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SHORT COMMUNICATION

Efficacy and safety of perampanel in the subgroup of elderly patients included in the phase III epilepsy clinical trials

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Summary Clinical data regarding use of antiepileptic drugs in the elderly are generally scarce. Therefore, a subanalysis of subjects aged ≥65 years who participated in the 3 phase III perampanel studies was undertaken to determine efficacy and safety in these patients. Efficacy (change in seizure frequency/28 days and 50% responder rate) in the elderly subgroup was found to be consistent with the adult population. Adverse event rates were also largely similar, with some exceptions. Because risks of falls, dizziness, and fatigue were greater in the elderly, careful titration of perampanel in patients aged ≥65 years is suggested, especially at higher doses, where balancing tolerability and clinical response is necessary.

Introduction

Perampanel, a selective, orally active, noncompetitive AMPA receptor antagonist (Hanada et al., 2011) has demonstrated efficacy and tolerability for patients with partial seizures in three multinational phase III studies (French et al., 2012, 2013; Krauss et al., 2012; Steinhoff et al., 2013). Perampanel is approved in ≥40 countries for adjunctive treatment of partial seizures with or without secondarily generalized seizures in patients with epilepsy, including the US and the EU (ages ≥12 years) and Canada (ages ≥18 years) (Fycompa Product Monograph 2013; Fycompa

Abbreviations: AE, adverse event; AED, antiepileptic drug; LOCF, last observation carried forward; MedDRA, Medical Dictionary for Regulatory Activities; PER, perampanel; PK, pharmacokinetic; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.

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Prescribing Information 2014; Fycompa Summary of Product Characteristics 2012).

The elderly are a rapidly growing segment of the epilepsy population, and obtaining information regarding the efficacy and safety of antiepileptic drugs (AEDs) in this population is essential. Evaluating AEDs in elderly patients has been challenging, and these patients have been underrepresented in clinical studies, partly due to intentional exclusion of patients aged ≥65 years in many studies. Studies that do include older patients are generally small, making safety and efficacy analyses difficult or impossible (Leppik et al., 2006). Moreover, identifying the presence and types of seizures in older patients, and distinguishing them from other neurological conditions, can be difficult and can predispose to misdiagnosis (Brodie et al., 2009). Recruiting elderly patients for phase III studies is also challenging, since comorbidities (e.g., dementia or diabetes) or physical frailty may interfere with trial participation and affect outcomes (Brodie et al., 2009; Leppik et al., 2006).

Population pharmacokinetic (PK) analyses have shown that perampanel clearance is not meaningfully affected by age. Therefore, we undertook a subanalysis of the three phase III studies in subjects with partial seizures aged ≥65 years treated with perampanel to describe its efficacy and safety in this population.

Methods

The three phase III studies (study 304, NCT00699972; study 305, NCT00699582; study 306, NCT00700310) were multinational, randomized, double-blind, and placebo-controlled (French et al., 2012, 2013; Krauss et al., 2012). Each involved a 6-week pre-randomization baseline, 19-week double-blind phase (6-week titration and 13-week maintenance), and 4-week follow-up. During titration, perampanel doses increased weekly (2 mg/day/week) until the randomized dose or intolerability was reached. Perampanel dosing was 8 and 12 mg/day in studies 304 and 305, and 2, 4, and 8 mg/day in study 306. All studies complied with the Helsinki Declaration, European Medicines Agency requirements, and the US Code of Federal Regulations, as appropriate. All subjects provided written informed consent (French et al., 2012, 2013; Krauss et al., 2012).

Eligible subjects, aged ≥12 years and diagnosed with partial seizures, according to the 1981 International League Against Epilepsy Classification of Epileptic Seizures (ILAE, 1981), must have had uncontrolled partial seizures, failed ≥2 AEDs in the previous 2 years, had ≥5 partial seizures during 6-week baseline, and been taking a stable regimen of 1–3 AEDs (French et al., 2012, 2013; Krauss et al., 2012). The current analysis included all elderly subjects aged ≥65 years in the pooled study population, with comparison to those aged ≥18–<65 years. An additional analysis included subjects aged ≥60 years, considered an older population.

