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Effect of adjunctive perampanel on daytime sleepiness and quality of life in adults with focal–onset seizures: Post hoc analyses of the AMPA study

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ABSTRACT

Objective: Assess the relationship between subjective daytime sleepiness and therapeutic effect of adjunctive perampanel in a post hoc analysis of AMPA (NCT04257604), a prospective, observational study in Italy.
Methods: AMPA included people with epilepsy (PWE) aged ≥ 12 years with insufficiently controlled focal-onset seizures, with/without focal to bilateral tonic-clonic seizures, on 1–3 baseline anti-seizure medications, who were prescribed adjunctive perampanel. Full Analysis Set (FAS) included PWE (≥ 18 years) who received ≥ 1 perampanel dose, with baseline Epworth Sleepiness Scale (ESS) scores. ESS was administered at baseline and each study visit for ≤ 12 months. Excessive daytime sleepiness was defined as ESS ≥ 11 points. Quality of life (QoL) was assessed using QOLIE-31-P.
Results: FAS included 202 PWE. Mean (SD) ESS was 6.3 (4.5) at baseline (N = 202) and 6.2 (4.4) at end of treatment (EoT; n = 177); 29 PWE reported ≥ 4–point decreases from baseline ESS at EoT, while 31 reported ≥ 4–point increases. Median percent reductions in seizure frequency/28 days from baseline were 85.6% in improved ESS group and 77.6% in worsened ESS group (n = 14 each). At EoT, 14 PWE with no excessive daytime sleepiness reported a mean (SD) QOLIE-31-P score change of + 7.9 (12.9) points while 11 PWE with excessive daytime sleepiness had a mean (SD) change of −3.4 (18.6). Overall incidence of treatment–emergent adverse events was 56.9%; most commonly, dizziness/vertigo (22.8%) and somnolence (8.4%).
Conclusion: In the FAS, adjunctive perampanel did not worsen daytime sleepiness for ≤ 12 months. In a small subset of patients, seizure frequency was reduced, regardless of ESS changes, and mean QoL at EoT was improved for those without excessive daytime sleepiness but declined for those with excessive daytime sleepiness. No new safety signals emerged.

1. Introduction

Excessive daytime sleepiness is a common comorbidity of epilepsy [1] and can present independently of other sleep disorders [2] or comorbidities (e.g. depression) [3], affecting health-related quality of life in people with epilepsy (PWE) [4–6]. Reciprocal interactions between sleep and epileptic seizures have been reported, and seizure-related sleep disturbances can impair daytime function and worsen seizure occurrence, contributing to excessive daytime sleepiness in PWE [5,7]. The interaction between epilepsy and daytime sleepiness may be compounded by the use of certain anti-seizure medications (ASMs). For instance, benzodiazepine, lamotrigine, and phenobarbital can negatively impact overall sleep quality as a side effect, whereas other ASMs, such as brivaracetam, lacosamide, and perampanel, have a positive effect on sleep, even though all of these ASMs offer seizure control [4,8–12]. Given the complexity of ASMs' impact on sleep, clinical implications of ASM therapies for daytime sleepiness are underappreciated among healthcare providers. Aside from uncontrolled seizures, other factors (e.g. aging and sex) can influence daytime sleep propensity. The incidence of epilepsy has been found to increase among adults aged ≥

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60 years vs individuals aged 15–59 years [13], and they are likely to encounter reduced sleep efficiency [14,15]. Findings from ELEVATE, a prospective, open-label, interventional, Phase 4 study of perampanel as monotherapy or first adjunctive therapy for epilepsy, showed that perampanel did not worsen subjective sleep quality over 12 months [16]. Another open-label, interventional study demonstrated that overall improvements in sleep quality were in conjunction with no worsening in daytime sleep propensity following ≤ 6-month treatment with adjunctive perampanel in PWE aged ≥ 16 years with focal-onset seizures (FOS), although somnolence was the most frequently reported adverse event during the study [17].

The effectiveness and safety of adjunctive perampanel in PWE with FOS, with or without focal to bilateral tonic-clonic seizures (FBTCS), was assessed in A Mirroring clinical practice study of Perampanel in Adults and adolescents (AMPA; NCT04257604). AMPA was a multicenter, prospective, real-world, observational 12-month study conducted in Italy between January 2016 and April 2019 [18]. The primary analysis confirmed the effectiveness of adjunctive perampanel in improving control over FOS (with or without FBTCS), and safety outcomes were consistent with previous findings [18,19]. As somnolence is one of the most common treatment-emergent adverse events (TEAEs) for perampanel, daytime sleep propensity in relation to epilepsy was evaluated in AMPA using the Epworth Sleepiness Scale (ESS), a self-rated questionnaire assessing the likelihood of daytime sleepiness based on individuals' evaluations of their chances of falling asleep while engaged in eight daily activities [20]. The clinical usefulness of ESS in epilepsy has been validated [3,21]; however, ESS scores are subjective as the perception of daytime sleep propensity in each survey scenario may vary for each individual. Moreover, daytime sleep propensity may be underestimated by the ESS total score in PWE, especially among people with treatment-resistant epilepsy whose seizures persist despite treatment regimens being administered, because these individuals are restricted from some of the surveyed activities, such as driving a car.

