freedom was reported in 11.1% of placebo-treated patients compared with 23.1% of perampanel-treated patients (statistical significance not reported due to small patient numbers; Fig. 3C).

For patients with partial-onset or SG seizures who were only receiving non-EIAEDs during baseline, and compared with placebo, perampanel 8 and 12 mg/day were associated with significantly greater median percent reductions in seizure frequency per 28 days (partial-onset seizures:15.4% vs 52.7% and 66.1%, respectively [both $P < 0.01$]; SG seizures: 26.8% vs 66.6% and 68.6%, respectively [both $P < 0.05$; Supplementary Fig. S1A]), significantly greater 50% responder rates (partial-onset seizures: 21.3% vs 57.8% and 73.7%, respectively [both $P < 0.001$; Supplementary Fig. S2A]; SG seizures: 21.4% vs 78.1% [$P < 0.001$] and 75.0% [$P < 0.05$], respectively [Supplementary Fig. S3A]), and significantly greater 75% responder rates (partial-onset seizures: 12.8% vs 41.0% [$P < 0.001$] and 36.8% [$P < 0.05$], respectively [Supplementary Fig. S2A]; SG seizures: 14.3% vs 56.3% [$P < 0.01$] and 62.5% [$P < 0.05$], respectively [Supplementary Fig. S3A]). Compared with placebo, partial-onset and SG seizure-freedom rates were also greater with perampanel 8 and 12 mg/day for patients only receiving non-EIAEDs during baseline; statistical significance was reached for the perampanel 8mg/day dose for partial-onset and SG seizures, and for the 12mg/day dose for SG seizures only (Supplementary Figs. S2A and S3A).

For patients with partial-onset and SG seizures who were receiving an EIAED during baseline, statistically significant differences between placebo and perampanel were not observed for the majority of efficacy outcomes (Supplementary Figs. S1B, S2B, and S3B); however, compared with placebo, perampanel 8 mg/day was associated with a significantly greater median percent reduction in seizure frequency per 28 days (7.9% vs 75.7%; $P < 0.05$) and a significantly greater seizure-freedom rate (13.0% vs 40.9%; $P < 0.05$) in patients with SG seizures during baseline.

For all seizure types, the mean (standard deviation [SD]) plasma perampanel concentration (taken across all perampanel doses and normalized by dose) was higher in adolescent patients receiving concomitant non-EIAEDs compared with those receiving concomitant EIAEDs: 568.3 (427.2) ng/mL vs 231.8 (227.6) ng/mL, respectively, in patients with partial-onset seizures, with or without SG seizures; and 487.7 (267.8) ng/mL vs 290.0 (61.6) ng/mL, respectively, in patients with PGTC seizures.

Efficacy outcomes in adolescent patients were broadly consistent with the equivalent outcomes in adult patients (aged ≥18 years) who were also receiving placebo or adjunctive perampanel 2, 4, 8, or 12 mg/day (Table 2).

3.3. Safety outcomes

Across the six double-blind studies, TEAEs were experienced by 268 adolescent patients (placebo, n = 76 [66.7%]; perampanel, n = 192 [74.4%]; Table 3). With perampanel, the most common TEAEs were dizziness, somnolence, headache, and nasopharyngitis (Table 3). The majority of patients had TEAEs that were considered as mild

a)

Study	Placebo (n=114)	Perampanel mg/day 2 (n=21)	4 (n=36)	8 (n=167)	12 (n=34)	Combined total (N=372)
304, n (%)	14 (12.3)	0 (0.0)	0 (0.0)	15 (9.0)	10 (29.4)	39 (10.5)
305, n (%)	17 (14.9)	0 (0.0)	0 (0.0)	17 (10.2)	10 (29.4)	44 (11.8)
306, n (%)	14 (12.3)	21 (100.0)	13 (36.1)	12 (7.2)	0 (0.0)	60 (16.1)
335, n (%)	12 (10.5)	0 (0.0)	23 (63.9)	25 (15.0)	14 (41.2)	74 (19.9)
235, n (%)	48 (42.1)	0 (0.0)	0 (0.0)	85 (50.9)	0 (0.0)	133 (35.8)
332, n (%)	9 (7.9)	0 (0.0)	0 (0.0)	13 (7.8)	0 (0.0)	22 (5.9)

b)