The primary efficacy endpoint for the current analysis was median percent change in seizure frequency/28 days during the double-blind period relative to baseline; the secondary efficacy endpoint was the 50% responder rate (percent of patients achieving ≥50% reduction in seizure frequency/28 days during maintenance vs baseline, with the last observation carried forward [LOCF]). Treatment-emergent adverse events (TEAEs) were also recorded to assess safety.

Results

Baseline population characteristics

The elderly group comprised 1.9% of the total pooled phase III population, with data being derived for 28 subjects aged ≥65 years vs 1307 adult subjects (≥18–<65 years). Baseline characteristics were similar between elderly and adult subgroups. Complex partial seizures were the most common type experienced by both the elderly (89.3%) and adult subgroups (85.5%) at baseline (Table 1). Most subjects were taking 2 concomitant AEDs at baseline (elderly: 42.9% vs adult: 51.3%, Table 1). Stroke etiology accounted for 7.1%

Table 1 Patient baseline characteristics: elderly and adult subgroups.

	Elderly subgroup (≥65 years) (*n* = 28)	Adult subgroup (≥18–<65 years) (*n* = 1307)
Mean age*, years (SD)	68.5 (3.5)	36.3 (11.8)
Females, *n* (%)	17 (60.7)	683 (52.3)
Mean weight, kg (SD)	72.9 (15.9)	71.4 (17.5)
Seizure type, *n* (%)		
Simple partial without motor signs	7 (25.0)	447 (34.2)
Simple partial with motor signs	5 (17.9)	378 (28.9)
Complex partial	25 (89.3)	1117 (85.5)
Partial with secondary generalization	15 (53.6)	920 (70.4)
AEDs at baseline, *n* (%)		
Total	28 (100.0)	1307 (100.0)
1 AED	7 (25.0)	173 (13.2)
2 AEDs	12 (42.9)	671 (51.3)
3 AEDs	9 (32.1)	463 (35.4)

AED, antiepileptic drug; SD, standard deviation.
* Age at consent.

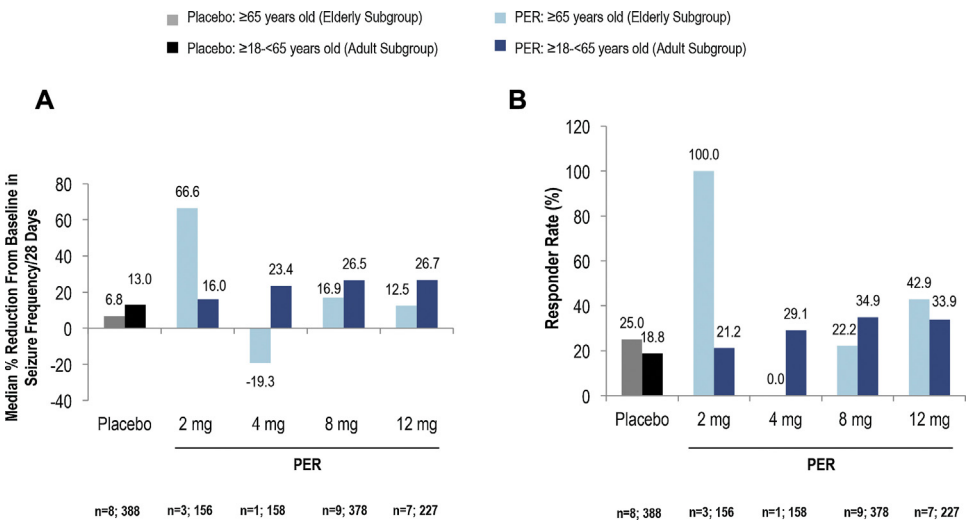

Fig. 1 Median percent change from baseline in seizure frequency per 28 days (A) and 50% responder rates (B) for elderly and adult subgroups in three phase III studies. PER = perampanel.

and 1.1% of the elderly and adult subgroups, respectively. Structural brain anomalies were the most common known etiology for both subgroups (elderly: 17.9% vs adult: 15.2%).