This exploratory post hoc analysis of daytime sleepiness, by ESS total score and item score, and seizure data collected during AMPA, primarily explored daytime sleepiness in relation to seizure control following perampanel treatment. Analyses by clinical characteristic of interest were also performed to further identify potential prognostic factors for daytime sleep propensity in individuals with treatment-resistant epilepsy. As a secondary subgroup analysis, the association between quality of life and daytime sleepiness was evaluated.

2. Material and methods

2.1. Study design and population

The design of AMPA has been previously described; briefly, this study enrolled PWE aged ≥ 12 years with inadequately controlled FOS (with or without FBTCS) who were on 1–3 ASMs and were prescribed adjunctive perampanel per the approved indication [18]. The decision to prescribe perampanel was made before and independently of the treating physician's decision to include the individual in AMPA. No restrictions were applied to concomitant medications; dose adjustments of concomitant ASMs were permitted per the treating physician's clinical judgment [18]. Treatment duration was 12 months with four study visits scheduled at Months 0, 3, 6, and 12. For PWE who discontinued before study completion, an early termination visit was scheduled to record assessment data. These outcomes were counted as End-of-Treatment (EoT) measurements along with those recorded at Month 12 in PWE who completed the 12-month study period.

The primary endpoint was median percent change vs baseline in seizure frequency per 28 days at Month 6. Secondary endpoints included other effectiveness measurements (e.g. 50% responder and seizure-freedom rates), safety measurements (e.g. TEAEs and treatment-related TEAEs), changes in the score of 31-item quality of life in epilepsy inventory (QOLIE-31-P, a self-rated questionnaire designed for people with epilepsy [22]), and changes in ESS score. PWE who were ≥ 18 years of age, received ≥ 1 dose of perampanel during AMPA, and recorded ESS scores at baseline were included in the Full Analysis Set of this post hoc analysis. All data, including safety, ESS, and QOLIE-31-P assessments, were analyzed in the Full Analysis Set. This non-interventional study was conducted according to relevant regulations (Determinazione 20/03/2008). The final protocol, the informed consent form, and the case report form were approved by ethics committees.

2.2. Assessments

Seizure data were captured in seizure diaries that were given to each eligible individual at Baseline Visit (Supplemental Fig. 1). PWE recorded the number and type of seizures on a daily basis over the study, and 'no seizures' was recorded if no seizures occurred that day; seizure diaries were collected at each study visit, and seizure frequency based on daily seizure diaries was reported in medical records. Seizure control was assessed based on median percent reductions in seizure frequency per 28 days from baseline, 50% and 75% responder rates, and seizure-freedom rates at Months 6 and 12, using seizure diaries or medical records.

ESS was administered in PWE aged ≥ 18 years at each study visit throughout AMPA (Supplemental Fig. 1). The scale includes eight items that evaluate likelihood of falling asleep while engaged in surveyed everyday activities [20]. Each item is rated on a 4-point scale (from 0 to 3), so the ESS total score ranges from 0 to 24, and a higher score indicates greater daytime sleep propensity. A ≥ 11-point total score suggests excessive daytime sleepiness overall, whereas a 3-point item score indicates a high likelihood of falling asleep when engaging in the specific scenario surveyed in the ESS item. Based on experience from clinical practice, a ≥ 4-point change in the total ESS score from baseline was deemed clinically relevant [3].

The Italian version of QOLIE-31-P was administered in PWE aged ≥ 18 years at Baseline and Months 6 and 12 (or EoT) Visits. Further information on the QOLIE-31-P scale can be found in the supplementary methods. The exploratory secondary subgroup analysis of changes in QOLIE-31-P scores was assessed as described in Section 2.3.

2.3. Statistical analyses

Given the post hoc nature of this analysis, it was not powered to detect any statistically significant difference in changes in daytime sleepiness. All results were therefore reported descriptively. Only PWE with data at both Baseline and one or more post-Baseline study visit were included in the secondary subgroup analysis of changes in ESS and QOLIE-31-P scores at EoT vs baseline. Last observation carried forward (LOCF) method was used to account for missing data resulting from early discontinuations. Clinical characteristics at baseline and clinical outcomes over the study were summarized, and classified by age (≤ 60 vs > 60 years), sex (male vs female), number of baseline ASMs (≤ 2 vs > 2), and type of baseline ASMs (with vs without benzodiazepines [clonazepam and clobazam], lamotrigine, oxcarbazepine, phenobarbital, and/or valproic acid [including sodium valproate]), because previous findings suggested that these ASMs may aggravate daytime sleepiness [8,9], whether through direct sedative effects (e.g., benzodiazepines, phenobarbital, often via GABAergic action), indirect contributions like insomnia induced by certain ASMs (e.g., lamotrigine) leading to secondary daytime sleepiness, or the cumulative effect of polytherapy with other sedating agents [8,23]). Seizure outcomes were categorized by ESS total score and item score to explore the relationship between daytime sleep propensity and therapeutic effect of perampanel.

ESS total scores were summarized overall and by clinical characteristic of interest to explore potential prognostic factors for daytime sleepiness. Clinically relevant changes in daytime sleep propensity over AMPA were summarized and stratified by type of baseline ASMs. An item-by-item analysis of ESS data and seizure outcomes was performed to adjust for the underestimation of the total score, exploring if any of the surveyed activities could better evaluate the propensity for daytime sleepiness in PWE. Responses to the question 'In a car, stopping for a few minutes in the traffic' were excluded from the item-by-item analysis because of the common bias in individuals' interpretation of this question and considering that driving is not permitted in the absence of seizure freedom.