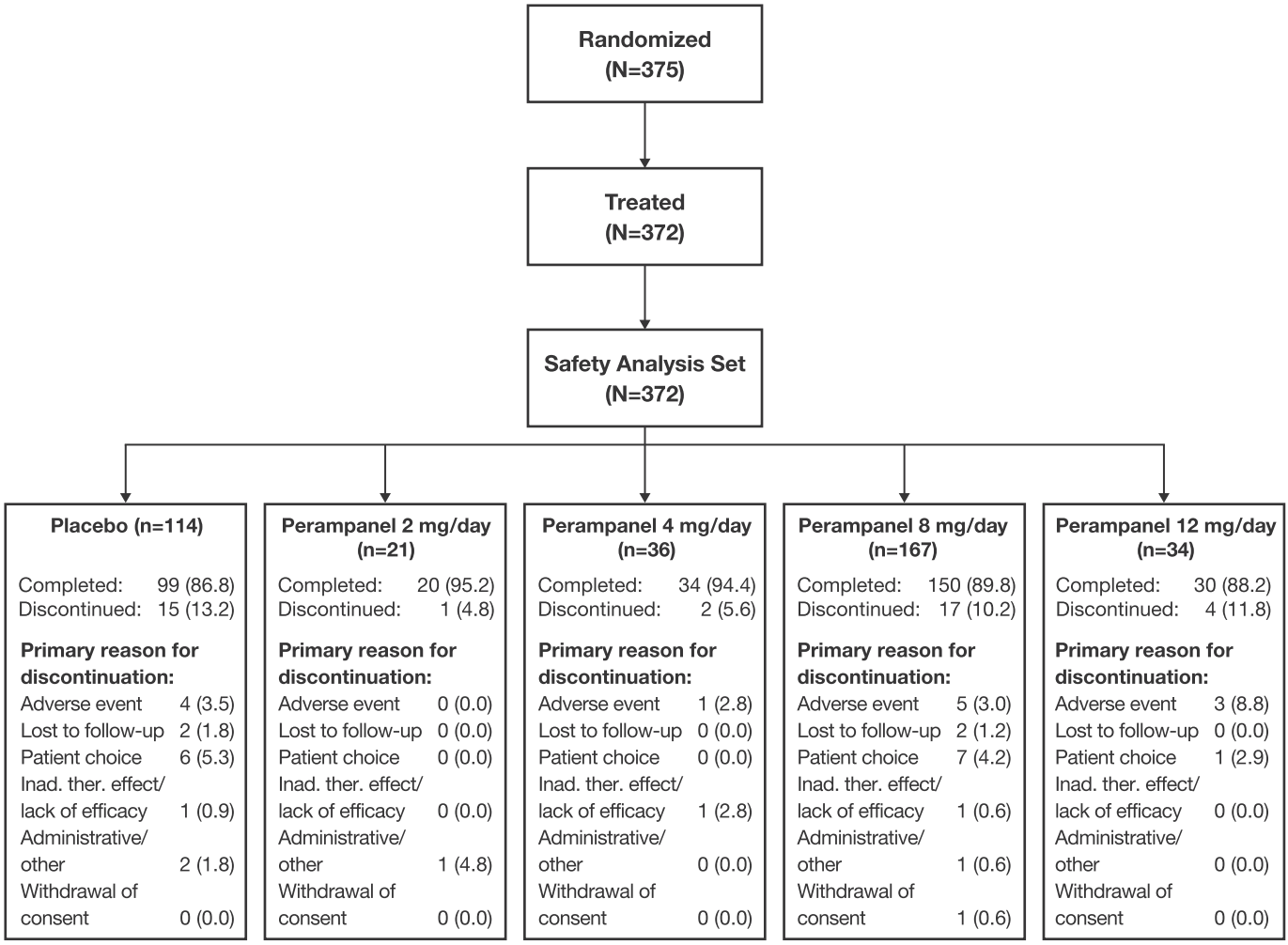

Fig. 1. (a) Adolescent patient numbers by individual study and (b) adolescent patient disposition (Safety Analysis Set). Inad. ther. effect, inadequate therapeutic effect.

(placebo, n = 49 [43.0%]; perampanel, n = 107 [41.5%]) or moderate (placebo, n = 21 [18.4%]; perampanel, n = 71 [27.5%]) in severity; severe TEAEs were experienced by 6 (5.3%) placebo-treated patients and 14 (5.4%) perampanel-treated patients.

Serious TEAEs were reported in 5 (4.4%) placebo-treated patients and 11 (4.3%) perampanel-treated patients (2 mg, n = 1; 8 mg, n = 6; 12 mg, n = 4) (Table 3 and Supplementary Table S2). Serious TEAEs related to psychiatric or nervous system disorders, by randomized treatment

Table 1
Demographic and clinical characteristics in adolescent patients (aged ≥12 to ≤17 years) during baseline (Safety Analysis Set split by seizure type).

