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Research Paper

A multicenter Phase II randomized, placebo-controlled single-blind trial with the SV2A ligand seletracetam in photosensitive epilepsy patients

Dorothee Kasteleijn-Nolst Trenité [a,b,1,*], Armel Stockis [c], Edouard Hirsch [d], Pierre Genton [e], Bassel W. Abou-Khalil [f], Jacqueline A. French [g], Pascal Masnou [h], Wolfgang Löscher [i,1,*]

[a] Department of Neurosurgery and Epilepsy, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Nesmos Department, Faculty of Medicine and Psychology, Sapienza University, Roma, Italy
[c] UCB Pharma, Braine-l'Alleud, Belgium
[d] Epilepsy Unit "Francis Rohmer," ERN EpiCare, French Centre de Référence des Épilepsies Rares (CréER), Neurology Department, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
[e] Neurology Department, Centre Hospitalier du Pays d'Aix, Aix-en-Provence, France
[f] Department of Neurology, Vanderbilt University, Nashville, TN, USA
[g] Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, USA
[h] Department of Neurology, University Hospital Kremlin-Bicêtre, Paris, France
[i] Translational Neuropharmacology Lab, NIFE, Department of Experimental Otology of the ENT Clinics, Hannover Medical School, Hannover, Germany

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ABSTRACT

The objective of this study was to evaluate the effect of seletracetam (SEL), a potent modulator of synaptic vesicle glycoprotein 2A (SV2A), in patients with photoparoxysmal EEG response (PPR) to intermittent photic stimulation (IPS) as proof-of-principle of efficacy in patients with epilepsy. In this multicenter, single-blind Phase II study, adults with photosensitive epilepsy, with/without concomitant antiseizure medication therapy, underwent IPS under 3 eye conditions (at eye closure, eyes closed and eyes open) after a single oral dose of placebo (day − 1) or SEL (day 1; 0.5, 1, 2, 4, 10, or 20 mg). Complete suppression was a standardized photosensitivity range reduction to 0 over ≥ 1 time points for all eye conditions. Partial suppression was a ≥ 3-point reduction over ≥ 3 testing times vs the same time points on day − 1 in ≥ 1 eye condition. In addition, pharmacokinetics and safety were assessed. Of 27 evaluable patients, 9 reentered to receive a 2nd dosing 1–6 months later, providing a total of 36 individual exposures. At all doses administered − even the lowest −, several subjects reached a complete abolishment of PPR, with a rapid onset of effect. Overall, complete abolishment of PPR was obtained in 40–71 % of the patients; the effect increasing with the dose. In terms of effective doses to suppress PPR, SEL was at least 1,500 times more potent than levetiracetam and 10–20 times more potent than brivaracetam. Adverse events of SEL, including dizziness and somnolence, were mild to moderate. Pharmacokinetics of SEL demonstrated rapid absorption and a linear dose:plasma level relationship. This proof-of-principle study demonstrates that – based on our own experience − SEL is the most potent compound ever tested in the photosensitivity model.

Abbreviations: ARCI, addiction research center inventory; ARS, acute repetitive seizures; ASM, antiseizure medication; AUC, area under the curve; AUEC, area under the effect curve; BRV, brivaracetam; C_{max}, maximum plasma concentration; ECG, electrocardiography; EEG, electroencephalogram; GTCS, generalized tonic-clonic seizure; IPS, intermittent photic stimulation; LC/MSMS, liquid chromatography with tandem mass spectrometry detection; LEV, levetiracetam; LTG, lamotrigine; PCAG, Pentobarbital-Chlorpromazine-Alcohol group; PET, positron emission tomography; POP, proof of principle; PPR, photoparoxysmal EEG response; RCT, randomized controlled trial; REST, rapid epileptic seizure termination; SEL, seletracetam; SPR, standard photosensitivity range; SV2A, synaptic vesicle glycoprotein 2A; $t_{1/2}$, elimination half-life; t_{max}, time of the maximum plasma concentration; VAS, visual analog scale; VPA, valproate.

* Corresponding authors.
E-mail addresses: dkasteleijn@planet.nl (D. Kasteleijn-Nolst Trenité), Loescher.Wolfgang@mh-hannover.de (W. Löscher).
[1] Shared senior authorship.

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1. Introduction

The benchmark antiseizure medication (ASM), levetiracetam (LEV), and its structural analog brivaracetam (BRV), both modulators of neurotransmitter release via targeting synaptic vesicle glycoprotein 2A (SV2A; [17], have been successfully studied in their early phases of drug development in patients with photosensitive epilepsy, i.e., the "photosensitivity model" [12,11]. Both compounds have also been compared head-to-head as iv-infusion in phase IV for rapidity of brain entry and efficacy in a randomized controlled trial (RCT) using the same, adapted model[22]. In line with positron emission tomography (PET) studies showing a significantly faster brain penetration of BRV vs. LEV[5,21], the onset of the effect of BRV in photosensitive epilepsy patients was about 4-times more rapid compared to LEV[22].

BRV was discovered by a drug discovery program at UCB Pharma in which ~ 12,000 compounds were screened in vitro for SV2A binding affinity; 1,200 were further screened in vivo for seizure protection in an animal model, the audiogenic seizure-prone DBA/2 mouse model of reflex epilepsy[14]. This led to the identification of two distinct antiseizure families with high affinity for SV2A; they were named after their lead compounds: BRV (a 4-n-propyl LEV homolog) and seletracetam (SEL; a difluorovinyl derivative) (Fig. 1). SEL has a one-log-unit higher affinity for SV2A than LEV and is more selective[2,20]. SEL is also much more lipophilic than LEV (log*P* 0.51 [SEL] vs. −0.64 [LEV]) and up to 200 times more potent than LEV (and up to 90 times more potent than BRV) in acute and chronic animal models of focal and generalized seizures[17]. For instance, effective doses (ED_{50}s) against sound-induced generalized convulsive seizures in DBA/2 mice were 0.17 mg/kg (SEL) vs. 30 mg/kg (LEV) and 2.4 mg/kg (BRV), respectively. Minimum active doses in the amygdala kindling model of temporal lobe epilepsy were 0.0074 mg/kg for SEL, 1.25 mg/kg for LEV, and 0.68 mg/kg for BRV, respectively[17]. Despite its high antiseizure potency, the protective index of SEL is 10–40 times higher than that of LEV or BRV in mice and rats, indicating higher tolerability of SEL vs. the two other racetams [2,20,17]. The good tolerability was substantiated in Phase I studies in healthy volunteers, in which treatment-emergent adverse events of SEL at doses as high as 600 mg were of mild to moderate severity, were mostly of CNS origin, and resolved within 24 h[2]. Despite these promising characteristics, UCB Pharma decided to evaluate only BRV in large multicenter Phase III trials, and BRV was approved by the FDA in 2015 for the treatment of focal-onset seizures[13,16].

In the present proof-of-principle (POP) clinical study, the effects of single oral doses of SEL on the photic-evoked EEG parameter, the photoparoxysmal EEG response (PPR), were evaluated. This allowed us to compare the antiseizure effects of SEL with those of LEV and BRV because similar study designs were followed in all three compounds [12,11]. In addition, the safety and pharmacokinetics of SEL were determined in the photosensitive epilepsy patients.

