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Levetiracetam in patients with refractory epilepsy: Results of the SKATE trial in Austria, Germany and Switzerland

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Summary

Purpose: To further evaluate the safety, efficacy and optimal dose of levetiracetam (LEV) in daily clinical practice among patients with uncontrolled partial epilepsy with or without secondary generalization.
Methods: In this phase IV, open-label, 16-week community-based study, 178 at least 16-year-old patients with refractory focal epilepsy were treated with 1000, 2000 or 3000 mg levetiracetam as adjunctive therapy. All patients started with 500 mg LEV b.i.d. (1000 mg/day); the dose was adjusted in 2-week intervals up to 1500 b.i.d. (3000 mg/day) depending on seizure control and tolerability. The main objectives were the adverse events, the percentage reduction in partial and total seizure frequency per week from baseline and the retention rate, defined as the percentage of patients taking LEV at the end of the 16-week treatment period.
Results: Of the 178 patients who took at least one dose of LEV 151 completed the study. Thus, the retention rate (number of patients taking LEV at the end of the 16-week treatment period) was 84.8%. Most frequently reported adverse events were asthenia, dizziness, headache, nausea, somnolence and hostility; the majority of these events were of mild to moderate intensity. The seizure-free rate of the ITT population with focal seizures was 16.7%, for all seizures 16.6%; the median reduction of focal seizure frequency was 47.6%, and 46.5% for all seizures. The 50% responder rate was 46.6% for focal seizures and 45.1% for all seizures.
Conclusion: Add-on treatment with LEV in patients with refractory partial epilepsy was safe and effective in this study.

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Introduction

Levetiracetam (LEV, Keppra®) has been approved since the year 2000 as an add-on treatment for adult patients with focal seizures with or without secondary generalization. The results of the placebo-controlled studies leading to approval and the open-label extension studies indicate that LEV constitutes a considerable progress in the treatment of epilepsy.[2,3,14] Only half of patients achieve adequate seizure control following monotherapy with the initial antiepileptic drug (AED)[8] which requires add-on therapy with a second or even third agent. In placebo-controlled trials investigating this add-on treatment, responder rates with LEV were significantly higher compared to placebo. The occurrence of adverse events was comparable for LEV and placebo; slightly more frequent in the LEV group were asthenia, somnolence and headache.

In addition to the advantageous efficacy and safety properties, LEV has an almost perfect pharmacokinetic profile[12,13]: about 100% bioavailability, less than 48 h to steady state, linear kinetics, twice-daily dosing, protein binding less than 10%, no hepatic metabolism, minimal metabolism in blood, no significant interactions with other AEDs. Recently, the binding site of LEV was discovered[9]: the synaptic vesicle protein SV2A is the brain-binding site of LEV. Probably, LEV acts by modulating the function of SV2A, supporting previous indications that LEV possesses a mechanism of action that is different from other AEDs. There are reports of other effects of LEV, including the partial inhibition of N-type high-voltage-gated Ca^{2+} channels and the reduction of inhibition of GABA and glycine-gated currents.[10] Furthermore, LEV has been shown to delay the development of kindling, indicating that it may have disease-modifying properties to the development that results in reduced seizure threshold.[7]

The SKATE study (*S*afety of *K*eppra® as *A*djunctive *T*herapy in *E*pilepsy) was conducted to evaluate the safety and efficacy of LEV in a population that represents the patients seen by physicians in their daily clinical practice. In general, 50% of epilepsy patients become seizure-free with the first monotherapy, further 25% become seizure-free with an alternative mono- or combination therapy, whereas 25% are refractory to any drug treatment. In the phase III studies, which led to LEV approval, the participants were chosen from the 25% of patients whose seizures are refractory to any treatment. In the SKATE study, patients were recruited whose seizures could not be sufficiently controlled with one or two AEDs thus reflecting a very similar population. This report displays the result of the pooled data of the Austrian, German and Swiss part of the SKATE study, in order to provide useful information to clinicians on the optimal use of LEV as add-on treatment in a relevant number of patients with epilepsy.