	Partial-onset seizures (with or without SG seizures)						SG seizures[a]						PGTC seizures	
	Placebo (n = 105)	Perampanel mg/day					Placebo (n = 38)	Perampanel mg/day					Placebo (n = 9)	Perampanel 8 mg/day (n = 13)
		2 (n = 21)	4 (n = 36)	8 (n = 154)	12 (n = 34)	Perampanel 4–12 mg/day combined (n = 224)		2 (n = 5)	4 (n = 17)	8 (n = 55)	12 (n = 12)	Perampanel 4–12 mg/day combined (n = 84)		
Mean age, years (SD)	14.4 (1.7)	15.1 (1.7)	14.6 (1.7)	14.6 (1.8)	14.8 (1.5)	14.6 (1.8)	14.3 (1.6)	14.4 (2.0)	14.6 (1.8)	15.0 (1.7)	15.3 (1.2)	15.0 (1.7)	15.4 (1.1)	14.8 (1.5)
Female, n (%)	43 (41.0)	12 (57.1)	18 (50.0)	61 (39.6)	15 (44.1)	94 (42.0)	12 (31.6)	2 (40.0)	9 (52.9)	24 (43.6)	3 (25.0)	36 (42.9)	7 (77.8)	8 (61.5)
Race, n (%)														
Caucasian	66 (62.9)	18 (85.7)	10 (27.8)	85 (55.2)	16 (47.1)	111 (49.6)	22 (57.9)	5 (100.0)	6 (35.3)	30 (54.5)	5 (41.7)	41 (48.8)	4 (44.4)	5 (38.5)
Asian	33 (31.4)	3 (14.3)	26 (72.2)	60 (39.0)	15 (44.1)	101 (45.1)	13 (34.2)	0 (0.0)	11 (64.7)	17 (30.9)	6 (50.0)	34 (40.5)	5 (55.6)	7 (53.8)
Black/African American	3 (2.9)	0 (0.0)	0 (0.0)	3 (1.9)	1 (2.9)	4 (1.8)	2 (5.3)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	2 (2.4)	0 (0.0)	1 (7.7)
Other[b]	3 (2.9)	0 (0.0)	0 (0.0)	6 (3.9)	2 (5.9)	8 (3.6)	1 (2.6)	0 (0.0)	0 (0.0)	6 (10.9)	1 (8.3)	7 (8.3)	0 (0.0)	0 (0.0)
Receiving a concomitant EIAED[c], n (%)														
Yes	57 (54.3)	13 (61.9)	18 (50.0)	69 (44.8)	15 (44.1)	102 (45.5)	24 (63.2)	2 (40.0)	7 (41.2)	22 (40.0)	4 (33.3)	33 (39.3)	2 (22.2)	1 (7.7)
No	48 (45.7)	8 (38.1)	18 (50.0)	85 (55.2)	19 (55.9)	122 (54.5)	14 (36.8)	3 (60.0)	10 (58.8)	33 (60.0)	8 (66.7)	51 (60.7)	7 (77.8)	12 (92.3)

EIAED, enzyme-inducing antiepileptic drug; max, maximum; min, minimum; PGTC, primary generalized tonic–clonic; SD, standard deviation; SG, secondarily generalized.
[a] Patients with partial-onset seizures who experienced SG seizures during baseline.
[b] Includes American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, and other.
[c] EIAEDs include carbamazepine, oxcarbazepine, phenytoin, and eslicarbazepine.

group, included aggression (perampanel 2 mg, n = 1; perampanel 8 mg, n = 2; perampanel 12 mg, n = 2), convulsion (placebo, n = 2), status epilepticus (placebo, n = 1; perampanel 12 mg, n = 1), and partial-onset seizures with secondary generalization (perampanel 8 mg, n = 1). The majority of serious TEAEs were considered to be possibly related to study drug by the investigator, and most patients recovered without sequelae (Supplementary Table S2). The patient described above who experienced a serious TEAE of aggression while receiving perampanel 2 mg did not recover, but continued to receive treatment with perampanel 2 mg/day. Three patients were withdrawn from the study because of serious TEAEs; one of these patients experienced a traumatic brain injury while receiving placebo (recovered with sequelae), one experienced status epilepticus while receiving perampanel 8 mg (recovered), and one experienced aggression while receiving perampanel 10 mg (recovered). There was an additional patient who experienced a serious AE of epileptic seizures during the prerandomization phase of Study 235, but this patient recovered and no action was required.

Treatment-emergent adverse events led to the discontinuation of 5 (4.4%) placebo-treated patients and 12 (4.7%) perampanel-treated patients (4 mg, n = 1; 8 mg, n = 8; 12 mg, n = 3) (Table 3). A list of all TEAEs leading to discontinuation by actual perampanel dose at onset is provided in Supplementary Table S3; those that led to the discontinuation of >1 patient across treatment groups included the following: aggression (dose at onset: 6 mg, 8 mg, and 10 mg, all n = 1 each), irritability (2 mg, 4 mg, and 8 mg, all n = 1 each), convulsion (placebo and 6 mg, both n = 1 each), and somnolence (2 mg, n = 2). As described above and in Supplementary Table S2, three patients discontinued because of TEAEs that were considered as serious (traumatic brain injury [placebo]; status epilepticus [8 mg perampanel dose at onset]; and aggression [10 mg perampanel dose at onset]).

Treatment-emergent adverse events related to hostility and/or aggression using both narrow and broad standardized MedDRA query (SMQ) terms were reported in 7 (6.1%) placebo-treated patients and 38 (14.7%) perampanel-treated patients (2 mg, n = 1; 4 mg, n = 1; 8 mg, n = 28; 12 mg, n = 8) (Supplementary Table S4). For placebo, the most common TEAEs related to hostility and/or aggression were irritability (n = 3 [2.6%]) and skin laceration (n = 2 [1.8%]). Skin laceration is included as an SMQ term related to hostility and/or aggression, as this may or may not have been self-inflicted; across the double-blind studies, skin laceration included the following: laceration to face, laceration to left foot, raised laceration on back of head, head laceration, and cuts on head. For perampanel, the most common TEAEs were aggression (n = 18 [7.0%]) and irritability (n = 15 [5.8%]). There was 1 (0.4%) perampanel-treated patient who experienced events of both aggression and irritability. Of the patients who experienced TEAEs related to hostility and/or aggression, a previous history of psychiatric or behavioral events was reported in 1/7 (14.3%) placebo-treated patient and 14/38 (36.8%) perampanel-treated patients (8 mg, n = 9; 12 mg, n = 5); the most common were attention-deficit hyperactivity disorder (ADHD; 8 mg, n = 4; 12 mg, n = 1), insomnia (8 mg, n = 2; 12 mg, n = 2), abnormal behavior (placebo, n = 1; 8 mg, n = 1; 12 mg, n = 1), bipolar disorder (placebo, n = 1; 8 mg, n = 2), and anxiety (8 mg, n = 3). None of these patients had a previous history of aggression or irritability.

