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A retrospective, multicentre study of perampanel given as monotherapy in routine clinical care in people with epilepsy

Antonio Gil-Nagel[a,*], Sergey Burd[b], Manuel Toledo[c], Josemir W. Sander[d,e,f], Anna Lebedeva[b], Anna Patten[g], Antonio Laurenza[h], on behalf of the Study 504 investigator group

[a] Hospital Ruber Internacional, Calle de la Masó 38, 28034 Madrid, Spain
[b] Pirogov Russian National Research Medical University, Ostrovitianov Str. 1, Moscow, 117997, Russia
[c] Hospital Universitario Vall d'Hebron, Passeig de la Vall d'Hebron 119-129, 08035 Barcelona, Spain
[d] UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK
[e] Chalfont Centre for Epilepsy, Chalfont St Peter, Gerrards Cross, SL9 0RJ, UK
[f] Stichting Epilepsie Instellingen Nederland (SEIN), Achterweg 5, Heemstede, 2103 SW, The Netherlands
[g] Eisai Ltd., European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN, UK
[h] Eisai Inc., 100 Tice Blvd, Woodcliff Lake, NJ 07677, USA

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ABSTRACT

Purpose: Perampanel is approved for adjunctive treatment of focal seizures, with or without secondarily generalised seizures, and for primary generalised tonic-clonic seizures in people with epilepsy aged ≥12 years. Perampanel was recently approved for monotherapy use for partial seizures in the United States. This study provides insight into the feasibility of perampanel monotherapy in real-world settings.
Methods: This retrospective, non-interventional, multicentre study (NCT02736162) was conducted between January 2013 and March 2016 in specialist epilepsy centres in Europe and Russia. Eligible individuals had a diagnosis of epilepsy and received perampanel primary or secondary monotherapy as routine clinical care. The primary endpoint was proportion of individuals remaining on perampanel monotherapy, after conversion from perampanel adjunctive treatment, at 3, 6, 12, 18 and 24 months (retention rate).
Results: Sixty individuals were in the safety set (female, 63%; white, 97%; aged 18 to <65 years, 73%). Most (85%) received secondary monotherapy with perampanel. At study cut-off, 68% of individuals were continuing on perampanel monotherapy (secondary monotherapy: 55%). The median duration of retention was not calculable due to the high number of individuals ongoing on monotherapy. Twelve individuals had treatment-emergent adverse events that started during perampanel monotherapy, the most frequent was dizziness (5%). One serious treatment-emergent adverse event was reported (pneumonia during adjunctive perampanel treatment).
Conclusions: In this small retrospective study of individuals who received perampanel monotherapy, the majority maintained monotherapy. Perampanel monotherapy may be an achievable option in some people with epilepsy.

1. Introduction

Perampanel, a selective, non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, is approved for adjunctive treatment of focal seizures with or without secondarily generalised seizures and for primary generalised tonic-clonic seizures in people with epilepsy aged ≥12 years [1,2]. Perampanel was recently approved for monotherapy use for focal seizures in the United States. Approval of perampanel as an adjunctive treatment was based on Phase III clinical trial data in adjunctive settings [3–6] and reflects the usual

Abbreviations: AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EIAED, enzyme-inducing antiepileptic drug; IGE, idiopathic generalised epilepsy; ILAE, International League Against Epilepsy; TEAE, treatment-emergent adverse event.

* Corresponding author at: Department of Neurology, Epilepsy Program, Hospital Ruber Internacional, C/La Masó no 38, 28034 Madrid, Spain.
E-mail addresses: agnagel@ruberinternacional.es (A. Gil-Nagel), nevrcao@gmail.com (S. Burd), mtoledo@vhebron.net (M. Toledo), l.sander@ucl.ac.uk (J.W. Sander), av_lebedeva@mail.ru (A. Lebedeva), anna_patten@eisai.net (A. Patten), antonio_laurenza@eisai.com (A. Laurenza).

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initial indication for antiepileptic drugs (AEDs). Specific labelling of AEDs as adjunctive treatments is, however, unique among central nervous system drugs and can restrict on-label use to polytherapy settings, which has been associated with increased toxicity, non-compliance and cost [7,8]. Due to these restrictions and ethical concerns around the use of placebo-controlled trials for AED monotherapy [7,9], open-label trials and specific epilepsy syndrome indications have been recommended to support monotherapy use [7].