For the secondary subgroup analysis of QOLIE-31-P scores, changes were categorized by patients' excessive daytime sleepiness status at EoT (ESS score of < 11 vs ≥ 11 points). This specific quality of life subgroup analysis, being exploratory and post hoc, was not powered to detect statistically significant differences in quality of life changes between these groups, and all results were therefore reported descriptively.

3. Results

3.1. Baseline characteristics and ESS outcomes in AMPA

In AMPA, a total of 202 adult PWE from the Safety Analysis Set recorded ESS scores at baseline and were included in the Full Analysis Set (Table 1); 177 of these PWE reported ESS data at EoT using LOCF method, and 172 (85.1%) PWE were aged < 60 years when entering the study. The most common ASMs administered at baseline were carbamazepine (35.1%), levetiracetam (15.8%), and oxcarbazepine (15.3%). The mean (standard deviation [SD]) last dose of perampanel was 6.0 (2.6) mg/day.

The median ESS total score was 5 (range: 0–24) at baseline, and this remained the same in the 177 PWE who had EoT ESS data; the median change was 0 (range: −21 to 16) points. No relevant change in ESS total score from baseline was detected over AMPA even in the presence of concomitant use of benzodiazepine, lamotrigine, oxcarbazepine, phenobarbital, and valproic acid (Table 2). Changes in the mean total ESS score were < 1 point across subgroups by baseline characteristic.

In the Full Analysis Set, 60 PWE had a clinically relevant change in daytime sleepiness over the study (i.e. a ≥ 4-point difference in ESS total score at EoT vs baseline), with 29 and 31 showing a clinically relevant improvement or worsening in overall daytime sleepiness, respectively. The mean (SD) last perampanel dose was 6.8 (2.7) mg/day in PWE with a clinically relevant improvement and 5.8 (2.3) mg/day in those with a clinically relevant worsening. Among the 29 PWE with clinically relevant improvements in daytime sleepiness, 19 (65.5%) received

Table 1
Baseline demographics and clinical characteristics in PWE aged ≥ 18 years with baseline ESS scores (Full Analysis Set).

	Perampanel (N = 202)
Median (min, max) age[a], years	40 (18, 84)
Age group, n (%)	
18 to < 60 years	172 (85.1)
≥ 60 years	30 (14.9)
Caucasian, n (%)	201 (99.5)
Mean (SD) age at epilepsy diagnosis, years	19.7 (15.0)
Mean (SD) time since epilepsy diagnosis, years	21.8 (15.1)
Number of baseline ASMs[b], n (%)	
0	1 (0.5)
1	37 (18.3)
2	90 (44.6)
≥ 3	74 (36.6)
Baseline ASM use, n (%)	
EIASM[c]	118 (58.4)
Benzodiazepine, lamotrigine, oxcarbazepine, phenobarbital, and valproic acid	134 (66.3)
Most common ASMs at baseline (in ≥ 10% of PWE), n (%)	
Carbamazepine	71 (35.1)
Levetiracetam	32 (15.8)
Oxcarbazepine	31 (15.3)
Lamotrigine	30 (14.9)
Lacosamide	26 (12.9)
Valproic acid	23 (11.4)

ASM, anti-seizure medication; EIASM, enzyme-inducing ASM; ESS, Epworth Sleepiness Scale; max, maximum; min, minimum; PWE, people with epilepsy; SD, standard deviation.

[a] Age was calculated at date of informed consent.

[b] Individuals reporting the same ASM more than once were counted only once, and one patient had no ASM recorded at baseline.

[c] Individuals with baseline EIASM use took ≥ 1 EIASM at baseline; EIASMs included carbamazepine, eslicarbazepine, oxcarbazepine, and phenytoin. All other ASMs were non-EIASMs.

Table 2
Overview of ESS total scores over AMPA, stratified by baseline characteristics (Full Analysis Set).

Characteristic	Mean (SD) ESS total score		Mean (SD) difference vs baseline	Δ[b]
	Baseline	EoT		
Age group				
18 to < 60 years	6.3 (4.4) (n = 172)	6.3 (4.4) (n = 154)	0.1 (4.5) (n = 154)	0.0
≥ 60 years	6.6 (5.3) (n = 30)	5.8 (4.6) (n = 23)	−0.4 (5.8) (n = 23)	−0.8
Sex				
Female	6.0 (4.6) (n = 106)	6.3 (4.5) (n = 92)	0.5 (3.9) (n = 90)	0.3
Male	6.6 (4.4) (n = 96)	6.1 (4.3) (n = 85)	−0.5 (5.3) (n = 84)	−0.5
Number of baseline ASMs[a]				
≤ 2	6.4 (4.9) (n = 127)	6.0 (4.6) (n = 107)	0.0 (5.0) (n = 106)	−0.4
> 2	6.3 (3.8) (n = 74)	6.5 (4.2) (n = 69)	0.1 (4.0) (n = 67)	0.2
Type of baseline ASMs[a]				
With benzodiazepine, lamotrigine, oxcarbazepine, phenobarbital, and valproic acid	6.6 (4.7) (n = 134)	6.6 (4.7) (n = 118)	0.1 (4.9) (n = 117)	0.0
Without benzodiazepine, lamotrigine, oxcarbazepine, phenobarbital, or valproic acid	5.9 (4.2) (n = 67)	5.3 (3.7) (n = 58)	−0.3 (4.0) (n = 56)	−0.6
Overall	6.3 (4.5) (n = 202)	6.2 (4.4) (n = 177)	0.0 (4.7) (n = 174)	−0.1

AMPA, A Mirroring clinical practice study of Perampanel in Adults and adolescents; ASM, anti-seizure medication; EoT, End of Treatment; ESS, Epworth Sleepiness Scale; SD, standard deviation.