Aggression was considered as a serious TEAE in 5 (1.9%) perampanel-treated patients (Supplementary Table S2). Two of these patients had a previous history of psychiatric and behavioral events (one patient had anxiety disorder, ADHD, and bipolar disorder; and the other patient had ADHD and affective disorder); neither of these patients discontinued treatment. None of the other TEAEs related to hostility and/or aggression were considered serious TEAEs. Aggression led to the discontinuation of 3 (1.2%) perampanel-treated patients (Supplementary Table S3); two of these patients had no history of psychiatric and behavioral events, but one patient reported a history of altered mood. Irritability led to the discontinuation of 3 (1.2%) perampanel-treated patients (Supplementary Table S3); two of these patients had no history of psychiatric and behavioral events, but one patient reported a history of irritability.

By comparison, the post hoc analysis of safety outcomes in adult patients demonstrated that aggression was experienced by 24/2111 (1.1%) patients (placebo, n = 2 [0.3%]; perampanel 4 mg, n = 4 [1.3%]; 8 mg, n = 8 [1.3%]; 12 mg, n = 10 [2.5%]) and irritability was experienced by 114/2111 (5.4%) patients (placebo, n = 14 [2.2%]; perampanel 2 mg, n = 7 [4.4%]; 4 mg, n = 15 [4.8%]; 8 mg, n = 41 [6.8%]; 12 mg, n = 37 [9.2%]).

During the double-blind treatment phases of these six studies, there were no deaths or events of homicidal ideation and/or threat or suicidal