Perampanel monotherapy has shown anti-seizure effects in several animal models of epilepsy and status epilepticus [10,11] but there have been no controlled trials of perampanel monotherapy in humans. Real-world evidence may be a useful approach to explore the feasibility of AED monotherapy in the clinic. We report the results of a retrospective study evaluating perampanel monotherapy in the routine clinical care of people with epilepsy.

2. Methods

2.1. Study design and population

This was a retrospective, non-interventional, multicentre study to investigate the dosage, efficacy and safety of perampanel given as monotherapy in routine clinical care to individuals with epilepsy (Eisai Inc. protocol E2007-G000-504; ClinicalTrials.gov identifier: NCT02736162). Data were collected retrospectively for individuals with epilepsy who received perampanel as primary or secondary (conversion) monotherapy between 1 January 2013 and 1 March 2016 at specialist epilepsy centres across Austria, Denmark, Germany, Russia, Spain and the United Kingdom (i.e., countries where perampanel was commercially available and being prescribed). Primary monotherapy was defined as the administration of perampanel in the absence of any concomitant AEDs, and secondary (conversion) monotherapy was defined as the conversion of perampanel from adjunctive therapy to monotherapy by withdrawing concomitant AEDs. Those defined as being on primary monotherapy may have previously taken other AEDs but would have permanently discontinued these prior to starting perampanel monotherapy (e.g. due to being in remission or subject choice), although this information was not specifically captured as part of this study.

Cases were identified by centres from electronic/paper medical and pharmacy records of individuals who were attending their usual epilepsy clinic and were prescribed perampanel as monotherapy based on the treating clinician's recommendation.

Given that this was a non-interventional study, the risk to participants in the study was limited to the possibility of a breach in their confidentiality with regard to personal identifiers or health information. Anonymised information was collected from medical records without any involvement or participation of individuals, and the sponsor had no access to individual medical records. Where applicable, Independent Ethics Committee and regulatory authority review and approval were obtained in accordance with local legislation.

2.2. Data collection

Each centre was responsible for its own data collection and reporting; available data were entered by centres into paper case report forms.

Where available, data on AED history, seizure frequency and safety were collected. Data for evaluation of seizure outcomes were obtained from medical records or seizure diaries, where available; if not available, investigator assessment of the therapeutic response was used.

Written informed consent must have been provided by each individual, or their legally authorised representative, for the use of the medical records, as per local requirements.

2.3. Objectives and analyses

All individuals who had received at least 1 dose of perampanel were included in the safety set and all individuals who had received perampanel and had seizure frequency data available (including data at pre-perampanel baseline) were included in the full analysis set.

The primary objective of the study was to assess the retention rate of perampanel when given as secondary monotherapy in routine clinical care. Accordingly, the proportions of individuals remaining on perampanel monotherapy (retention rates) at 3, 6, 12, 18 and 24 months were evaluated as primary endpoints, with an additional analysis at the study cut-off date of 1 March 2016. The denominators for these retention rates were the numbers of individuals who could have been exposed for each period of time. Retention rates were assessed in the safety set for a population of individuals who specifically received secondary monotherapy, and additional analyses included all individuals receiving primary or secondary monotherapy.

The following secondary endpoints, relating to changes in seizure frequency, were assessed in the full analysis set: the proportion of individuals who were seizure free for at least 3 months while receiving perampanel monotherapy; and changes in seizure frequency between pre-perampanel baseline (up to 3 months prior to the initiation of perampanel) and (1) the last 3 months of perampanel adjunctive treatment (only determined for individuals who received secondary monotherapy), (2) the first 3 months of perampanel monotherapy and (3) the last 3 months of perampanel monotherapy before the last follow-up (only determined for individuals with a minimum of 6 months of follow-up). Specifically, changes in seizure frequency were assessed as the following: median percent change in seizure frequency per 28 days; proportions of individuals with a reduction in seizure frequency of 50% (50% responder rate); and proportions of individuals with no change or a worsening of seizure frequency, based on qualitative clinical impression (i.e., investigator response of "stable/no change" or "worsened") or seizure frequency (i.e., no change or an increase in seizure frequency). Seizure-freedom rates were also assessed at the same 3 time periods; individuals with a seizure-free status recorded as unknown were included as not seizure free.

Maximum and median doses of perampanel during adjunctive treatment and monotherapy were recorded. Other safety endpoints included treatment-emergent adverse events (TEAEs) and serious TEAEs, assessed in the safety set from the initiation of perampanel monotherapy until 30 days after the last dose of perampanel monotherapy.