Materials and methods

The SKATE study is a 16-week, phase IV, multi-centre, open-label, community-based trial of LEV as add-on therapy in patients with uncontrolled focal seizures. The study is conducted in accordance with ICH-GCP guidelines, the Declaration of Helsinki, and the national laws of the countries involved. This article reports the study results of the patients recruited for the SKATE study in Austria, Germany and Switzerland.

Patients

At least 16-year-old men and women experiencing focal epileptic seizures with or without secondary generalization that were classifiable according to the International Classification of Epileptic Seizures[4] could be enrolled. Eligible patients had at least 1 but not more than 14 focal seizures per month in the 3-month baseline period, resulting in 3—42 seizures in the period preceding study entry. The patients had been receiving one or two marketed AEDs at a stable dosage for at least 4 weeks before study entry; benzodiazepines used on a daily basis were considered as one of the concomitant AEDs, regardless of the prescribed indication.

Previous treatment with LEV, felbamate within 18 months prior to the study, vigabatrin treatment at visit 1 and participation in another clinical study within 12 weeks prior to the screening visit were not permitted. Other exclusion criteria were questionable compliance, serious psychiatric disorders within the previous 5 years, any condition that may influence the pharmacokinetics of medication (patients with mild to moderate renal impairment were eligible), progressive cerebral or degenerative neurological disease, cerebral tumors, terminal illness or any medical condition that may interfere with the patient's study participation (e.g. scheduled elective surgery). Pseudoseizures within the last year and uncountable seizures (clusters) or convulsive status epilepticus within the last 5 years led to ineligibility. Pregnant or lactating women were not eligible. Women of childbearing potential had to use a medically acceptable contraceptive method. Allergy to LEV and hematological abnormalities expressed by a neutrophil count $< 1800/mm^3$ and/or platelets $< 100{,}000/mm^3$ also led to ineligibility.

All patients or a legally acceptable representative had to give written informed consent prior to

any study specific procedures. The study was approved by the local ethical committees.

Study treatment and visits

Treatment

All patients started with an initial dose of 2 × 500 mg LEV per day, to be taken orally with or without a meal. If insufficient seizure control was achieved with that dose, the LEV dose could be increased in 1000 mg/day steps every 2 weeks up to 3000 mg daily provided that LEV was well tolerated. Between weeks 4 and 16 of treatment, the LEV dose could be modified between 1000 and 3000 mg/day in increments of 1000 mg at the investigator's discretion to achieve maximum benefit regarding safety and efficacy. A flowchart about the study course is given in Fig. 1.

In patients with mild renal insufficiency (creatinine clearance 50—79 ml/m), the maximal permitted daily dose of LEV was limited to 2000 mg, in the case of moderate renal insufficiency (creatinine clearance 30—49 ml/min) the permitted daily LEV dose was 500—1500 mg/day. After the final visit (week 16 or early discontinuation), LEV treatment could be continued on a prescription basis or the patient could be progressively withdrawn from LEV treatment, depending on the decision of the investigator. In the case of withdrawal, the patient was recommended to reduce LEV in steps of 1000 mg every 2 weeks. The accompanying AED therapy had to remain stable during the study, unless an urgent medical problem required a modification. The use of any other concomitant medication had to be recorded in the CRF including drug name, dose, date of administration and indication.