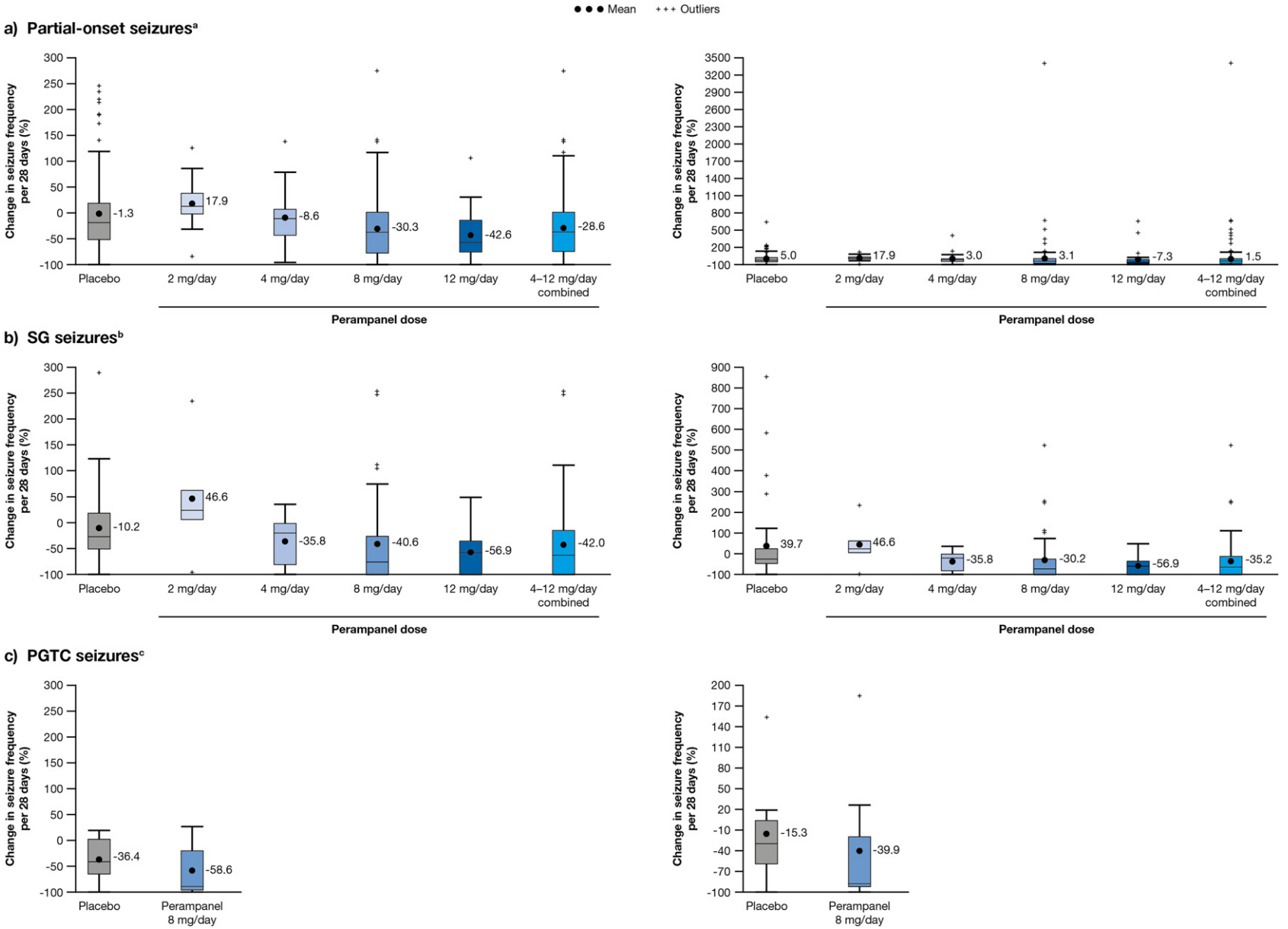

Fig. 2. Box and whisker plots presenting median and mean percent change in seizure frequency per 28 days, with (left panel) extreme outliers excluded and (right panel) extreme outliers included, for (a) partial-onset seizures,[a] (b) SG seizures,[b] and (c) PGTC seizures[c] in adolescent patients (aged ≥12 to ≤17 years; Full Analysis Set). Box and whisker plots present the median (horizontal line within box), Q1 (lower edge of box), Q3 (upper edge of box), minimum (lower whisker), and maximum (upper whisker) percent change in seizure frequency per 28 days for each treatment group. Mean percent change in seizure frequency per 28 days for each treatment group is presented as a filled circle, with the corresponding value labeled. [a]In the left-hand panel, the following extreme outliers were removed before calculation of mean values: 352.2%, 410.0%, 456.8%, 522.2%, 644.7%, 659.7%, 672.6%, and 3404.0%. [b]Patients with partial-onset seizures who experienced SG seizures during baseline; in the left-hand panel, the following extreme outliers were removed before calculation of mean values: 377.9%, 522.4%, 583.3%, and 854.6%. [c]In the left-hand panel, the following extreme outliers were removed before calculation of mean values: 153.6% and 184.5%. PGTC, primary generalized tonic–clonic; Q1, quartile 1; Q3, quartile 3; SG, secondarily generalized.