Other post hoc analyses explored the impact of prior AED use (including the use of enzyme-inducing AEDs [EIAEDs]) and epilepsy history. These analyses are described in more detail in Supplementary Methods A.1 in Appendix A.

3. Results

3.1. Study population and AED exposure

Data collection was started on 19 April 2016 and the last data items were collected on 14 July 2016. Of 1225 individuals prescribed perampanel across the centres, 69 (6%) were prescribed perampanel as monotherapy. Data were provided for 60 individuals (from 19 centres) who were included in the safety set; most had received perampanel as secondary monotherapy (n = 51; 85%)

rather than primary monotherapy (n = 9; 15%). There were 40 individuals included in the full analysis set (secondary monotherapy, n = 37; primary monotherapy, n = 3). Disposition is shown in Fig. 1.

Demographics and clinical characteristics for the safety set are shown in Table 1. Most were aged between 18 and <65 years (44/60; 73%), most had been diagnosed with epilepsy ≥5 years previously (41/60; 68%) and most were experiencing focal seizures according to International League Against Epilepsy classification (48/60; 80%).

Of the 60 individuals in the safety set, 14 (23%) had previously received 1–2 AEDs, 18 (30%) had previously received 3–5 AEDs and 7 (12%) had previously received 6–10 AEDs, which were stopped before receiving perampanel; the most frequent were levetiracetam (n = 27; 45%), valproic acid (n = 20; 33%) and lamotrigine (n = 19; 32%). The remaining 21 individuals (35%) had not previously received any other AEDs that were stopped before receiving perampanel.

Of the 51 individuals in the safety set who had started perampanel as an adjunctive treatment (prior to conversion to secondary monotherapy), 42 (82%) were receiving just 1 other AED at the first dose of perampanel and 9 (18%) were receiving 2 other AEDs (none were receiving ≥3 other AEDs); the most frequently co-administered AEDs were levetiracetam (n = 11; 22%), lacosamide (n = 9; 18%) and valproic acid (n = 9; 18%).

3.2. Retention rates

A Kaplan-Meier analysis of time to discontinuation of perampanel monotherapy treatment is shown in Fig. 2. Due to insufficient events, it was not possible to calculate the median duration of retention and upper confidence interval (lower confidence interval: 258.0 days). Retention rates at 3 and 6 months were 95% and 74%, respectively (secondary monotherapy: 96% and 71%, respectively; Supplementary Fig. B.1 in Appendix B). At the study cut-off date, there were 41 individuals (68%) continuing on perampanel monotherapy; of these, 33 were receiving perampanel as secondary monotherapy (see disposition shown in Fig. 1). Conversely, 19 individuals (32%) had discontinued from perampanel monotherapy, most commonly due to inadequate therapeutic effect (n = 11) or adverse events (n = 6).

3.3. Changes in seizure frequency

Of the 40 individuals who had seizure frequency data available and were thus included in the full analysis set, more than half (n = 22; 55%) were seizure free for at least 3 months at any time while receiving perampanel primary or secondary monotherapy. Median percent reductions in seizure frequency, 50% responder rates and seizure-freedom rates throughout 3-month periods during adjunctive therapy and monotherapy are shown in Supplementary Fig. B.2 in Appendix B. For individuals in the full analysis set, the median number of seizures per 28 days was 3.0 at baseline, 1.0 during the last 3 months of perampanel adjunctive treatment and 0.5 throughout the first 3 months of perampanel monotherapy.

Compared with pre-perampanel baseline, there was no change or worsening of seizure frequency for 9/37 individuals (24%) during the last 3 months of perampanel adjunctive treatment and 6/40 individuals (15%) throughout the first 3 months of perampanel monotherapy. All other individuals experienced improvements in seizure frequency.