Efficacy

Elderly subjects were generally responsive to perampanel vs placebo (Fig. 1). Median percent reductions in seizure frequency/28 days were 16.9% and 12.5% for the 8- and 12-mg groups, respectively, vs 6.8% for placebo. Sample sizes for the 2- ($n = 3$) and 4-mg ($n = 1$) groups were insufficient for meaningful comparisons. 50% responder rates were 22.2% and 42.9% in the 8- and 12-mg groups, respectively, vs 25% for placebo. Efficacy endpoint results for elderly and adult patients were consistent.

Safety

Overall, TEAE incidence rates were similar between elderly and adult subgroups treated with perampanel (85.0% vs 77.4%, respectively). Very common TEAEs (≥10% in the entire population of the double-blind clinical studies) observed in elderly subjects receiving perampanel included dizziness, somnolence, fatigue, irritability, and fall (Fig. 2); dizziness, fatigue, and falls occurred somewhat more frequently compared to the adult subgroup. Other common TEAEs observed in the elderly perampanel group related to falls risk (Weerdesteyn et al., 2008) were gait disturbance ($n = 3$, 15%) and balance disorder ($n = 2$, 10%).

Serious adverse events (SAEs) were reported in 5 subjects aged ≥65 years. One placebo subject experienced a subdural hemorrhage, considered unrelated to study drug.

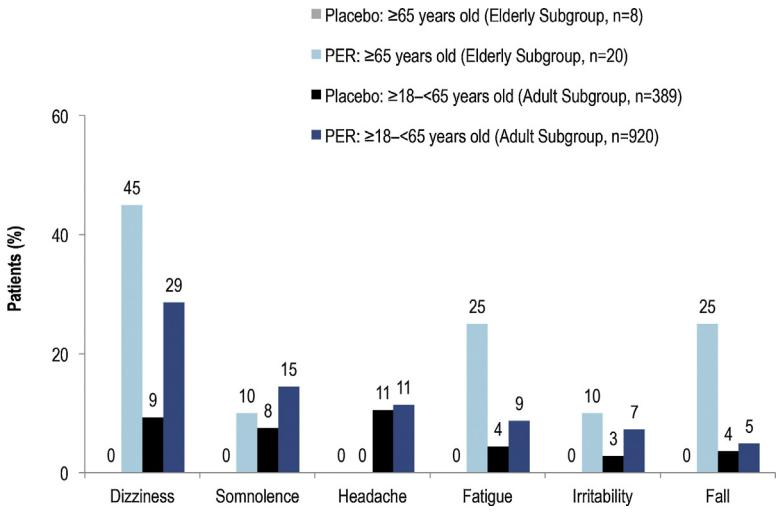

Fig. 2 Very common* treatment-emergent adverse events (TEAEs) among subjects ≥65 years of age and ≥18—<65 years of age in three phase III studies. PER = perampanel. * Very common TEAEs (adverse event that begins on/after first dose and up to 30 days after last dose of study drug; or begins before the first dose date and increases in severity during the treatment period) are those that occurred in ≥10% of subjects in any treatment group in the entire epilepsy phase III double-blind pool.

Another subject, receiving 8-mg perampanel, experienced aortic stenosis, believed to be unrelated to study drug. SAEs in elderly patients receiving 12-mg perampanel ($n = 3$) included: subject-1, grand mal convulsion (with fall and wrist fracture) designated as possibly treatment related; subject-2, head injury, hyponatremia (twice), convulsion (with disorientation), none of which were categorized as treatment related; subject-3, status epilepticus (with urinary incontinence), reported as possibly treatment related. There were no reports of serious psychiatric or behavioral reactions in elderly subjects. Study subjects recovered from all reported SAEs.

Four (20.0%) elderly subjects receiving perampanel discontinued due to adverse events (AEs); all were in the 12-mg group. Two subjects discontinued due to an SAE (described above): grand mal convulsion (with a fall) or status epilepticus. The remaining 2 subjects withdrew after experiencing ataxia, dizziness, and gait disturbance or after experiencing a ''drunken feeling.'' In all cases, the subjects recovered from the event that caused withdrawal.