[a] An individual who had no ASM recorded at baseline was excluded from analyses based on concomitant ASM use.

[b] Values were calculated by subtracting the mean ESS total score at baseline from the mean score at EoT, and a negative value indicates lessened daytime sleepiness from baseline.

benzodiazepine, lamotrigine, oxcarbazepine, phenobarbital, and/or valproic acid concomitantly at EoT. Comparably, 24 (80.0%) of the 30 PWE with clinically relevant worsening in daytime sleepiness received at least one of these five types of ASMs concomitantly at EoT.

In the item-by-item analysis, > 10% of PWE reported a 3-point item score at baseline when they were: lying down to rest in the afternoon when having the opportunity (43.6%), watching television (25.2%), and as a car passenger for an hour without stop (11.4%). Similar trends were seen at EoT, and the most common activities associated with high daytime sleepiness remained the same as seen at baseline with incidences of 36.2%, 17.5%, and 11.3%, respectively.

3.2. Effect of perampanel in relation to changes in daytime sleepiness

3.2.1. PWE with presence or absence of excessive daytime sleepiness

Of the 60 PWE with clinically relevant changes in overall daytime sleepiness, 28 had seizure data recorded over the study. At EoT, the median percent reduction in seizure frequency per 28 days from baseline was 85.6% (95% confidence interval [CI]: 19.7–100) in the 14 PWE with a clinically relevant improvement and 77.6% (95% CI: –36.4–87.5) in the 14 with a clinically relevant worsening.

When stratified by change in ESS item score from baseline, similar trends for positive correlations between greater percent reductions in seizure frequency (Fig. 1) and ≥ 1-point decreases in item scores were consistently observed; it should be noted that reductions in seizure frequency were restricted from assessments of statistical significance due to study design. Among PWE who rated a 3-point score to an individual item at baseline (i.e. high daytime sleep propensity in a specific scenario), impact of baseline characteristics on seizure control with perampanel varied by ESS item (Supplemental Table 1).

3.2.2. Subgroup analysis of PWE with excessive daytime sleepiness at baseline

A total of 28 (13.9%) PWE recorded a ≥ 11-point ESS total score (i.e. excessive daytime sleepiness) at baseline. The majority (85.7%) of these PWE were aged < 60 years, and 82.1% received benzodiazepine, lamotrigine, oxcarbazepine, phenobarbital, and/or valproic acid at baseline (Table 3). Among PWE with baseline excessive daytime sleepiness, 17 (60.7%) recorded an ESS score of < 11 points at EoT, indicating an alleviation of excessive daytime sleepiness over the study. These 17 PWE received a mean (SD) modal dose of perampanel 6.2 (2.7) mg/day and had a mean (SD) duration of perampanel exposure of 43.1 (13.5) weeks. For the 11 PWE who continued to experience excessive daytime sleepiness, the mean (SD) modal dose (6.2 [1.7] mg/day) and duration of perampanel exposure (43.1 [16.5] weeks) were similar to those of PWE experiencing alleviation.

In AMPA, 203 adult PWE reported QOLIE-31-P data at baseline, and median (range) change in QOLIE-31-P score from baseline was 0.2 (−57.0 to 48.4 [n = 157; LOCF]) at EoT. Among PWE with baseline excessive daytime sleepiness who had QOLIE-31-P data, a mean (SD) change of 7.9 (12.9) points in QOLIE-31-P score was seen in 14 PWE who had an ESS score of < 11 points at EoT, while the mean (SD) change was −3.4 (18.6) in 11 PWE who had an ESS EoT score of ≥ 11 points. Notably, most substantial changes across all seven QOLIE-31-P domains were observed in the medication effects domain for PWE with normal daytime sleep propensity at EoT, which showed a mean (SD) change of 14.3 (23.0) points, and in the seizure worry domain for those with sustained excessive daytime sleepiness, which showed a mean (SD)