2. Materials and methods

2.1. Drug

SEL (ucb 44212) was synthesized by UCB Pharma SA (Brussels, Belgium), and was formulated as oral capsules containing 0.5–10 mg of SEL, Avicel PH102, and magnesium stearate. Placebo capsules containing microcrystalline cellulose were used as a control.

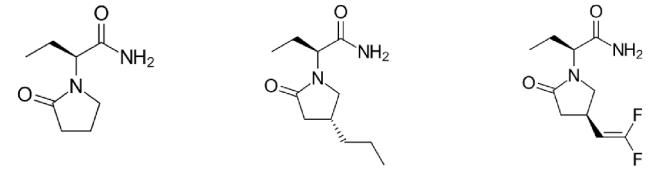


Fig. 1. Chemical structures of the racetams levetiracetam, brivaracetam and seletracetam.

2.2. Patients

The main inclusion criteria were as follows:

- Adult male or female subjects (18–60 years) with photosensitive epilepsy, with or without concurrent seizures as long as the seizure frequency and type were not interfering with the conduct of the study;
- subjects who previously exhibited a generalized PPR on routine EEG investigation (i.e. generalized epileptiform discharges with or without a focal onset and/or outlasting the IPS stimulus train);
- subjects showing a clear and consistent photosensitivity range in at least one eye condition as confirmed at screening and pre-dose;
- subjects with stable intake of ASMs (if any) as prescribed for at least 4 weeks before the SEL trial (same dosage and timing of ASM administration before and during the study);
- a maximum of two concomitant ASMs was allowed.

The main exclusion criteria were as follows:

- Lactating or pregnant females or females of childbearing potential insufficiently protected against pregnancy;
- subjects who started a new ASM, or modified the existing one, less than 4 weeks before dosing with SEL;
- subjects taking more than two concomitant ASMs, including benzodiazepines (BDZs);
- history of rapid progressive neurological or psychiatric disorder;
- occasional use of BDZs (orally, IM, or suppository) as escape medication;
- drugs that could interfere seriously with SEL or the conduct of the study or the interpretation of the results such as some neuroleptics (piperazine and thioxanthene derivatives, butyrophenones and diphenylpiperidine derivatives, benzamides derivatives);
- history of severe allergic reactions or intolerance, especially to pyrrolidine derivatives and/or excipients;
- history of status epilepticus;
- history or presence of drug addiction or excessive use of alcohol (weekly intake of more than 28 units of alcohol; one unit of alcohol equals ½ a pint of beer or lager, a glass of wine, or a measure of spirits);
- any serious disease, other than epilepsy, that could interfere with the assessment of efficacy, safety, or pharmacodynamic parameters;
- any clinically significant abnormality in standard laboratory tests (except if written sponsor approval obtained);
- heavy caffeine drinker (drinking > 5 cups of coffee, tea, etc. per day);
- participation in another trial, blood donation, or significant blood loss (> 450 mL) less than 12 weeks before the study drug administration;
- subjects unable to understand and follow the study requirements.

Further information on the patients enrolled in this study is given in section 3.1.

2.3. Ethics

Before starting the study, the protocol, the subject information sheet, and the informed consent form were approved by Independent Ethics Committees or Institutional Review Boards as appropriate. The study was carried out in accordance with the International Conference on Harmonisation (ICH) E6 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)(1), and applicable local laws and regulations. All the subjects provided written informed consent before taking part in the

study.

2.4. Design of the clinical study

The present study was performed in 2005 and 2006, shortly after the study with BRV was conducted in the photosensitivity model in 2004 [11]. The study design was similar to the previous Phase IIa trials with LEV and BRV[12,11]. The present multicenter Phase-IIa placebo-controlled, single-blind, single-period study, was likewise conducted in a three-day period (with an extension to 5 days if the EEG response to IPS did not return to baseline) and patients underwent standardized IPS to define the standard photosensitivity range (SPR) at fixed time points and in three eye conditions (at eye closure, eyes closed and eyes open). The SPR is derived from upper and lower sensitivity thresholds as measured with a standard amount of flash frequencies starting at 2 Hz and going upwards until a generalized PPR is seen and then from 60 Hz flashing going downwards. A Grass PS33 photic stimulator was used in all patients, who were seated 30 cm from the stimulator in a dimly lit room. Subjects were blinded to the study drugs they received (placebo, SEL).

On the 1st placebo day, photic stimulation range determinations were done at hours 0.5, 1, 2, 4, 6, and 8 after dosing, while on the 2nd day, single oral doses of SEL were given with IPS testing at the same hours post-dosing, but with extension to hours 24, 28, 32 and 48 after dosing. In this way, both the onset and the duration of the suppressive effect on PPR could be determined. Plasma levels of SEL and concomitant ASMs were monitored up to 72 h post-dose with blood sampling shortly before or after the above-mentioned time points of the IPS procedure that takes at maximum 7 min when complete suppression is found and thus all frequencies are tested.

Based on antiseizure potency in animal models and safety data in healthy volunteers, it was decided to start at 10 mg SEL and then continue with subsequently lower or higher doses depending on the results of efficacy and tolerability of the previous group. Doses to be tested were 0.5, 1, 2, 4, 10, 20, and 40 mg.

SPR was the main parameter to identify the lowest single dose of SEL producing maximal decrease or suppression of the IPS-evoked photoparoxysmal EEG response (PPR) comparing the SPRs before and after intake of SEL within the same patient. Pharmacodynamic outcomes (PPR and SPR) were analyzed by an independent central EEG reader and combined with pharmacokinetic data of SEL and concomitant ASMs as prescribed in a steady state. The methodology is described in detail in the article on BRV[11].

The primary objective of the study was to identify the lowest single oral dose of SEL producing suppression of the IPS-evoked PPR in photosensitive epileptic subjects. Secondary objectives were (1) to assess the relationship between plasma concentrations of SEL, changes in the photosensitive frequency range, time of onset, and duration of the effect; (2) to document the safety of SEL in epilepsy patients; and (3) to gain information on possible effects of SEL on mood in epilepsy patients by using a standardized scale (Bond and Lader Visual Analog Scale [VAS]; Bond and Lader, 1974) and the rating questionnaire of the Addiction Research Center Inventory (ARCI-49; Haertzen et al., 1963).

2.5. Parameters used

2.5.1. Pharmacodynamic parameters

The primary pharmacodynamic parameter was the reduction from baseline (values recorded at pre-dose time on day −1 [placebo] and day 1 [SEL]) and corresponding placebo time points of the SPR. SPR was defined as the number of frequencies (steps) between the lowest and highest frequencies that consistently elicited a PPR. SPR was assessed in 3 distinct eye conditions in the following order: at eye-closure, with eyes-closed and eyes-open. Average values of SPR were computed per time point for placebo and active treatment. Response in terms of photosensitivity was classified as “no change”, “response but no abolishment”, and “complete abolishment”. “Complete abolishment” meant that at all frequencies there was no PPR at least at one time point. Partial response (i.e., “response but no abolishment”) was a reduction in PPR by at least three steps − similar to the BRV study published by us previously [11]and lasted in general also for hours.