Study procedures

Following visit 1 at week 0, patient visits were scheduled for weeks 2, 4, 10, and 16 and, if applicable, 2 weeks following drug withdrawal. At the selection visit, written informed consent was obtained and demographic data collected. A detailed history (medical, epilepsy, sum of seizures for the past 3 months for each seizure type, AED and other concomitant therapy) was recorded. A laboratory screening was conducted unless done within 4 weeks prior to V 1 and a pregnancy test was conducted if applicable. The Austrian patients (n = 10) filled in a QOLIE-10-P (*Q*uality *O*f *L*ife *I*n *E*pilepsy). This is comparable to the Quolie-31-P and includes items about distress and hierarchy of domains.[5] Due to this methodological inhomogenity among the three countries, the results are not displayed in this report. After a physical and neurological examination, the Daily Record Cards were given and explained to the patients and LEV was dispensed in a dosage of 1000 mg/day.

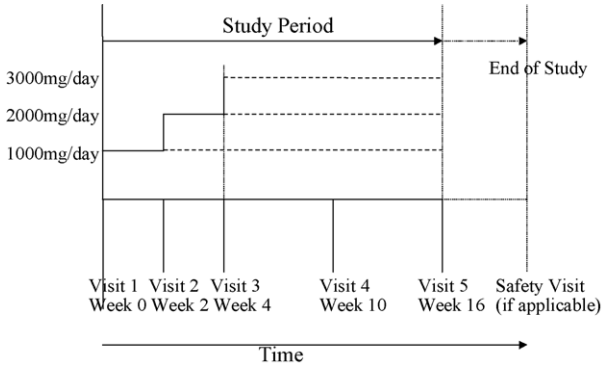

Figure 1 Schematic timeline.

At the visits scheduled for weeks 2, 4, 10, and 16, seizure count, concomitant medication and adverse events were documented; the Daily Record Cards and the study medication were returned and dispensed. Any change in LEV dosage was documented at each visit. A pregnancy test was repeated at weeks 4, 10, 16 and at early discontinuation. At the last visit of the treatment period and the early discontinuation visit, a physical and neurological examination was conducted and the investigator assessed the development of the disease (Global Evaluation Scale) during the treatment period.

At the last visit of the treatment period, LEV could be continued on a prescription basis or the patient could be withdrawn from LEV treatment in steps of 1000 mg/day every 2 weeks. In the latter case, the patients were asked to return 2 weeks following the last dose of LEV for a safety visit, which included a physical and neurological examination, the recording of concomitant medications, adverse events and seizure count.

Efficacy and safety variables

Extent of exposure

In order to define the LEV dosing regimen, a particular interest was given to dose/duration of exposure and titration schedules.

Safety variables

Safety assessments were made using the reporting of adverse events.

Efficacy variables

The percentage reduction from historical baseline in the focal onset (type I) and total (types I + II + III) seizure frequency per week over the 16-weeks treatment period.

The retention rate at 16-weeks, defined as the number of patients taking LEV at the end of the 16-weeks treatment period divided by the number of patients in the intention-to-treat (ITT) population.

The prospective variables described herein were analyzed. Seizure-freedom and additional parameters derived from the seizure counts were also analyzed.

Statistical and analytical issues

The analysis was based on the ITT population consisting of all subjects included in the study who took at least one dose of study medication. The consistency of safety and efficacy results was investigated by performing summary statistics by country on adverse events and percentage change from historical baseline in focal onset seizure frequency per week over the 16-week treatment period. In this report, the results of Austria, Germany and Switzerland were pooled.

Results

Baseline demographic and clinical characteristics

Of the 178 patients who received at least one dose of LEV (ITT population), 151 patients (84.8%) completed the study. The number of males and females was nearly equivalent, the mean age was 40.7 years (standard deviation ±14.7 years, Table 1). The mean epilepsy duration was 24.9 ± 15.0 years with a mean onset age of 15.8 ± 13.5 years. At study entry, 45.5% of the patients were on AED monotherapy; and 49.4% were taking two AEDs; 1.1% were receiving three or more AEDs and 2.8% were receiving no AEDs. Both were a protocol deviation since inclusion criteria specified that only one or two AEDs should be taken at baseline. Patients without AED treatment had discontinued previous AEDs due to a lack of efficacy and/or the presence of adverse events. Most frequently used AEDs at study entry were carbamazepine (39.9%), lamotrigine (28.1%), valproic acid (20.8%), oxcarbazepine (13.5%) and topiramate (12.4%).