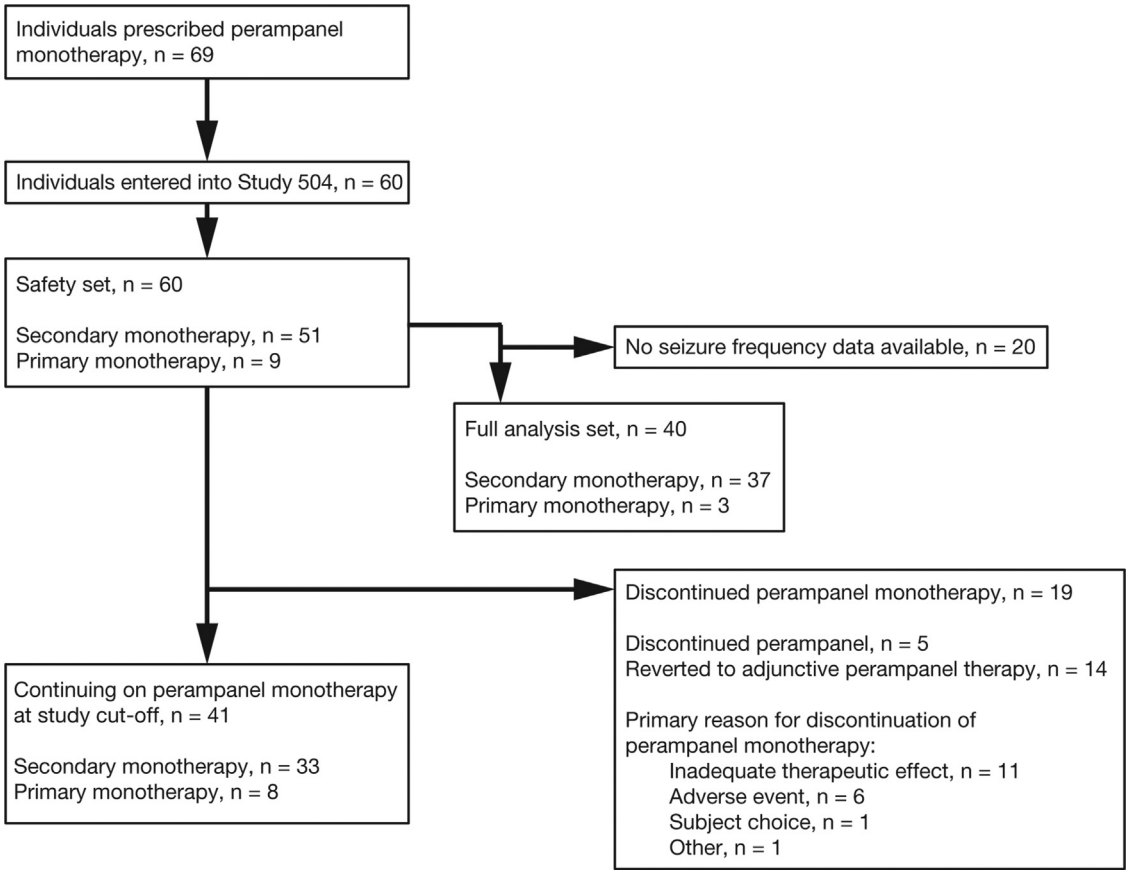

Fig. 1. Disposition.

Table 1
Demographics and clinical characteristics (safety set).

	Safety set (N = 60)
Female, n (%)	38 (63)
Age, n (%)	
<12 years	8 (13)
12 to <18 years	6 (10)
18 to <65 years	44 (73)
≥65 years	2 (3)
Race, n (%)	
White	58 (97)
Unknown	1 (2)
Missing	1 (2)
Country, n (%)	
Spain	29 (48)
United Kingdom	15 (25)
Russia	12 (20)
Germany	2 (3)
Austria	1 (2)
Denmark	1 (2)
Age at epilepsy diagnosis, n (%)	
<12 years	18 (30)
12–17 years	19 (32)
18–64 years	22 (37)
Unknown	1 (2)
Time since epilepsy diagnosis, n (%)	
<1 year	4 (7)
1 to <3 years	8 (13)
3 to <5 years	6 (10)
5 to <10 years	15 (25)
10 to <20 years	15 (25)
≥20 years	11 (18)
Missing	1 (2)
Seizure type, n (%)	
Simple partial without motor signs	13 (22)
Simple partial with motor signs	18 (30)
Complex partial	41 (68)
Partial with secondary generalisation	37 (62)
Generalised tonic-clonic	18 (30)
Myoclonic	5 (8)
Absence	6 (10)
Tonic	6 (10)
Clonic	1 (2)
Atonic	1 (2)
ILAE classification, n (%)	
Focal seizures	48 (80)
IGE	8 (13)
Unknown	3 (5)
Missing	1 (2)

IGE, idiopathic generalised epilepsy; ILAE, International League Against Epilepsy.