The secondary pharmacodynamic parameters were (1) number of responders (i.e., patients with complete or partial suppression of PPR); (2) duration of response; (3) time to first response; (4) maximal reduction; (5) time to maximal reduction; (6) the area under the effect curve from 0-8 h [AUEC(08)], calculated as SPR change from baseline and using the linear trapezoidal rule; (7) relationship between primary pharmacodynamic parameter (reduction from baseline in SPR) and SEL plasma concentrations; and (8) Bond-Lader and ARCI-49 rating scales.

2.5.2. Plasma drug determination and pharmacokinetic calculations

Blood samples were collected on lithium heparin. Following centrifugation (1600 g, 4 °C) and separation, plasma samples were stored at −20 °C until assayed. SEL determinations were carried out by high performance liquid chromatography with tandem mass spectrometry detection (LC/MSMS) using a validated procedure with a lower limit of quantification of 1 ng/mL. Plasma levels of ASMs were determined by a contract laboratory (Analytico Medinet BV, Breda, The Netherlands) using validated proprietary methods.

The value and time of the maximum plasma drug concentration, C_{max} and t_{max}, were directly obtained from the observations; the area under the plasma concentration vs. time curve from time 0 h up to the last measurable time point, AUC(0-t), was computed using the linear trapezoidal rule; the area under the plasma drug concentration vs. time curve extrapolated to infinity, AUCinf, was obtained using the following formula: $AUCinf = AUC(0 - t) + C_{last}/\lambda_z$, where C_{last} was the last measurable concentration; λ_z, the terminal elimination rate constant, was the slope of the linear regression of ln concentration vs. time; the plasma elimination half-life $t_{½}$, was calculated as $\ln(2)/\lambda_z$. All pharmacokinetic calculations were carried out using WinNonlin version 4.01 (Pharsight Corporation, Mountain View, CA, USA).

2.5.3. Safety

Safety was assessed through reported adverse events, physical and neurological examinations, laboratory results (hematology, biochemistry, urinalysis), 12-lead electrocardiography (ECG), and vital signs.

2.6. Statistical methods

Pharmacodynamic parameters were analyzed using descriptive statistics by dose and time points. Area Under the Effect Curve [AUEC (0–8)] from pre-dose to 8 h for placebo and active treatment was analyzed using descriptive statistics. AUEC(0–8) was calculated per eye condition for the change from pre-dose in SPR.

Number of responders, time to first response, duration of response, time to maximal reduction, and maximal reduction were derived and analyzed descriptively by dose. According to the continuous or categorical nature of the dependent variables analyzed, a General Linear Model (GLM) was used to analyze the effect of concomitant treatment with LEV or other ASMs on the response to SEL. Barnard’s test was used to compare the effects of SEL vs. LEV and BRV on PPR. ARCI-49 and Bond-Lader VAS (subscales) were analyzed descriptively.

All statistical calculations were carried out using SAS release 8.02 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patients

Six centers (4 in France; 2 in the US) participated in the trial. A total of 28 patients (23F, 5 M; mean age (± SD) of 26.5 (± 9.5) years, range 18–51 years) were investigated. One patient (patient #5) was excluded

from the per-protocol analysis due to emesis after intake of SEL. Nine patients (7F, 2 M) returned for a 2nd dosing 1–6 months later, providing a total of 36 individual exposures. Thus, 36 individual exposures (27 patients) to different dosages of SEL were evaluated after a blinded central reading.

In Table 1, clinical information is given: 18/27 (67 %) patients had a history of visually induced seizures, either generalized tonic-clonic seizures (GTCS), eyelid myoclonia, generalized myoclonus, and/or absence seizures. One patient had a history of focal seizures. All patients exhibited PPRs in response to IPS despite chronic treatment with ASMs. During IPS, most frequently eyelid myoclonia was seen (9/19 [47 %]) of those with signs during IPS); others had myoclonus or absence seizures. One showed automatisms. All evoked clinical signs were minor.

3.2. SPR suppression or abolishment

The first 3 patients from Center #1 reacted with full suppression of PPR on 10 mg SEL (see Fig. 2A,B as example). Complete suppression of PPRs, clinical symptoms, and spontaneous generalized discharges occurred starting at 1–2 hrs after oral administration and lasted for 32 to 48 hrs. Thus the next 4 patients received a 1 mg dose, then 7 patients 2 mg, 5 patients 4 mg, 5 patients 0.5 mg, and 8 patients 20 mg. The 40 mg dose was not evaluated because of the high potency of SEL obtained with the lower doses.

At all doses administered – even the lowest, several subjects reached an abolishment of SPR for at least one time point (Table 2). In practice, all full responders reacted at least for 8 hr with complete suppression. Overall, abolishment of SPR was obtained in 40–71 % of the patients, at doses of 0.5–20 mg. The strongest effect was seen with 10 mg. The finding that the effect did not further increase at the highest dose (20 mg) of SEL may be due to the fact that in this group more patients were comedicated with LEV (see below). Overall, in 32/36 exposures (88 %), a partial or complete suppression of the epileptiform EEG response was found. In 19/36 (53 %) exposures to SEL there was complete suppression of the epileptiform EEG response, and in 13/36 (36 %) there was a marked decrease in SPR. After placebo, almost no changes were observed in SPR compared to pre-dose (whatever the dose group; not illustrated).

Dose-effect relationships of SEL showed a positive linear relationship between the log of the administered dose and the maximum SPR reduction ($P = 0.01$; Suppl. Fig. S1) as well as the AUEC (0–8) (not illustrated). In all the subjects who received a second dose of SEL, the effect of SEL increased with the dose (as measured by AUEC(0–8)).

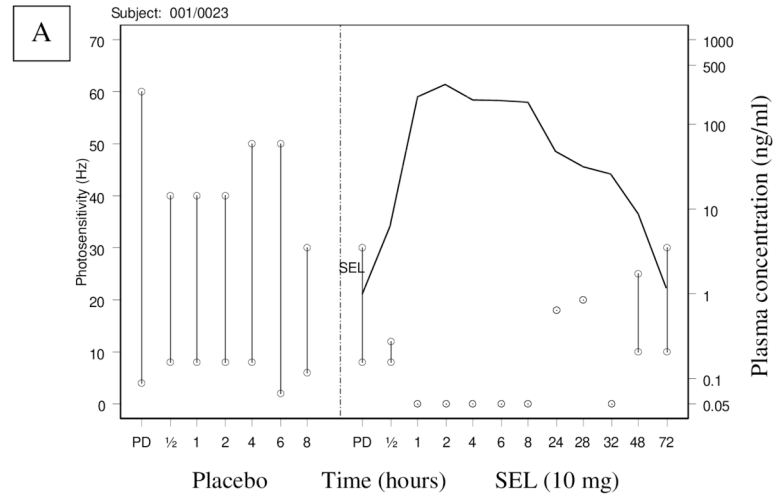
Only responders were included in the analysis of time to first response and duration of response. After each SEL dose, the first response was observed at the first IPS (0.5 h after oral administration). Thus, it cannot be excluded that the onset of the effect occurred earlier. Median times to first response and ranges are shown in Table 3.