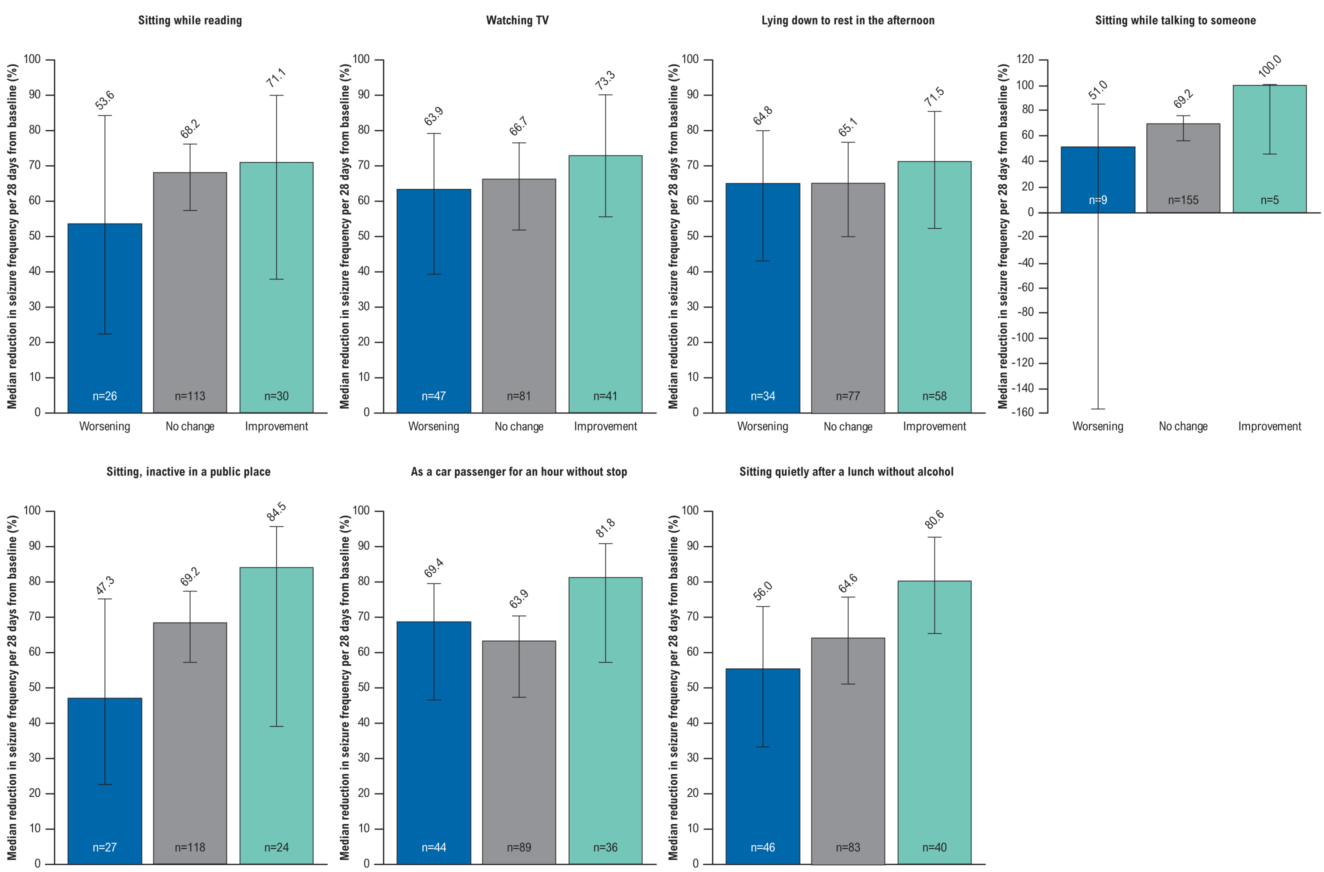

Fig. 1. Median (95% CI) percent reduction in seizure frequency per 28 days from baseline at EoT, stratified by change from baseline in ESS item score[a] (Full Analysis Set). Error bars represent 95% CIs. [a]A ≥ 1-point increase/decrease from baseline in ESS item score was required to qualify for this post hoc analysis, and only individuals with available seizure data at both baseline and any post-baseline study visits were included. CI, confidence interval; EoT, end of treatment; ESS, Epworth Sleepiness Scale.

Table 3
Baseline demographics and clinical characteristics in PWE with excessive daytime sleepiness (≥ 11-point ESS total score) at baseline and breakdown by EoT score (Full Analysis Set).

	EoT ESS score < 11 points (n = 17)	EoT ESS score ≥ 11 points (n = 11)	Total (n = 28)
Median (min, max) age, years	31.0 (18, 68)	49.0 (26, 77)	38.5 (18, 77)
Age group, n (%)			
18 to < 60 years	15 (88.2)	9 (81.8)	24 (85.7)
≥ 60 years	2 (11.8)	2 (18.2)	4 (14.3)
Sex, n (%)			
Female	7 (41.2)	6 (54.5)	13 (46.4)
Male	10 (58.8)	5 (45.5)	15 (53.6)
Number of ASMs at baseline, n (%)			
≤ 2	10 (58.8)	6 (54.5)	16 (57.1)
> 2	7 (41.2)	5 (45.5)	12 (42.9)
Type of AMSs, n (%)			
With benzodiazepine, lamotrigine, oxcarbazepine, phenobarbital, and valproic acid	14 (82.4)	9 (81.8)	23 (82.1)
Without benzodiazepine, lamotrigine, oxcarbazepine, phenobarbital, and valproic acid	3 (17.6)	2 (18.2)	5 (17.9)

ASM, anti-seizure medication; max, maximum; min, minimum; EoT, end of treatment;
ESS, Epworth Sleepiness Scale; PWE, people with epilepsy.

change of −11.7 (26.8) points. A numerically greater median percent reduction from baseline in seizure frequency was seen in PWE who had normal daytime sleep propensity at EoT, compared with that of PWE who continued to experience excessive daytime sleepiness (Fig. 2).