Reasons for early discontinuation were adverse events (17 patients, 9.6%), lack of efficacy (3 patients, 1.7%), loss to follow-up (2 patients, 1.1%), withdrawal of consent (1 patient, 0.6%), and other reasons (3 patients, 1.7%). In addition, the final status of study completion or discontinuation was unknown for one subject.

Table 1 Baseline demographic and clinical characteristics of patients enrolled in SKATE.

Parameter	Value
Age (years), mean ± S.D.	40.7 ± 14.70
Age distribution	
N (%) age 16–65 years	165 (92.7%)
N (%) age ≥65 years	13 (7.3%)
Female/male, *n* (%)	90/88 (50.6%/49.4%)
Body mass index (kg/m^2), mean ± S.D.	25.00 ± 4.65
Duration of epilepsy, mean ± S.D.	24.88 ± 14.98
Age at epilepsy onset, mean ± SD	15.83 ± 13.52
Etiology of epilepsy, *n* (%)	
Unknown	80 (44.9%)
Perinatal/birth events	24 (13.5%)
Congenital malformation	18 (10.1%)
Cerebral infection	12 (6.7%)
Cranial trauma	9 (5.1%)
Cerebral neoplasm	7 (3.9%)
Brain surgery	6 (3.4%)
Cerebrovascular accident	3 (1.7%)
Genetic origin	3 (1.7%)
Primary degenerative lesion	2 (1.1%)
Other	24 (13.5%)
Number of AEDs at study entry, *n* (%)	
0 (protocol deviation)	5 (2.8%)
1	81 (45.5%)
2	88 (49.4%)
≥3 (protocol deviation)	2 (1.1%)

Extent of exposure

The mean duration of LEV treatment in this study was 108.6 ± 34.5 days; the median duration of exposure was 113 days (Q_{25}–Q_{75} = 109.5–120.5). There were neither marked differences in exposure duration by gender nor by age. The mean daily dose of LEV was 1847 ± 304 mg (range 250–6000 mg/day); the median daily dose was 2000 mg (Q_{25}–Q_{75} = 1000–3000 mg). Again, no significant differences in LEV dose by gender or by age could be detected.

Safety

Altogether 108 patients (60.7%) of the ITT population experienced at least one adverse event during the treatment period, 8 patients (4.5%) suffered from a serious adverse event (SAE). Serious adverse events with a possible relationship to LEV treatment were reported from 4 patients (2.2%) including a series of seizures with hospitalization, an acute episode of agitated depression with somatoform symptoms, tremor and psychosis. Except for the series of

Table 2 Treatment-emergent adverse events experienced overall by ≥5% of the 178 patients enrolled, broken down by intensity or relationship to LEV treatment.

Adverse event	Total *N* (%)	Intensity			Relationship to LEV treatment	
		Mild *N*	Moderate *N*	Severe *N*	Not related *N*	Related *N* (%)
Asthenia	29 (16.3%)	18	9	2	3	26 (14.6%)
Dizziness	20 (11.2%)	9	11	0	4	16 (9.0%)
Headache	15 (8.4%)	3	7	5	5	10 (5.6%)
Nausea	12 (6.7%)	6	4	2	2	10 (5.6%)
Somnolence	12 (6.7%)	6	4	2	1	11 (6.2%)
Hostility	9 (5.1%)	7	2	0	0	9 (5.1%)

seizures, these events led to discontinuation of LEV treatment. One SUDEP (*S*udden *U*nexplained *D*eath in *EP*ilepsy) occurred in the study which was assessed as unlikely to be related to LEV treatment. Likewise, the three remaining SAEs were assessed as unlikely to be related to LEV treatment: humerus fracture, status epilepticus and eczema.