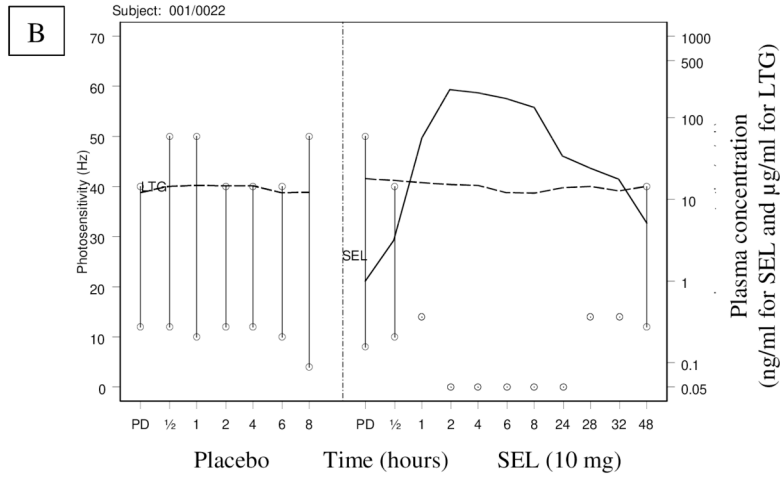
The duration of response was defined as the difference in time between the first and the last observed response. As shown in Table 3, the median duration of response lasted at least 22.8 h for all the administered doses but one (16.3 h after 20 mg).

Table 1
Clinical data of the patients enrolled in the study. Abbreviations: A, absences; CBZ, carbamazepine; EM, eyelid myoclonia; EMA, eyelid myoclonia with absences; F, focal; GM, generalized myoclonic seizures; GTCS, generalized tonic-clonic seizures; LEV, levetiracetam; LTG, lamotrigine; M, myoclonic seizures; ND, not detected; PB, phenobarbital; PHT, phenytoin; PPR, photoparoxysmal EEG response; T, tonic seizures; TPM, topiramate; VPA, valproate.

Pat #	Sex/ Age in yrs	ASM (mg/day)	Spontaneous seizures	Visually induced seizures	Seizure type	PPR since age (year)	EEG with spontaneous generalized epileptiform discharges	Signs during PPR
1	F/25	LTG (200)	Yes	ND	ND	18	Yes	EMA, F
2	F/20	LTG (300)	Yes	ND	GTCS	15	Yes	EMA, A
3	F/51	None	No	Yes	GTCS, EMA, T	49	Yes	EMA
4	F/37	CBZ (400)	Yes	ND	GTCS	10	Yes	ND
(5)[a]	F/25	TPM (150)	Yes	Yes	GTCS, FOCAL	9	No	ND
6	F/19	LTG (400)	ND	ND	GM	18	No	GM
7	F/25	PB (65) PHT (50)	Yes	Yes	GTCS, M	8	Yes	ND
8	M/18	VPA (1000)	ND	Yes	GTCS	12	Yes	EMA
9	F/19	LTG (325) LEV (2000)	Yes	ND	ND	12	No	ND
10	F/36	LTG (200) LEV (1000)	Yes	Yes	GTCS, GM, A	8	Yes	EM
11	F/22	None	No	Yes	GTCS	21	No	ND
12	F/20	None	Yes	Yes	ND	19	Yes	A
13	F/18	VPA (500)	Yes	Yes	GTCS, M, A	11	Yes	ND
14	F/39	LTG (200) LEV (1000)	Yes	Yes	GTCS, M, A	35	Yes	EMA
15	F/23	VPA (1000)	Yes	Yes	M	4	Yes	M
16	F/25	VPA (1000)	Yes	ND	GM	11	No	ND
17	M/27	VPA (1000) LEV (1000)	ND	Yes	GTCS, EM, GM	24	Yes	ND
18	F/21	None	Yes	Yes	EM, A	15	Yes	GM, M
19	F/26	TPM (50)	ND	Yes	ND	13	No	ND
20	F/20	None	Yes	ND	GTCS	14	Yes	GM
21	F/35	LTG (200) TPM (200)	Yes	Yes	ND	8	No	ND
22	F/34	LTG (100) LEV (500)	Yes	ND	A	Not known	Yes	A
23	F/20	VPA (800)	Yes	Yes	GTCS	16	Yes	GM
24	F/24	None	Yes	ND	GM	14	Yes	
25	F/ 23	VPA (500)	Yes	Yes	GTCS	11	Yes	GM
26	F/20	VPA (750) LEV (1500)	Yes	ND	GTCS, EM, A	13	Yes	ND
27[b]	M/17	VPA (875)	Yes	ND	GTCS	12	No	ND
28[b]	M/17	VPA (875)	ND	Yes	GTCS	11	No	EMA

[a] Patient excluded from PPP due to emesis
[b] Homozygous twins





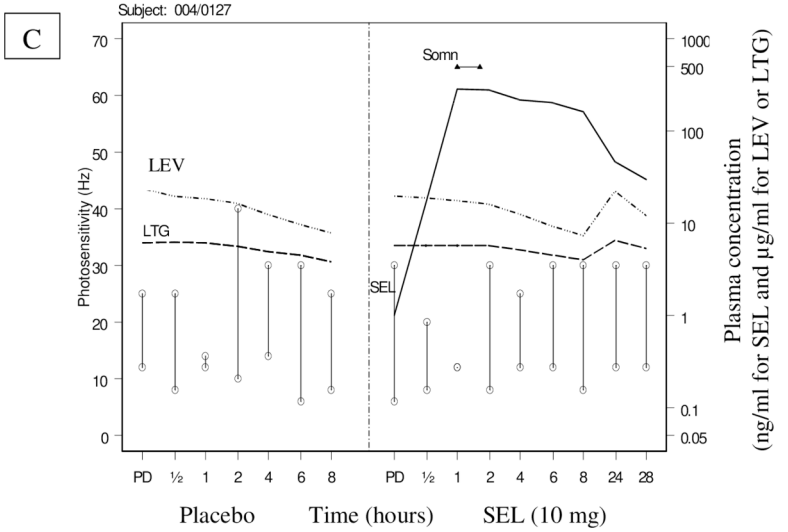


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Fig. 2. Representative examples of individual photosensitive epilepsy patients who were treated with placebo (day −1; left graphs) and seletracetam (SEL; day 1; right graphs). The effect of oral intake of 10 mg SEL on the photosensitivity range (upper minus lower limit, in Hz) is shown for three patients. The limits are graphically expressed as small circles. The left y-axis shows the photosensitivity in Hz while the right y-axis shows the plasma drug concentration of SEL (in ng/mL) or other antiseizure medications (ASMs; in μg/mL). (A): Subject 001/0023 was not pretreated with any other ASM. SEL completely abolished the response. Plasma levels of SEL are shown by the solid line in the right graph. (B) Subject 001/0022 was pretreated with lamotrigine (LTG). Plasma levels of LTG are shown by the hyphenated line. SEL completely abolished the response. (C) Subject 004/0127 was pretreated with LTG and levetiracetam (LEV). SEL was also not effective in this patient. The appearance of somnolence after SEL is indicated.

Table 2
Classification of responses to seletracetam compared to corresponding placebo time-points for eye-closure condition (per-protocol population). After placebo, almost no changes were observed in SPR compared to pre-dose (whatever the dose group).