3.3. Safety of perampanel in relation to daytime sleepiness

One or more TEAEs occurred in 115 PWE (56.9%), and dizziness/vertigo (22.8%) was the most common TEAE over the study (Table 4). Safety outcomes were comparable between PWE with or without excessive daytime sleepiness at EoT vs baseline. The clinical relevance of these differences could not be determined given the small number of PWE in each subgroup. Somnolence occurred in 17 (8.4%) PWE during AMPA; among PWE who had available ESS data (n = 13), two and three PWE experiencing event(s) of somnolence reported a clinically relevant improvement or worsening in daytime sleepiness, respectively, and the other eight PWE had no clinically relevant changes in daytime sleepiness over the ≤ 12-month study period. However, these findings should be interpreted with caution as only a small number of PWE recorded somnolence as a TEAE in this real-world setting.

4. Discussion

To our knowledge, this post hoc analysis of data from AMPA is the first investigation exploring if PWE with treatment-resistant epilepsy would be more likely to report high levels of daytime sleep propensity in certain activities. Overall, 86.1% of PWE from AMPA had no excessive daytime sleepiness at baseline and generally retained normal daytime sleep propensity over the 12-month treatment period based on ESS assessments. Concomitant use of benzodiazepine, lamotrigine, oxcarbazepine, phenobarbital, and valproic acid was common at baseline (66.3%); PWE receiving these five types of ASMs at baseline reported numerically higher ESS total scores relative to those who had no baseline use of these ASMs, and this observation is in line with previous findings [8,9]. A similar pattern of ESS scores was observed at EoT. The majority of PWE who reported either a clinically relevant improvement or worsening in overall daytime sleep propensity concomitantly received ASMs that were shown to aggravate daytime sleepiness at EoT. Hence, incorporation of perampanel in the existing ASM treatment regimen may not affect daytime sleep propensity in individuals with treatment-resistant FOS (with or without FBTCS), even in the presence of ASMs that are reported to be likely to aggravate daytime sleepiness. Moreover, a positive correlation between seizure control and lessened daytime sleep propensity was consistently observed across ESS items, further confirming that adjunctive perampanel is not likely to worsen daytime sleepiness.

These findings are in accordance with previous studies. Perampanel showed no negative effect on sleep quality and/or daytime sleepiness when administered as a second- or later-line ASM [4,8,17], although data on the positive effect of perampanel on sleep were mixed and warrant further investigation. For instance, real-world studies have indicated perampanel's potential to improve nocturnal sleep quality, and in some cases, insomnia symptoms and overall quality of life; however, its impact on daytime sleepiness has been less clear, with findings ranging from no significant change to only slight improvement [24,25]. Similar observations were seen in ELEVATE, in which perampanel was administered as monotherapy or first adjunctive therapy [16]. These observations together encourage the early use of perampanel in ASM treatment paradigm. A large online survey conducted in five European countries, including Italy, showed that perampanel might have a positive effect on sleep and daytime function in adult PWE with treatment-resistant epilepsy [4]. Another case series showed that adjunctive perampanel was associated with a significant reduction in monthly seizure frequency alongside a significant improvement in objective daytime sleep propensity [10], suggesting that perampanel may provide more therapeutic benefits when administered early, as most PWE included in this case series received only one ASM at baseline.

ESS is a questionnaire that can be used to identify subjective excessive daytime sleepiness in the case of an ESS total score of ≥ 11 [20]. However, when considering daily activities of people with epilepsy, those with treatment-resistant epilepsy are restricted from driving due to the absence of long-term seizure freedom. Therefore, in the item-by-item analysis, data related to the question ‘In a car, stopping for a few minutes in the traffic’ were excluded based on clinical experience that PWE tended to interpret this question as being a car passenger rather than a driver. Furthermore, since no cutoff scores have been established for the PWE population, excessive daytime sleepiness among patients with treatment-resistant epilepsy may be underestimated. As such, modifications in the previously validated cutoff scores for excessive daytime sleepiness should be considered to optimize the clinical feasibility of ESS among PWE. Given these restrictions, an item–by-item analysis of certain ESS scores could be a practical tool to better inform care providers of excessive daytime sleepiness in PWE under different scenarios. In AMPA, ≥ 10% of PWE reported high levels of daytime sleepiness at both baseline and EoT when they were lying down to rest in the afternoon when they had an opportunity, when watching television, and as a car passenger for an hour without stop. More than 30% of PWE in this study have experienced high propensity for daytime sleepiness when they were lying down to rest in the afternoon, regardless of treatment with perampanel, highlighting the importance of monitoring this time of day in people with epilepsy for understanding the daytime propensity to sleep. Therefore, ESS item scores rated for individual daytime activities may provide more nuance of the impact of epilepsy on daytime sleepiness than the ESS overall score.