Older population

We also sought to determine the efficacy and safety of perampanel in older subjects, i.e., ≥60 years old (total $n = 65$ subjects). Median percent reductions in seizure frequency for 8-mg and 12-mg perampanel were 36.0% ($n = 24$) and 16.4% ($n = 14$), respectively, which was similar to the ≥18—<60-year-old subgroup (8-mg = 26.3% and 12-mg = 27.2%) and numerically higher than subjects aged ≥65 years (8-mg = 16.9% and 12-mg = 12.5%; Fig. 1). Although the responder rate for the older population (8-mg = 29.2%; 12-mg = 28.6%) was similar to the ≥18—<60-year-old subgroup (8-mg = 35.0%; 12-mg = 34.5%), it was quite high in the older placebo group ($n = 20$; 35%). Overall, the incidence of TEAEs was similar between subjects aged ≥60 years and those ≥18—<60 years treated with perampanel (86.7% vs 77.1%, respectively). The incidence of very common TEAEs was also similar in subjects aged ≥60 (data not shown) relative to the elderly subgroup (≥65; Fig. 2).

Discussion

The physiological status of the elderly population often increases their susceptibility to safety and tolerability issues with AEDs (Brodie et al., 2009). Age-related conditions including chronic renal disease, which may interfere with drug clearance; dementia, affecting treatment adherence; and physical frailty put elderly patients at higher risk for AEs, making them less likely to be recruited for clinical studies. Elderly patients frequently use several drugs to treat multiple morbidities (polypharmacy), increasing their risk for clinically important drug interactions (Perucca et al., 2006). In addition, the efficacy of therapies may be compromised by comorbidities (Brodie et al., 2009; Leppik et al., 2006).

In our analysis, the efficacy results for the 8- and 12-mg doses were comparable between the elderly and adult subgroups. The elderly experienced an elevated risk of falls, which may be related to age-related comorbidities. The subjects had a relatively high rate of stroke etiology, which is itself a significant risk for falls (Weerdesteyn et al., 2008). In the elderly subgroup, dizziness and fatigue, in addition to falls and related AEs (ataxia, balance disorder), were somewhat more frequent vs the adult subgroup (≥18 to <65 years). The elevated risk of selected AEs, particularly falls, underscores the importance of a cautious approach to dose titration, especially toward higher dose levels, in elderly patients.

Although this analysis of perampanel is limited by the size of the elderly subgroup (28 patients), the results are largely consistent with existing perampanel data. We were also interested in the efficacy and safety of perampanel in an older population, aged ≥60 years. The median percent reduction in seizure frequency was numerically higher when patients aged ≥60 were included, and the incidence of very common TEAEs was similar relative to the elderly subgroup (≥65 years). Although ''elderly'' is defined by the WHO as aged ≥65 in developed countries (WHO, 2014), studying subjects aged ≥60 provides additional context and support for perampanel use in these patients.

Conclusions

This analysis of patients with partial seizures aged ≥65 years who had participated in perampanel phase III studies demonstrates similar efficacy rates compared to the larger adult population. The incidence of most AEs was not elevated in elderly patients, but falls, dizziness, fatigue, and balance disorders were more common. Consequently, it is advisable that dosing titration proceed cautiously in patients aged ≥65 years, especially toward higher doses, where a balance between tolerability and clinical response is needed (Fycompa Prescribing Information 2014).

Author contributions

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

Disclosures

IE Leppik is an employee of the University of Minnesota and has received research support from Lundbeck and compensation from UCB Pharma, Eisai Inc., and Upsher-Smith. RT Wechsler is the owner of Consultants in Epilepsy & Neurology PLLC and Medical Director of the Idaho Comprehensive Epilepsy Center. He has served as a paid consultant for Eisai Inc., Cyberonics, Gerson Lehman Group, Inc., Lundbeck, Sunovion, UCB Pharma, and Upsher-Smith; has been on the speaker bureau for Eisai, Cyberonics, Lundbeck, and UCB

Pharma; and has been a clinical investigator for trials sponsored by Eisai, Lundbeck, Pfizer, SK Life Science, Sunovion, UCB Pharma, Upsher-Smith, and Vertex. B Williams, A Laurenza, H Yang, and S Zhou are employees of Eisai Inc.

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