SPR response	Dose of seletracetam (number of patients)						Total/%
	0.5 mg (n = 5)	1 mg (n = 4)	2 mg (n = 7)	4 mg (n = 5)	10 mg (n = 7)	20 mg (n = 8)	
No change	1/5 (20 %)	0/4 (0 %)	3/7 (43 %)	0/5 (0 %)	0/7 (0 %)	0/8 (0 %)	4/36 (11.1 %)
Reduction	2/5 (40 %)	2/4 (50 %)	0/7 (0 %)	3/5 (60 %)	2/7 (29 %)	4/8 (50 %)	13/36 (36.1 %)
Abolishment	2/5 (40 %)	2/4 (50 %)	4/7 (57 %)	2/5 (40 %)	5/7 (71 %)	4/8 (50 %)	19/36 (52.8 %)

Table 3
Time to first response and duration of response in hours (median and range; n) per administered dose for eye-closure condition (compared to placebo) (per-protocol population).

Dose of seletracetam	Time to First Response (h) Median (range) [n]	Duration of Response (h) Median (range) [n]
0.5 mg	3.0 (0.5; 8.0) [4]	22.8 (0.0; 28.0) [4]
1.0 mg	0.5 (0.5; 1.0) [4]	29.3 (7.5; 71.5) [4]
2.0 mg	0.5 (0.5; 28.0) [5]	31.0 (0.0; 31.5) [5]
4.0 mg	1.0 (0.5; 4.0) [5]	28.0 (0.0; 47.0) [5]
10 mg	1.0 (0.5; 1.0) [7]	31.0 (5.0; 71.5) [7]
20 mg	0.8 (0.5; 2.0) [8]	16.3 (0.0; 71.5) [8]
Overall	1.0 (0.5; 28.0) [33]	27.5 (0.0; 71.5) [33]

3.3. Effect of co-medication

Sub-analyses were performed to investigate the effect of co-medication, notably, the SV2A analog LEV, which has shown its efficacy in this model as well[12]. No patient was on BRV.

Figs. 2 and 3 show graphical examples of the effect of placebo and sel on the thresholds of evoked PPRs in Hz over time in patients with different co-medications, with and without LEV. Most patients taking LEV at baseline had a weaker response to SEL than those not taking LEV. Fig. 4 gives an overview of responses to SEL in patients with vs. without LEV. Although the presence of LEV reduced the efficacy of SEL in several patients, SEL still exerted marked effects in others. Due to the small sample size and narrow dose range of LEV, the relationship between the dose of LEV and its effect on the response to SEL was not tested.

We also calculated the AUEC(0–8) from pre-dose to 8 h for SEL in patients with vs. without comedication with LEV. As shown in Fig. 5, the highest effect was obtained in patients without LEV.

In line with Fig. 5, statistical modeling of the dose–effect relationship showed a significant effect of concomitant LEV (P = 0.0428), and to a lesser extent of other concomitant ASMs (P = 0.0597: see Suppl. Fig. S2): subjects taking concomitant LEV (or other ASMs) had a smaller response (lower SPR decrease) than subjects not taking LEV (or other ASMs) (n = 6; see Table 1). All statistical models show an increasing effect with increasing SEL doses with a plateau reached at 10 – 20 mg.

3.4. Adverse effects

Eighteen patients (64 %) reported adverse effects after SEL and 4 (14.3 %) after placebo. The most frequently reported adverse effects after SEL were somnolence (32 %), dizziness (21 %), headache (14 %), and feeling drunk (7 %)(Suppl. Table S1). In patients with somnolence, this adverse effect started within one hour in 6 patients (doses 0.5 to 10 mg SEL) and at 2, 3.5, and 4 hrs after intake of 1, 10, and 20 mg, respectively. The duration varied from 19 min to three hours (doses between 0.5 and 20 mg SEL) in 6, while 3 other patients reported a duration of 4.5 (4 mg), 7 (2 mg), and 19 (1 mg) hrs. Dizziness was reported by 4 other patients with onset between 15 min and 2. 5 h with duration between 23 min (10 mg SEL) and 5.5 h (10 mg SEL). Only a few adverse effects were reported after placebo; all had an incidence below 5 %. No evident association was observed between the incidence of adverse effects reported after SEL administration and the dose level. All but one of the adverse effects observed were mild to moderate. One subject had severe somnolence after 4 mg SEL lasting three hours. All treatment-emergent adverse effects resolved before the end of the study. No serious adverse effects occurred.

No effects of SEL on mood were observed in most subscales when using the ARCI-49 subscales (Suppl. Table S2). A small increase (median: +0.5) of sedation was detected at 3 h after SEL in PCAG subscale; this effect was not dose-related. Similarly, Bond & Lader VAS, showed no effects of SEL on alertness, contentedness, and calmness (Suppl. Table S3).

Results of ECG, physical and neurological examinations, laboratory results, and vital signs showed no relevant abnormalities.

3.5. Pharmacokinetics

Following 0.5 mg to 20 mg single oral doses, SEL was measurable in all post-dose plasma samples collected until at least 24 h (Fig. 6). After each dose, maximal plasma concentrations were reached within approximately 2 h and were followed by a mono-exponential decline. The concentration decreases after C_{max} were parallel for all doses as evidenced on the semi-logarithmic plot (Fig. 6), implying a similar terminal half-life across doses. Furthermore, plasma concentrations appeared to increase in linear proportion with the administered dose, as reported previously for healthy volunteers[2].

The likelihood of getting a reduction in SPR increased with higher SEL plasma concentrations. However, no adequate models were found to describe this relationship; both the intra- and inter-subject variability in the SPR measurements, the limited number of data, and some confounding factors (use vs no use of concomitant LEV and of other concomitant ASMs, or low SPR at baseline) could explain this.

Figs. 2 and 3 show examples of individual patients in which plasma levels of SEL are illustrated along with the effect of SEL on the photosensitivity ranges. As shown in Fig. 2A,B and Fig. 3B, complete suppression of the IPS response was observed at SEL plasma levels of about 50–200 ng/mL (i.e., 0.05–0.2 μg/mL), substantiating the potency of SEL.

The pharmacokinetic analysis revealed that SEL was rapidly absorbed, with median t_{max} ranging from 1.00 to 2.00 h across doses. Mean (SD) C_{max} ranged from 12.8 (3.4) ng/mL after the 0.5 mg dose to 495 (88) ng/mL following the 20 mg dose. Mean $t_{½}$ ranged from 7.9 to 8.6 h across doses, with individual values ranging from 6.2 to 11.6 h. The total exposure (AUC) increased from 151 (8.9) ng*h/mL after the 0.5 mg dose to 6986 (1458) ng*h/mL following the 20 mg dose. In all cases, AUC was