Treatment-emergent adverse events that occurred in ≥5% of patients were asthenia (29 patients, 16.3%), dizziness (20, 11.2%), headache (15, 8.4%), nausea and somnolence (12, 6.7% each) and hostility (9, 5.1%), most of these events were of mild or moderate intensity (Table 2).

Other adverse events related to the nervous system were rare: tremor (7 patients, 3.9%), convulsion (5, 2.8%), insomnia (4, 2.2%), ataxia, depression, abnormal thinking and nervousness (3, 1.7% each). Altogether, 19 patients (10.7%) experienced adverse events with severe intensity, reported from more than one patient were headache (5 patients, 2.8%), vomiting (3 patients, 1.7%), and asthenia, somnolence, malaise and nausea with 2 patients (1.1%) each. Other severe adverse events only occurred in single cases. Adverse events led to study drug discontinuation in 16 patients (9.0%), most frequent reasons were nausea, vomiting, asthenia, headache and tremor.

Efficacy

The add-on treatment of LEV to a stable AED medication led to a median reduction of seizure frequency over the 16-weeks treatment period for focal seizures of 47.6% (Q_{25}—Q_{75} = 4.7—87.6), for total seizures the reduction was 46.5% (Q_{25}—Q_{75} = 1.7—84.1, Table 3).

Table 3 Comparison of baseline demographic and epilepsy characteristics between phase III studies and SKATE.

Parameter	Phase III	SKATE
Mean age (years ± S.D.)	37.4 ± 11.3	40.7 ± 14.7
Median epilepsy duration (years)	22	23.7
Median age at epilepsy onset (years)	12	12.5
Median baseline seizure frequency per month	9	4

The 50% responder rate, defined as the percentage of patients experiencing a reduction in seizure frequency of 50% or more over the treatment period was 46.6% for focal and 45.1% for all seizures. Seizure freedom over the treatment period was achieved in 16.7% of the patients with focal seizures and in 16.6% of the patients with total seizures.

The retention rate (number of patients taking LEV at the end of the 16-week treatment period) was 84.8%.

Discussion

Compared with the pivotal studies conducted to get approval for LEV, the patient population of the SKATE study more closely reflects the patients seen in daily clinical practice. Thus, the pooled analysis of the patients enrolled in SKATE in Austria, Germany and Switzerland is able to provide safety and efficacy data which is a better reflection of the usual antiepileptic therapy. Nevertheless, all patients enrolled in SKATE had uncontrolled epilepsy and received one or two AEDs at baseline. AED monotherapy was taken by 45.5% of the patients at baseline, 49.4% were taking two AEDs; 1.1% were receiving three or more AEDs and 2.8% were receiving no AED. The rate of 84.8% of patients completing the trial is exceptionally high for a phase IV trail and similar to the rate of 85% seen in phase III controlled clinical studies.[2,3,14]

The results of SKATE in Austria, Germany and Switzerland match favourably with those from phase III controlled clinical studies[2,3,14] as well as with findings from another phase IV study with a similar design to SKATE, the KEEPER (*K*eppra *E*pilepsy *E*valuation of the *P*atient tim*E* to *R*esponse) trial.[11] The main difference between SKATE and the phase III studies was the randomized assignment of the phase III patients to a fixed dose of LEV after a

Table 4 Reduction in seizure frequency over the treatment period compared to baseline.

Seizure type	Baseline seizure frequency/week			Reduction from baseline (%)		
	N	Median	Q_{25}—Q_{75}	*N*	Median	Q_{25}—Q_{75}
Partial (type I)	177	0.93	0.5—1.9	168	47.6	4.7—87.6
Total (types I + II + III)	178	0.93	0.6—2.0	174	46.5	1.7—84.1

titration period. In the KEEPER study, the dose was increased by 500 mg b.i.d. every 2 weeks up to 1500 mg b.i.d. unless seizure freedom was achieved before. The dose was then to remain stable throughout the treatment period, whereas in SKATE the dose could be adjusted throughout the study according to efficacy and safety variables to achieve maximum benefit for the patients. Therefore, it could be expected that the efficacy and safety of LEV observed in the SKATE study might be slightly better compared with the phase III and the KEEPER study and thus compensate the theoretical drawbacks caused by the fact that more traditional European epilepsy centres participated in SKATE with a study population that might have been more refractory.