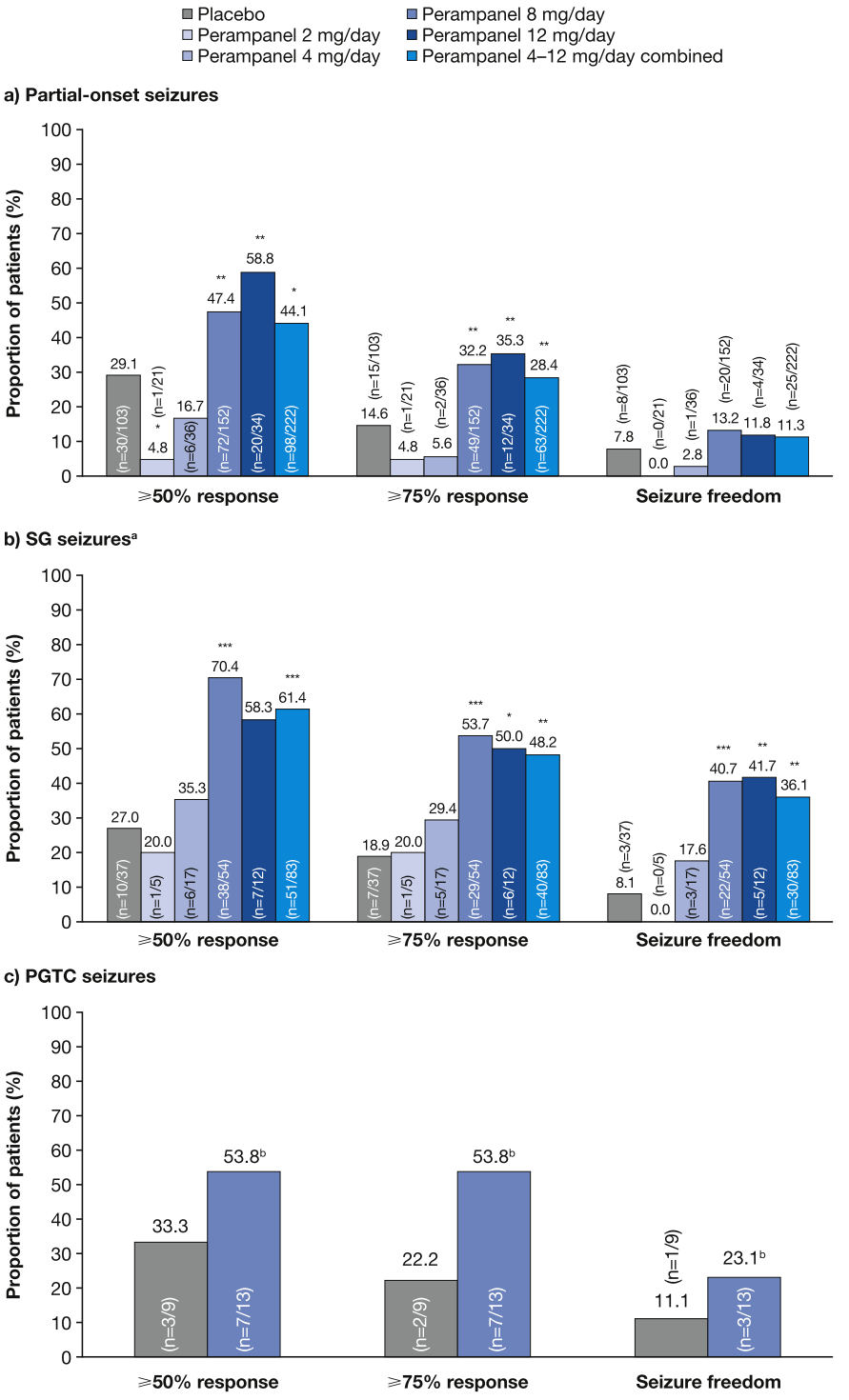

Fig. 3. 50% responder rates, 75% responder rates, and seizure-freedom rates for (a) partial-onset seizures, (b) SG seizures,[a] and (c) PGTC seizures in adolescent patients (aged ≥12 to ≤17 years; Full Analysis Set). *P*-value vs placebo: ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$. [a]Patients with partial-onset seizures who experienced SG seizures during baseline. [b]Statistical significance not reported due to the small number of adolescent patients with PGTC seizures. PGTC, primary generalized tonic–clonic; SG secondarily generalized.

ideation reported for adolescent patients receiving any dose of perampanel. The TEAEs reported in adolescent patients were also generally consistent with those reported in adult patients (Supplementary Table S5).

4. Discussion

In this post hoc analysis of six double-blind studies, once-daily adjunctive perampanel was generally well tolerated and the 8 and 12 mg/day doses were shown to confer additional efficacy compared with placebo in adolescent patients (aged ≥12 to ≤17 years) with uncontrolled partial-onset seizures, with or without SG seizures, or PGTC seizures. Efficacy outcomes for adolescent patients with partial-onset seizures, with or without SG seizures, were broadly similar to those for adolescents with PGTC seizures; however, greater improvements in seizure control with perampanel vs placebo were generally observed for patients with partial-onset seizures who experienced SG seizures during baseline, and for patients with PGTC seizures, than for all

Table 2
Efficacy outcomes in adult patients (aged ≥18 years) with partial-onset seizures, SG seizures,[a] or PGTC seizures (Full Analysis Set).

	Partial-onset seizures (with or without SG seizures)						SG seizures[a]						PGTC seizures	
	Placebo (n = 559)	Perampanel mg/day					Placebo (n = 207)	Perampanel mg/day					Placebo (n = 72)	Perampanel 8 mg/day (n = 68)
		2 (n = 159)	4 (n = 310)	8 (n = 537)	12 (n = 400)	Perampanel 4–12 mg/day combined (n = 1247)		2 (n = 63)	4 (n = 111)	8 (n = 185)	12 (n = 150)	Perampanel 4–12 mg/day combined (n = 446)		
Median reduction in seizure frequency per 28 days, %	12.6	16.6	20.3	26.6	30.1	26.3	19.0	33.8	40.0	62.3	52.7	53.8	38.4[b]	74.4
50% responder rate, %	19.0	22.6	26.8	35.8	36.8	33.8	36.7	46.0	44.1	59.5	56.0	54.5	40.3	66.2
75% responder rate, %	6.3	10.7	13.2	16.2	17.8	16.0	23.7	33.3	29.7	45.9	36.7	38.8	23.6	47.1
Seizure freedom, %	0.7	1.9	3.5	3.4	3.0	3.3	11.6	14.3	19.8	24.9	19.3	21.7	12.5	32.4

PGTC, primary generalized tonic–clonic; SG, secondarily generalized.
[a] Patients with partial-onset seizures who experienced SG seizures during baseline.
[b] For the analysis of median percent reduction in PGTC seizure frequency per 28 days, the value reported is based on a total of 71 placebo-treated patients aged ≥18 to <65 years. There was also one additional patient aged >65 years who received placebo and had a median percent reduction in PGTC seizure frequency per 28 days of 100.0%.

patients with partial-onset seizures (with or without SG seizures), although it should be noted that statistical significance was not reported for efficacy outcomes in patients with PGTC seizures because of small patient numbers. Overall, these results suggest that perampanel has efficacy compared with placebo across these seizure types, and these data are encouraging given the refractory nature of the patients and seizure types included in this analysis.

Efficacy outcomes in adolescent patients were also shown to be similar to those reported for adult patients with the same seizure types as part of this post hoc analysis. This is consistent with findings from a previous post hoc analysis of Studies 304, 305, and 306 in adolescent patients with partial-onset seizures, which showed that the efficacy of adjunctive perampanel in adolescents was generally consistent with that in the overall study population, which consisted mostly of adults [9]. Furthermore, a population PK analysis using pooled data from Studies 304, 305, 306, 335, and 235 has previously demonstrated that perampanel PK parameters and covariate effects in adolescents are similar to those in adults [31]. As such, perampanel dosing in adolescents

Table 3
Overall incidence of TEAEs and most frequent TEAEs (occurring in ≥5% of adolescent patients with any dose of perampanel) in adolescent patients (aged ≥12 to ≤17 years; Safety Analysis Set[a]).