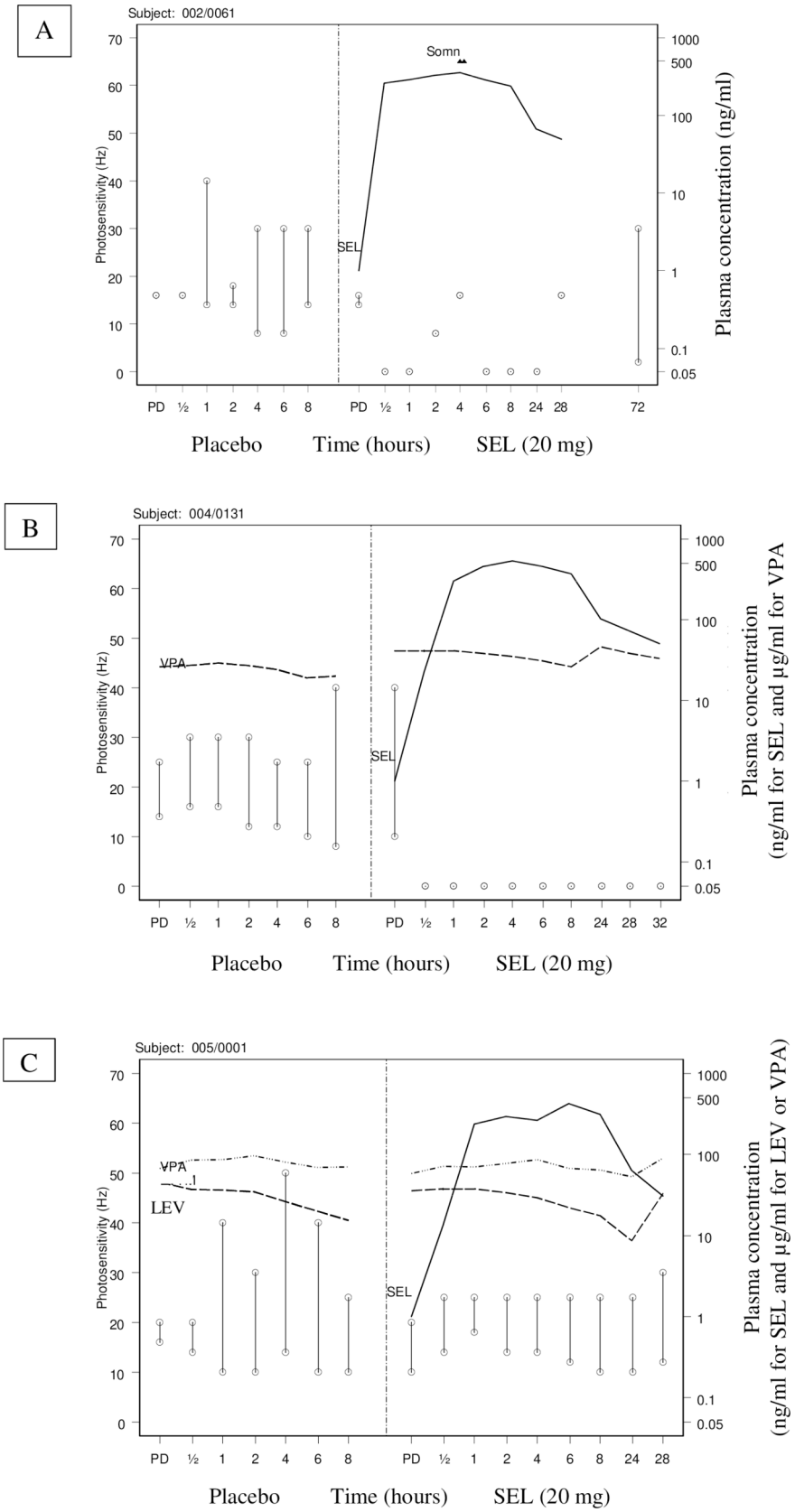

Fig. 3. Representative examples of individual photosensitive epilepsy patients who were treated with placebo (left graphs) and seletracetam (SEL; right graphs). The effect of oral intake of 20 mg SEL on the photosensitivity range (upper minus lower limit, in Hz) is shown for three patients. See Fig. 2 legend for further details. (A): Subject 002/0061 was not pretreated with any other antiseizure medication (ASM). SEL almost completely abolished the response to photostimulation. (B) Subject 004/0131 was pretreated with valproate (VPA). SEL completely abolished the response. (C) Subject 005/0001 was pretreated with VPA and levetiracetam (LEV). SEL was only partially effective in this patient.