The efficacy criteria 50% seizure reduction and seizure freedom rates for focal onset seizures in SKATE are commonly used in studies evaluating AEDs in patient populations with a wide range of variation as well as a non-normal distribution of epileptic seizures.[1,6] These efficacy parameters were also evaluated in the pivotal phase III clinical studies, which facilitates the comparison of LEV efficacy in the relatively homogeneous patient populations recruited in the phase III studies versus the more heterogeneous patient populations recruited for the SKATE study.

The demographic and baseline epilepsy characteristics of the patients in the phase III clinical trials and SKATE were similar (Table 4), except for the median baseline seizure frequency which was with 9.0 per month in the phase III studies higher than in SKATE with four per month.[2,3,14]

The 50% responder rate in SKATE confirms the results found in the phase III trials: 46.6% for focal onset seizures versus 28.5% for 1000 mg LEV, 34.3% for 2000 mg LEV and 41.3% for the 3000 mg LEV treatment group in the phase III studies. As mentioned before, the higher 50% responder rate in SKATE can be explained by the flexible dose that could be adapted to the patient's needs. The seizure freedom rates under LEV treatment in patients with focal-onset seizures support this explanation: 16.7% in SKATE, compared to 4.7% for 1000 mg, 6.3% for 2000 mg and 8.6% for 3000 mg LEV daily in the phase III studies.

Thus, results from SKATE in Austria, Germany and Switzerland reported here indicate that LEV is even more efficient than shown in phase III trials when used in a setting more closely reflecting daily practice with regard to patient population and treatment regimen.

Comparing the results of SKATE with another community-based LEV trial, the KEEPER study, the baseline characteristics of the patient populations were similar: mean age 42.2 $\pm$ 14.5 years in KEEPER versus 40.7 $\pm$ 14.7 years in SKATE, median epilepsy duration 18.4 versus 23.7 years and median age at epilepsy onset 18.3 versus 12.5 years, median baseline seizure frequency per month 3.6 (KEEPER) versus 4 in SKATE.[11] Thus, the patients in KEEPER were slightly older but had a shorter epilepsy duration with later onset age. The 50% responder rate for focal seizure patients in the KEEPER population was 57.9% versus 46.6% in SKATE; the seizure freedom rate was 20.0% in KEEPER versus 16.7% in SKATE. These slightly higher rates in KEEPER may result from the high percentage of patients treated in traditional European epilepsy centers who usually reflect a population of the most difficult-to-treat epilepsy patients. On the other hand, considering this possible selection drawback, the SKATE results emphasize the favorable efficacy profile of LEV.

SKATE also supports the safety data evaluated in the phase III studies with an equal rate of 9% of the patients discontinued permanently from the study due to an adverse event.[2,3,14] The adverse event profile was comparable in the phase III trials and SKATE: most frequent were asthenia 16.3% (SKATE) versus 14.1% (phase III), dizziness (11.2% versus 9.2%), headache (8.4% versus 13.1%) and somnolence (6.7% versus 14.9%). The frequency of these adverse events was similar in the SKATE interim analysis of all participating centers in the countries having entirely finished the study: asthenia 19.2%, dizziness 9.7%, headache 11.2% and somnolence 16.7%.

In conclusion, the results of the SKATE study centres in Austria, Germany and Switzerland support the efficacy and safety results of the phase III trials with an even more pronounced efficacy in a setting better reflecting the patients and treatment options appearing in daily clinical practice compared to the settings in the phase III studies.

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