3.4. Safety

There were 60 individuals in the safety set. All except 1 of these individuals received a maximum perampanel dose of between 2 and 12 mg, with the remaining individual receiving a maximum dose of 24 mg (recorded as 20 mg due to database constraints and considered as 20 mg for all average dose calculations). The median (range) maximum perampanel dose was 6.0 mg (2.0–10.0 mg) during adjunctive treatment and 8.0 mg (4.0–20.0 mg) during monotherapy (overall median maximum dose, 8.0 mg). The median (range) last daily dose of perampanel was 6.0 mg (2.0–10.0 mg) during adjunctive treatment and 6.0 mg (2.0–20.0 mg) during monotherapy.

Total exposure was 1767.0 subject-weeks on adjunctive perampanel and 2102.1 subject-weeks on perampanel monotherapy. At the cut-off date, the median duration of perampanel adjunctive therapy was 6.4 months (range, 2.0–29.3 months) and perampanel monotherapy had been maintained for a median of 6.1 months (range, 0.5–44.1 months).

Fifteen individuals had TEAEs that started during adjunctive perampanel treatment and 12 had TEAEs that started during perampanel monotherapy (Table 2). The most frequent TEAE was dizziness (n = 9; 15%).

There was 1 serious TEAE: an episode of pneumonia, which required hospitalisation, but was not life-threatening; this event occurred during adjunctive perampanel treatment and not during perampanel monotherapy. There were no deaths.

3.5. Post hoc analyses

For 14 individuals who received EIAEDs during adjunctive treatment, the median maximum dose of perampanel was 5.0 mg during adjunctive treatment and 7.0 mg during monotherapy (overall 7.0 mg). The median last daily dose of perampanel was 4.0 mg during adjunctive treatment and 6.0 mg during subsequent monotherapy. TEAEs were experienced by 4/14 individuals (29%) during adjunctive treatment and 1/14 individuals (7%) during monotherapy; the most frequent TEAEs were irritability (adjunctive treatment, n = 2; monotherapy, n = 1) and somnolence (adjunctive treatment, n = 2; monotherapy, n = 0).

Of these 14 individuals, 11 were continuing monotherapy at study cut-off; 3 reverted to adjunctive treatment due to inadequate therapeutic effect. Retention rates for these individuals were 100% (13/13 individuals) and 83% (10/12) at 3 and 6 months after the initiation of monotherapy, respectively. By comparison, retention rates for individuals who did not receive EIAEDs during adjunctive treatment were 94% (31/33 individuals) and 64% (14/22) at 3 and 6 months after the initiation of monotherapy, respectively. There were no clear correlations between retention rates and number of previous AEDs received and stopped prior to the initiation of perampanel, time since epilepsy diagnosis or epilepsy syndrome (Supplementary Table C.1 in Appendix C).

In the full analysis set, responder rates indicated that monotherapy could confer 50% reductions in seizure frequency, again with no clear correlation with prior AED use or epilepsy history (Supplementary Table C.2 in Appendix C).

4. Discussion

Our retrospective study included 60 individuals with epilepsy who received perampanel monotherapy as part of routine clinical care. The study population was considered to be representative of a real-world epilepsy population, with many individuals having a history of focal seizures, many receiving 1–5 AEDs at baseline and many having had epilepsy for more than 5 years. Most individuals who received perampanel monotherapy did so following conversion from polytherapy with adjunctive perampanel and other AEDs, which is the practical route for people to receive monotherapy with third-generation AEDs. We assume that the main reason for conversion to secondary monotherapy was to reduce side effects in people who experienced increased seizure control or seizure freedom while taking adjunctive perampanel. Reasons for initiation of primary monotherapy were most likely to improve compliance (due to perampanel's once-daily dosing) or avoid side effects associated with previous regimen(s). The stated reasons for conversion in each individual case were, however, not specifically captured as part of this study.

Many individuals in this retrospective study would not have met eligibility criteria for prospective clinical trials [9]. Of note, 35% of individuals had not previously received any other AEDs that were stopped before initiation of perampanel, whereas individuals