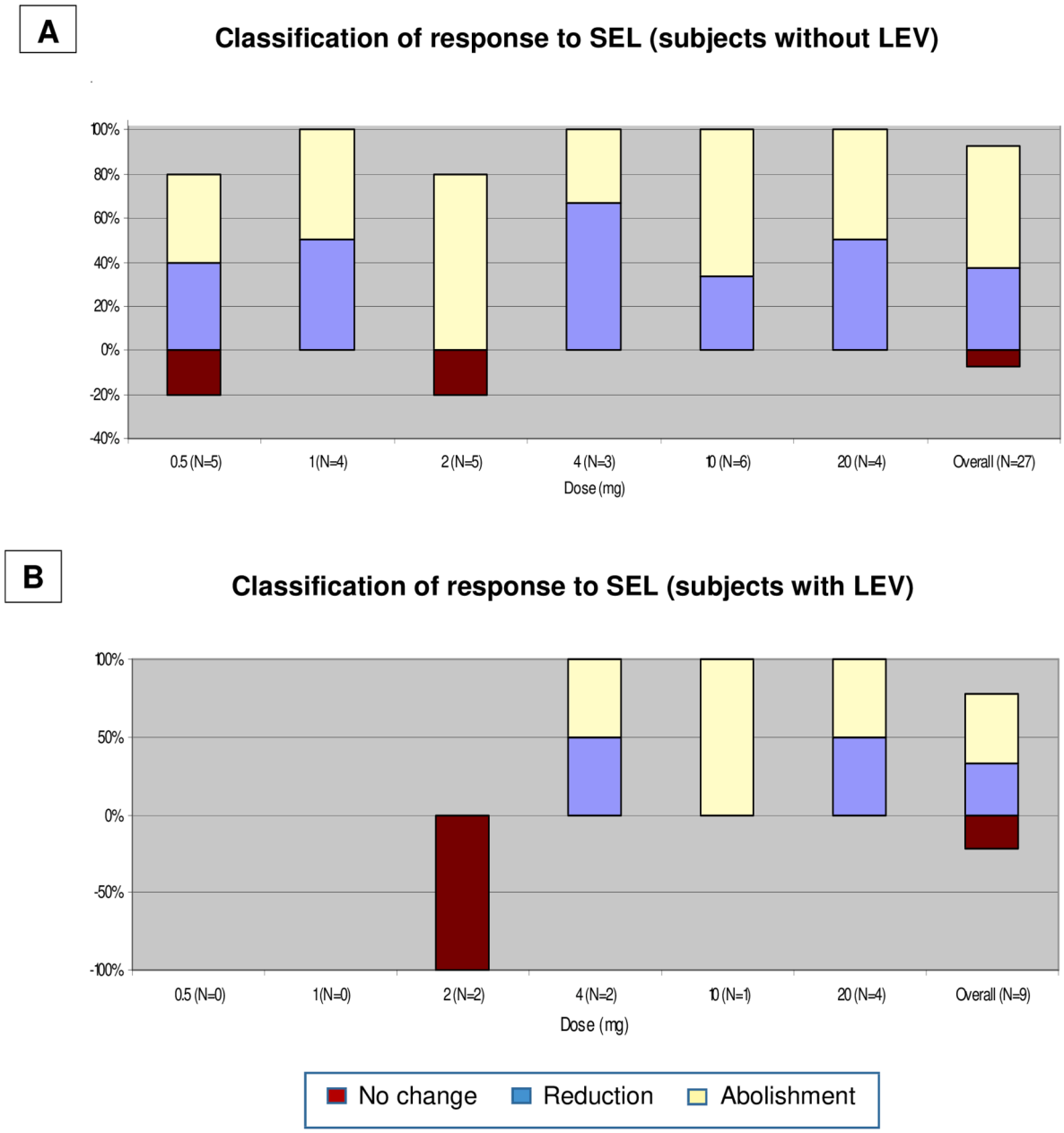

Fig. 4. Classification of the response to seletracetam (SEL) in photosensitive patients with vs. without concomitant treatment with levetiracetam (LEV). Response to photic stimulation (compared to placebo) is classified as no response, a partial response, and abolishment of the response for the six doses of SEL evaluated in this trial. (A) Subjects without LEV. Note that some of these patients were treated with other antiseizure medications (see Table 1). (B) Subjects with LEV.

accurately determined with the extrapolated area of less than 20 %. For both C_{max} and AUC, the mean parameters seem to increase proportionally to the dose. The pharmacokinetic parameters of SEL are summarized in Table S4.

Interestingly, when comparing the median time to the first response with plasma levels of SEL, a response was already observed before reaching t_{max}. This fast onset of action (before t_{max}) and long duration of action (after SEL plasma levels were below the limit of quantification) suggest that very low plasma levels are sufficient to produce an effect quickly and to maintain it.

Most of the patients were on steady-state treatment with 1–2 ASMs (Table 1). Data on plasma levels of these ASMs (see examples in Figs. 2 and 3) were limited but did not suggest obvious pharmacokinetic interactions between these ASMs and SEL.

3.6. Comparison of the antiseizure potency and efficacy of SEL vs. LEV and BRV

SEL (present study), LEV[12], and BRV[11]were all studied with a similar protocol in patients with photosensitive epilepsy, thus allowing comparing their potency (mg of the drug to induce an effect on PPR) and efficacy (size of the anti-PPR effect). As shown in Fig. 7, with LEV, only doses of 750 or 1000 mg abolished PPR, while at 250 or 500 mg PPR was reduced but not abolished (see Suppl. Table S5 for individual data). Thus, based on the dose range needed to abolish PPR, SEL was at least 1,500 times more potent than LEV. In terms of efficacy to suppress PPR, there was a tendency for more patients (80–100 %) with abolished response at high doses of LEV compared to SEL, but the difference between drugs was not statistically significant. With BRV, abolishment of PPR was observed at the lowest dose tested (10 mg), suggesting that BRV was more potent than LEV but – based on the available data – less potent

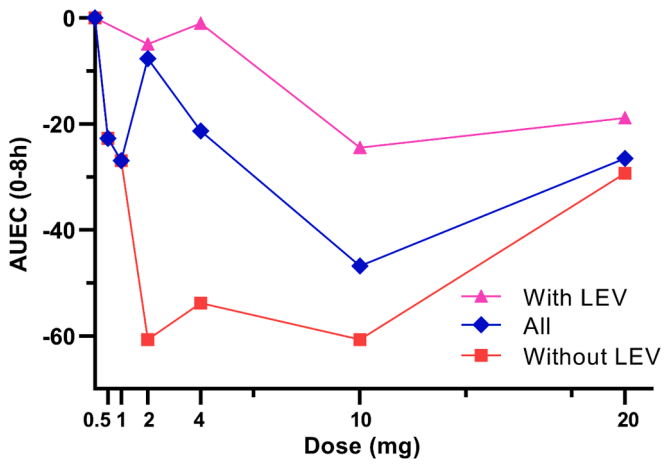

Fig. 5. Median Area Under the Effect Curve [AUEC(0–8)] from pre-dose to 8 h for treatment with different doses of seletracetam (SEL) in all photosensitive epilepsy patients ("All") and patients on comedication with levetiracetam (LEV) or patients without comedication with LEV. AUEC(0–8) represents the change from pre-dose in SPR, for the eye closure condition.

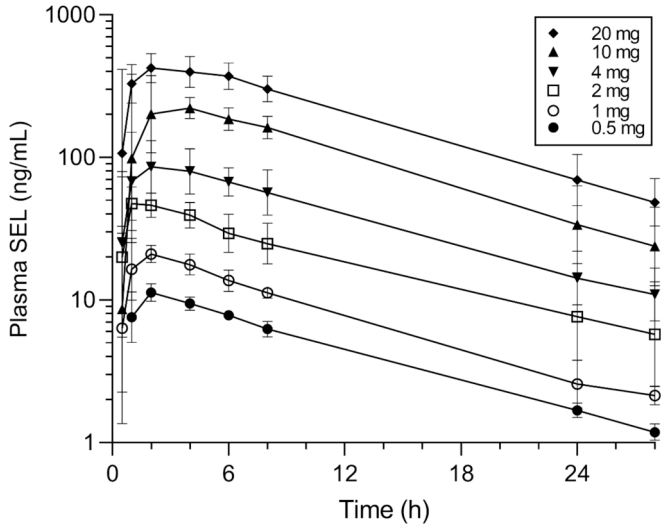

Fig. 6. Seletracetam (SEL) mean plasma concentration vs. time profiles. Data are shown as geometric mean ± SD following single oral doses of SEL 0.5 mg (n = 5), 1 mg (n = 4), 2 mg (n = 7), 4 mg (n = 5), 10 mg (n = 7), and 20 mg (n = 7) (PP Population). Results are displayed in semi-logarithmic scale.

than SEL (Fig. 7; see Suppl. Table S5 for individual data). At the highest BRV dose tested (80 mg), abolishment of PPR was observed in 100 % of patients, which, however, was not significantly different from the highest effect (71 %) observed with 10 mg SEL. Regarding the comparative anti-PPR efficacy of the three racetams, it is important to note that in 9/36 individual exposures to SEL, patients were on comedication with LEV, while only 2/19 patients treated with BRV were on comedication with LEV, and none of the 12 patients treated with LEV were comedicated with another racetam.

Four patients received BRV and SEL in different trials at an interval of 1–2 years. They are illustrated in Suppl. Fig. S3. At 10 mg, SEL was more effective in suppressing PPR than 20 mg BRV (Suppl. Fig. S3A). While BRV induced somnolence, this was not observed with SEL. Comparable efficacy with complete suppression of the PPR was observed in one patient at 80 mg BRV and 10 mg SEL (Suppl. Fig. S3B). While BRV induced dizziness at this dose, this was not observed with SEL. In another patient, 10 mg of BRV was more effective than 4 mg SEL (Suppl. Fig. S3C). A less favorable effect of SEL was obtained when the patient was concomitantly treated with LEV, although the dose of SEL (4 mg) was low in this patient (Suppl. Fig. S3D). Concomitant ASM treatments partially differed in the trials with BRV and SEL.