	Placebo (n = 114)	Perampanel mg/day				
		2 (n = 21)	4 (n = 36)	8 (n = 167)	12 (n = 34)	Perampanel 4–12 mg/day combined (n = 237)
TEAEs, n (%)	76 (66.7)	15 (71.4)	24 (66.7)	128 (76.6)	25 (73.5)	177 (74.7)
Treatment-related TEAEs	44 (38.6)	11 (52.4)	17 (47.2)	108 (64.7)	20 (58.8)	145 (61.2)
Severe TEAEs	6 (5.3)	0 (0.0)	0 (0.0)	9 (5.4)	5 (14.7)	14 (5.9)
Serious TEAEs	5 (4.4)	1 (4.8)	0 (0.0)	6 (3.6)	4 (11.8)	10 (4.2)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to study drug dose adjustment, n (%)	9 (7.9)	1 (4.8)	2 (5.6)	41 (24.6)	12 (35.3)	55 (23.2)
Withdrawal	5 (4.4)	0 (0.0)	1 (2.8)	8 (4.8)	3 (8.8)	12 (5.1)
Dose increase	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	2 (0.8)
Dose reduction	4 (3.5)	0 (0.0)	1 (2.8)	32 (19.2)	9 (26.5)	42 (17.7)
Dose interruption	0 (0.0)	1 (4.8)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.4)
Most frequent TEAEs (occurring in ≥ 5% of adolescent patients with any dose of perampanel),[b] n (%)						
Dizziness	12 (10.5)	2 (9.5)	8 (22.2)	42 (25.1)	10 (29.4)	60 (25.3)
Somnolence	6 (5.3)	3 (14.3)	4 (11.1)	24 (14.4)	10 (29.4)	38 (16.0)
Headache	17 (14.9)	1 (4.8)	3 (8.3)	21 (12.6)	4 (11.8)	28 (11.8)
Nasopharyngitis	8 (7.0)	3 (14.3)	5 (13.9)	17 (10.2)	0 (0.0)	22 (9.3)
Upper respiratory tract infection	3 (2.6)	1 (4.8)	3 (8.3)	9 (5.4)	5 (14.7)	17 (7.2)
Aggression	1 (0.9)	1 (4.8)	1 (2.8)	12 (7.2)	4 (11.8)	17 (7.2)
Irritability	3 (2.6)	0 (0.0)	0 (0.0)	13 (7.8)	2 (5.9)	15 (6.3)
Weight increased	1 (0.9)	1 (4.8)	2 (5.6)	8 (4.8)	2 (5.9)	12 (5.1)
Fatigue	5 (4.4)	1 (4.8)	0 (0.0)	10 (6.0)	1 (2.9)	11 (4.6)
Decreased appetite	2 (1.8)	0 (0.0)	0 (0.0)	7 (4.2)	4 (11.8)	11 (4.6)
Pyrexia	2 (1.8)	0 (0.0)	1 (2.8)	6 (3.6)	2 (5.9)	9 (3.8)
Blood creatine phosphokinase increased	3 (2.6)	0 (0.0)	3 (8.3)	3 (1.8)	2 (5.9)	8 (3.4)
Influenza	2 (1.8)	0 (0.0)	1 (2.8)	3 (1.8)	2 (5.9)	6 (2.5)
Toothache	0 (0.0)	2 (9.5)	0 (0.0)	3 (1.8)	1 (2.9)	4 (1.7)
Cough	6 (5.3)	0 (0.0)	0 (0.0)	3 (1.8)	2 (5.9)	5 (2.1)
Asthenia	2 (1.8)	0 (0.0)	0 (0.0)	3 (1.8)	2 (5.9)	5 (2.1)
Anxiety	1 (0.9)	2 (9.5)	0 (0.0)	3 (1.8)	0 (0.0)	3 (1.3)
Drooling	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	2 (5.9)	4 (1.7)
Limb injury	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	2 (5.9)	4 (1.7)
Gait disturbance	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (5.9)	3 (1.3)
Blood uric acid increased	0 (0.0)	0 (0.0)	2 (5.6)	0 (0.0)	0 (0.0)	2 (0.8)

Patients with ≥2 TEAEs in the same preferred term are counted only once for that preferred term.
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
[a] Pooled data from Studies 304, 305, 306, 335, 235, and 332.
[b] MedDRA preferred term.

has the same label recommendations as in adults [18,19]. However, further investigation may be required to confirm if the perampanel 4 mg/day dose confers improvements in seizure frequency in adolescent patients. Despite this, the 4 mg/day dose has previously been shown to be an efficacious dose in other populations [32], and as such, it may still be considered as an appropriate treatment option in adolescent patients.

When efficacy data were analyzed by concomitant EIAED use, improvements in seizure control were generally greater in adolescent patients receiving only concomitant non-EIAEDs during baseline compared with adolescent patients receiving an EIAED during baseline for partial-onset seizures and SG seizures. These results are consistent with those of a previous post hoc analysis, in which adjunctive treatment with perampanel 8 and 12 mg/day conferred smaller median percent reductions in seizure frequency in adolescent patients receiving concomitant EIAEDs compared with those receiving only concomitant non-EIAEDs [9]. These findings are not surprising, as it has previously been shown that EIAEDs reduce perampanel exposure [29,30], and indeed, in this study, plasma perampanel concentrations were lower in adolescent patients receiving a concomitant EIAED compared with those receiving only non-EIAEDs, which may explain the higher efficacy in patients receiving non-EIAEDs. Patients receiving concomitant EIAEDs may require higher doses of perampanel to achieve similar efficacy outcomes to patients receiving non-EIAEDs [29,30]. However, it should also be noted that statistical significance may not have been reached for the majority of efficacy outcomes by concomitant EIAED use because of the relatively small numbers of adolescent patients in some of the EIAED and non-EIAED groups across treatments.