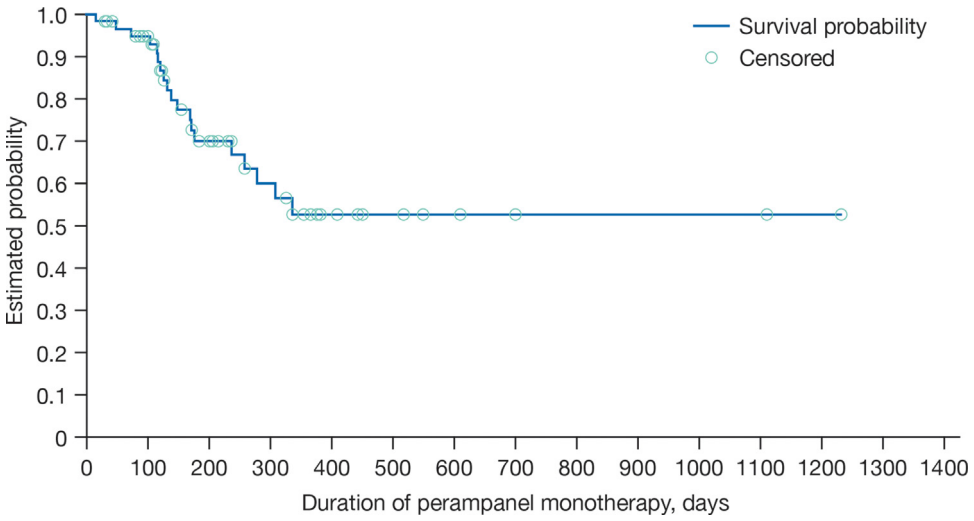

Fig. 2. Kaplan-Meier plot of retention on monotherapy (safety set).

Table 2
Summary of TEAEs that started during perampanel adjunctive treatment or monotherapy (safety set).

	Adjunctive treatment (n = 51)	Monotherapy (n = 60)
Any TEAE, n (%)[a]	15 (29)	12 (20)
Any serious TEAE, n (%)	1 (2)	0 (0)
Any TEAE leading to perampanel dose adjustment, n (%)	7 (14)	10 (17)
Withdrawal[b]	2 (4)	4 (7)
Dose increase	0 (0)	1 (2)
Dose reduction	6 (12)	7 (12)
Most frequent TEAEs (≥5% of individuals), n (%)		
Dizziness	6 (12)	3 (5)
Irritability	5 (10)	2 (3)
Somnolence	4 (8)	1 (2)
Headache	2 (4)	1 (2)

TEAE, treatment-emergent adverse event.
[a] Excludes 1 non-serious TEAE of anxiety, since the study period of onset was unknown.
[b] TEAEs leading to withdrawal included dizziness and irritability (2 individuals each), and asthenia, aggression, anxiety and mania (1 individual each).

in Phase III clinical trials of perampanel were required to have previously failed 2 or more AEDs [3,4,6]. This suggests that many individuals had epilepsy that was not as refractory as those included in clinical trials.

Most individuals were able to maintain perampanel monotherapy, whether given as a primary or secondary monotherapy. There was also some indication of efficacy with perampanel monotherapy, as most experienced some improvement in seizure control, while a smaller proportion had no change. This is consistent with other previous studies of conversion to AED monotherapy, including a study of conversion to lacosamide monotherapy [12].

The duration of perampanel monotherapy (median, 6.1 months) was considered sufficient to assess safety outcomes. Overall, it was generally well tolerated in this small population, with no new or unexpected TEAEs. The most frequently reported TEAEs of dizziness, irritability, somnolence and headache were also consistent with the TEAE profile reported in previous clinical trials [3–6].

Post hoc analyses did not identify any clear or consistent correlations between retention rates or responder rates and prior AED use or epilepsy history. There was some variation in outcomes but this was considered largely attributable to the inherent variability when dealing with small population sizes. It should also be considered that there may have been a selection bias, since only those individuals who did well on adjunctive treatment would have been converted to monotherapy. Perampanel levels may have increased in those individuals who underwent withdrawal of EIAEDs, which could have had implications for efficacy and tolerability (note that treating physicians did not elect to decrease the dose of perampanel in most of these cases, and only 1 case was associated with TEAEs during perampanel monotherapy [irritability leading to dose reduction; friction burn; fractured toe]).

This study has potential limitations, and the retrospective design and small population size may be key considerations. The study did not involve a comparator arm; however, in applying an observational design, a broad, real-world epilepsy population could be assessed without the limitations of the strict eligibility criteria associated with controlled trials. In addition, the early censoring of a large proportion of study subjects meant that although people were followed for up to 24 months, there were not enough subjects at time points beyond 6 months to allow meaningful analyses to be carried out.

Overall, the study may provide an initial insight into the feasibility of perampanel monotherapy in a real-world setting. The results indicate that perampanel monotherapy may be an achievable option for some people with epilepsy, irrespective of prior AED use. Such initial evidence is useful in determining whether larger monotherapy trials are warranted and how these

should be designed, although it remains the case that prospective trials are associated with inherent challenges.

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Appendices A–C. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2017.10.015.

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