Among the 28 PWE who experienced excessive daytime sleepiness at

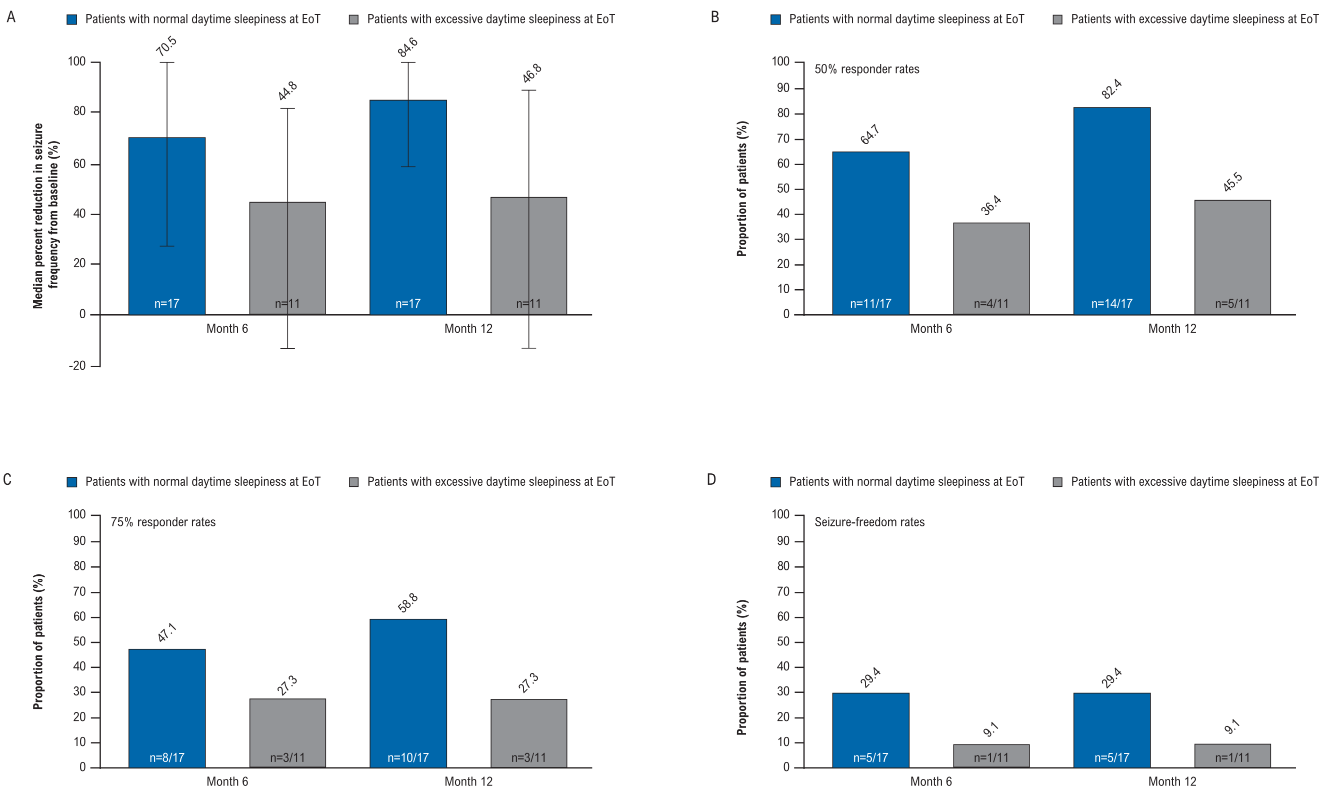

Fig. 2. (A) Median (95% CI) percent reduction in seizure frequency per 28 days from baseline at EoT, (B) 50% responder rates, (C) 75% responder rates, and (D) seizure-freedom rates in PWE with baseline excessive daytime sleepiness who had an ESS total score of < 11 (normal daytime sleepiness) or ≥ 11 points (excessive daytime sleepiness) at EoT. Error bars represent 95% CIs. [a]A negative value reflects an increase in seizure frequency. CI, confidence interval; EoT, end of treatment; ESS, Epworth Sleepiness Scale; PWE, people with epilepsy.

Table 4
Safety outcomes in all PWE and those with excessive daytime sleepiness at baseline (Full Analysis Set).

	PWE with baseline ESS scores ≥ 11 points (n = 28)		**Overall (N = 202)**
	EoT scores < 11 points (n = 17)	**EoT scores ≥ 11 points (n = 11)**	
All TEAEs, n (%)	9 (52.9)	8 (72.7)	115 (56.9)
Treatment-related TEAEs[a], n (%)	7 (41.2)	6 (54.5)	95 (47.0)
Serious TEAEs, n (%)	1 (5.9)	1 (9.1)	12 (5.9)
Deaths[b]	0	0	0
TEAEs leading to study drug dose modification, n (%)	5 (29.4)	6 (54.5)	75 (37.1)
Withdrawal	4 (23.5)	1 (9.1)	37 (18.3)
Dose reduction	1 (5.9)	4 (36.4)	31 (15.3)
Most common TEAEs (occurring in ≥ 5% of all PWE), n (%)			
Dizziness/vertigo	4 (23.5)	3 (27.3)	46 (22.8)
Somnolence	1 (5.9)	2 (18.2)	17 (8.4)
Irritability	0	1 (9.1)	15 (7.4)

EoT, End of Treatment; ESS, Epworth Sleepiness Scale; PWE, people with epilepsy;
TEAE, treatment-emergent adverse events.
[a] Includes TEAEs considered by the investigator to be related to perampanel or TEAEs with missing causality.
[b] Includes all PWE with serious TEAEs resulting in death.

baseline, a greater reduction in seizure frequency per 28 days from baseline at EoT was seen in PWE without excessive daytime sleepiness at EoT relative to those with sustained excessive daytime sleepiness at EoT.