Safety outcomes in adolescent patients were similar to those in adults, and the TEAEs experienced by adolescent patients reported here are consistent with the known safety profile of perampanel [18,19]. The proportion of patients experiencing aggression and/or irritability events was greater in the adolescent population compared with the adult population during adjunctive perampanel treatment; however, it should be noted that the number of adolescent patients experiencing each of these events was relatively low ($n = 18$ [7.0%] and $n = 15$ [5.8%], respectively), and ≤5 patients had events of aggression or irritability that were considered as serious TEAEs or led to discontinuation. Furthermore, nearly 40% of patients who experienced TEAEs related to hostility and/or aggression during adjunctive perampanel treatment had reported a previous history of psychiatric or behavioral events. These results are consistent with a previous post hoc analysis in patients with partial-onset seizures, in which the incidence of aggression was shown to be greater in the adolescent population compared with the overall population during perampanel treatment [9]. In accordance with the Food and Drug Administration prescribing information for perampanel, which contains a boxed warning for serious psychiatric and behavioral reactions, all patients should be monitored for these AEs, and the dose of perampanel should be reduced if these symptoms occur and discontinued if they are severe or worsening [19].

The potential for cognitive, behavioral, psychiatric, and neuropsychological AEs with the use of AEDs represents a major concern for the treatment of adolescents with epilepsy, especially since these AEs can have negative impacts upon academic performance and quality of life, which, in turn, may impact on patient adherence to treatment [33,34]. Although this post hoc analysis did not assess cognitive outcomes in adolescent patients, the cognitive effects of adjunctive perampanel in adolescent patients with partial-onset seizures were previously assessed in Study 235 [24,26]. The results of Study 235 suggested that perampanel does not confer any significant short- or long-term effects on the global cognition score in this patient population [24,26]. The relatively small number of patients who experienced TEAEs related to hostility and/or aggression in the present analysis, along with the cognition outcomes from Study 235, indicates that perampanel may be a suitable and well-tolerated treatment option for adolescent patients with partial-onset seizures or PGTC seizures.

Dosing regimen is also an important factor influencing treatment adherence among patients with epilepsy, with reports suggesting that adherence rates improve with lower daily dose frequencies [2,13–17]. This may be particularly relevant in adolescent patients, whose increased independence may result in them forgetting to take AEDs throughout the day since they rely less on parental reminders to take medication, or due to the perception of increased levels of stigma associated with taking AEDs at school [1,2,11,17,35]. As such, the once-daily, night-time dosing regimen of perampanel, in addition to its relatively long half-life (~105 h in the absence of EIAEDs) [18,19]—which would be beneficial in the event of a forgotten dose—may represent an appropriate treatment option for adolescent patients with epilepsy. Further analyses are required to determine if adherence rates in adolescent patients are higher with perampanel compared with other AEDs that require multiple daily intakes.

Potential limitations of this analysis include those inherent to post hoc analyses and the fact that this analysis was conducted across six double-blind studies with different patient populations and study designs. For example, Study 235 was primarily designed to assess the effects of perampanel on cognition in adolescent patients, with efficacy as an exploratory endpoint [24], whereas efficacy was a primary endpoint of the other five double-blind studies [20–23,25]. The small number of adolescent patients with PGTC seizures meant that statistical analysis was not appropriate for this seizure type. In addition, the small patient populations for some of the EIAED subgroups limit interpretation of the impact of concomitant EIAED administration on perampanel efficacy in adolescent patients; thus, further studies may be required to investigate this. Despite these limitations, we believe that the results of our analysis are encouraging, given the refractory nature of the patient populations.

5. Conclusion

The efficacy and safety data reported here demonstrate that adjunctive perampanel is efficacious and well tolerated in adolescent patients (aged ≥12 to ≤17 years) experiencing partial-onset seizures, SG seizures, or PGTC seizures. These findings support the potential of perampanel as a beneficial treatment option for adolescent patients with drug-resistant epilepsy.

Author contributions

All authors, including those who are current or former employees of the Sponsor, provided substantial contributions to the conception, design of the post hoc analyses, acquisition of data, or the data analysis. All authors were also involved in the interpretation of the results, the reviewing and approval of the manuscript, and in the decision to submit the article for publication. All authors also confirm accountability for the accuracy and integrity of the work.

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Declaration of competing interest

J Eric Piña-Garza has served as an advisor for Sunovion and UCB Pharma, as a speaker for Aquestive, Eisai, Greenwich Biosciences, Supernus, Sunovion, and UCB Pharma, and as an advisor and speaker for Eisai, Lundbeck, and Supernus.

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Kazunori Saeki is an employee of Eisai Co., Ltd.

Vicente Villanueva has participated in advisory boards and pharmaceutical-industry–sponsored symposia for Bial, Eisai, Esteve, GlaxoSmithKline, GW Pharmaceuticals, Medtronic, Novartis, Pfizer, and UCB Pharma.

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Anna Patten is an employee of Eisai Ltd.

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Appendix A. Supplementary data

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