Similarly, median percent reduction in seizure frequency per 28 days from baseline was numerically greater in patients with a clinically relevant improvement at EoT than those with a clinically relevant worsening. This observation is consistent with the established evidence that improved seizure control may have a beneficial effect on sleep quality and thus alleviate daytime sleepiness [26,27]. Reduced seizure frequency can benefit quality of life [28]; for instance, an individual with epilepsy is more likely to go for a walk or participate in ordinary life activities if the risk of seizures is lower. In AMPA, no changes of clinical concerns in overall QOLIE-31-P scores from baseline were observed over the ≤ 12-month study period, as a 5.2-point difference in QOLIE-31-P score was recommended to qualify for a minimally important change in quality of life for PWE with treatment-resistant FOS [29]. Among the 28 PWE with excessive daytime sleepiness at baseline, the 7.9-point increase in QOLIE-31-P score for the 14 PWE who had normal daytime sleep propensity at EoT could be deemed a clinically relevant improvement in quality of life [29]. This aspect is of particular interest for physicians and encourages them to monitor symptoms associated with epilepsy rather than seizure frequency during clinical follow-ups. Among these 14 PWE, greater seizure control over the ≤ 12-month study period was observed in conjunction with an improvement in the seizure worry domain score. Interestingly, an animal study showed that perampanel administration could promote the release of GABA, positively regulating sleep quality via AMPA antagonism; perampanel also demonstrated anti-anxiety effects by stimulating serotonin receptors in mice [30]. Furthermore, progress in health-related quality of life are commonly attributed to improvements in seizure control; however, other aspects could contribute to changes in quality of life. For instance, daytime sleepiness may interfere with behavior and cognition of PWE, and likelihood of conducting certain activities may vary by individual even if there is no disabling daytime sleepiness. Collectively, perampanel treatment may be able to reduce seizure risk and simultaneously improve quality of life and daytime sleepiness.

Primary safety outcomes of AMPA were consistent with the known safety profile of perampanel [18,19]. Findings of this post hoc analysis showed that most PWE who experienced event(s) of somnolence and recorded ESS data throughout had no relevant changes over the ≤ 12-month treatment with perampanel, suggesting that occurrence of somnolence is not a direct indicator of increased daytime sleep propensity.

This analysis is subject to limitations inherent in its design. First, this analysis is post hoc by nature, and its observational study design, while reflecting real-world clinical practice, introduces a potential for bias, particularly in subjective outcome measures. Therefore, it is not powered to detect statistical significance across groups, and findings should be interpreted with caution. Second, interpretation of data presented hereby is limited by the small number of PWE in certain groups. For instance, while 60 PWE experienced clinically relevant changes in daytime sleepiness, seizure data were only available for 28 of these patients. This substantial reduction in sample size introduces a potential for selection bias, meaning the reported seizure frequency outcomes for these 28 patients (14 with improvement in daytime sleepiness and 14 with worsening) may not be representative of the broader group of PWE with sleepiness changes, and thus cannot be broadly extrapolated. This is also relevant for the exploratory analysis of QOLIE-31-P score changes, which was conducted on a small subset of patients for whom QOLIE-31-P data were available and subsequently grouped by their excessive daytime sleepiness status at the EoT. Consequently, the findings regarding the association between quality of life and daytime sleepiness are exploratory and should be interpreted with caution, as they cannot be broadly extrapolated to the entire study population or to all PWE. Furthermore, because of the limited sample size, we were unable to perform robust statistical analyses to control for potential confounding factors. Such factors, including changes in seizure frequency or modifications to concomitant ASMs, may influence quality of life outcomes and the study outcomes more broadly. Additionally, ESS assessments are subjective so are not an objective evaluation of daytime sleep propensity. Lastly, the reconciliation of specific adverse event reports (e.g. somnolence) with overall ESS scores can be challenging due to the differing nature of these measures and data required to fully explain individual discrepancies were not within the scope of this analysis.

5. Conclusions

This post hoc analysis of data from the AMPA study provides evidence that perampanel, administered as an adjunctive anti-seizure therapy, does not exacerbate excessive daytime sleepiness in individuals who experience insufficiently controlled FOS (with or without FBTCS). These findings were confirmed by the item-by-item analysis of ESS data. As certain activities surveyed by ESS are often restricted among PWE, the item scores may be a more appropriate assessment of excessive daytime sleepiness in the corresponding scenario rather than the total score. In addition, adjunctive perampanel demonstrated seizure control among PWE included in AMPA [18]. The safety profile of perampanel seen in AMPA mirrors previous findings, with no new safety concerns being raised. Furthermore, findings from the present analysis suggest that adjunctive perampanel treatment does not worsen overall excessive daytime sleepiness. Exploratory observations also indicate promising outcomes regarding improvements in overall quality of life in certain patient subgroups, which warrant further evaluation in dedicated studies. These insights, while subject to the limitations of this post hoc analysis, offer valuable guidance for epileptologists to select the appropriate anti-seizure therapy for their patients.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Data availability statement

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

CRediT authorship contribution statement

Claudio Liguori: Data curation, Conceptualization. **Giovanni Assenza:** Data curation. **Martina Chiacchiaretta:** Data curation. **Anna Patten:** Data curation. **Ricardo Sáinz-Fuertes:** Data curation. **Anna Lisa Gentile:** Data curation.

Claudio Liguori contributed to the conception and design of the study. Claudio Liguori and Giovanni Assenza contributed to patient recruitment and enrollment. Anna Patten conducted the analysis of the data. Claudio Liguori, Giovanni Assenza, Martina Chiacchiaretta, Anna Patten, Ricardo Sáinz-Fuertes, and Anna Lisa Gentile contributed to data interpretation. All authors were involved in reviewing, and approval of the manuscript, and the decision to submit the article for publication.

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Declaration of competing interest

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2026.110962.

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