4. Discussion

4.1. Main study outcomes

This is the first SEL study conducted in subjects with epilepsy. Twenty-eight photosensitive epilepsy subjects (23 females, 5 males) were enrolled and 27 completed the study according to protocol and were further analyzed. Eighteen of the 27 subjects received a single dose of SEL, and nine received in addition a second dose, different from the first one, which totals 36 exposures. At all the doses (0.5, 1, 2, 4, 10, and 20 mg) administered, even the lowest, several (40–71 %) of the subjects reached a complete abolishment of SPR at least at one time point. Overall, in 32/36 exposures (88 %), a partial or complete suppression of the epileptiform EEG response was found. The maximum SPR decrease from time-matched placebo was dose-related and appeared to reach its maximal level at 10 mg.

4.2. SEL is more potent than LEV and BRV in the photosensitivity model

The results of this study suggest that SEL is quite effective in reducing the photoparoxysmal response in photosensitive epileptic subjects. In comparison to the results of a similar study carried out with BRV[11], this study shows that a similar benefit/risk ratio can be reached with SEL dosages eight times lower (10 mg vs. 80 mg). An even higher potency difference is obtained when comparing the dose efficacy ratio of SEL with LEV[12]. However, although the SEL, BRV, and LEV trials in photosensitive epilepsy patients used the same protocol, and some patients received both BRV and SEL in subsequent trials, no cross-sectional or randomized comparative trial has been performed with these three racetams. In the absence of such a trial, it cannot be finally judged whether SEL is more potent at PPR-suppression or better tolerated than LEV or BRV. Furthermore, whereas the potency difference between SEL and BRV was clearly indicated by the data obtained in the Phase IIa trials (see Fig. 7), we cannot exclude that lower doses of BRV than those tested in the photosensitivity model (10–80 mg) would have been effective in suppressing PPR. However, the same is true for SEL, for which it is likely that the minimally effective dose in humans may be below the lowest dose (0.5 mg) evaluated in the present study, at which SEL already exerted effects on PPR.

The potency differences between SEL vs. BRV and LEV observed here correspond to the high antiseizure potencies of SEL in animal models [17]. As described in the Introduction, in the rat amygdala kindling model of difficult-to-treat focal-onset seizures, SEL was 90 times more potent than BRV and 170 times more potent than LEV, respectively [20,17]. CNS adverse effects were observed in kindled rats only at much higher doses of SEL (TD_{50} = 520 mg/kg in the rotarod test), resulting in a huge safety margin (or protective index) of SEL in this model. The kindling model is highly predictive for clinical efficacy against drug-resistant focal-onset seizures[18]. SEL is one of the most potent and effective compounds ever tested in this model.

4.3. Onset of the effect of SEL and dose–effect relationship in the photosensitivity model

At all SEL doses administered here and for several subjects, PPR-suppression was already seen at the first time (30 min) recorded after drug intake, before plasma t_{max}. Duration of action was on average greater than 24 h and still present after SEL levels decreased below the detection limit. These findings suggest that very low concentrations of SEL are sufficient to produce an effect quickly and to maintain it. In line with the present clinical findings, preclinical experiments in an absence rat model indicated a rapid onset of SEL's antiseizure effect in that this

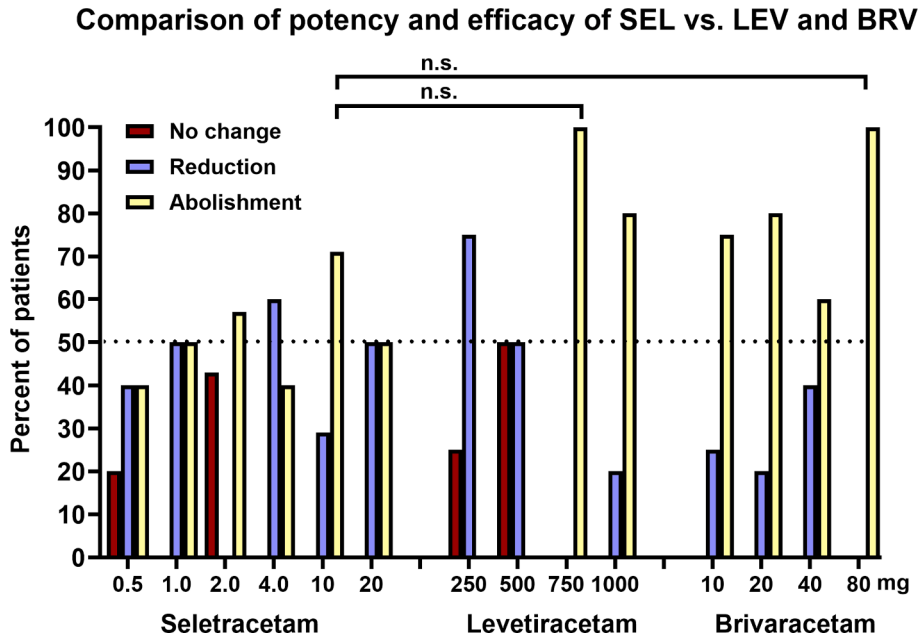

Fig. 7. Comparison of potency and efficacy of seletracetam (SEL) vs. levetiracetam (LEV) and brivaracetam (BRV) in photosensitive epilepsy patients. Response to photic stimulation (compared to placebo) is classified as no change, reduction, and abolishment of the response. Potency is reflected by the dose level to achieve a response while efficacy is the size of the response. An effect size of 50% is indicated by the hyphenated horizontal line. Note that the efficacy (in terms of % of patients with abolishment of PPR) was not significantly different between the three drugs, but the highest effect size was obtained at much lower doses of SEL compared to LEV and BRV. For the comparison of the potency and efficacy of the three racetams to suppress PPR, it is important to note that in 25% of the SEL exposures, patients were comedicated with LEV, while this was the case in only 10.5% of the BRV exposures (see text). Patients exposed to LEV were not comedicated with another racetam. Abbreviations: n.s., not significant.

effect on electrographic seizures already occurred in the first 20-min test interval after i.p. administration[20]. As described above, similar to BRV, SEL is highly lipophilic, which favors rapid absorption and brain penetration. Based on the high lipophilicity of SEL, we expect that the brain penetration and thus onset of CNS effects of SEL is as fast as previously observed for BRV[22].

We found a positive linear relationship between the maximum SPR reduction and the log of the administered dose. Most subjects taking concomitant LEV exhibited a lower response to SEL than those not taking LEV, which is a consequence of both drugs competing for the same target (SV2A). However, based on data reported by Correa-Basurto et al. [4], the specific pattern of interaction of SEL when bound to SV2A seems to differ from the patterns determined for BRV and LEV. Furthermore, in addition to the 10 times higher affinity of SEL vs. LEV for SV2A, SEL dissociates more slowly from SV2A than LEV (Michel Gillard, unpublished data). This, together with the higher affinity, may explain why SEL is a much more potent ASM than LEV both preclinically and clinically. It also explains why SEL exerted effects on PPR in some patients despite the presence of LEV. In addition to acting as an SV2A modulator, SEL has been shown to inhibit high-voltage-activated (HVA) Ca^{2+} currents much more potently than LEV (IC_{50} 0.27 μM vs. 13.9 μM, respectively; [19]. This may add to the antiseizure potency and efficacy of SEL.

All patients enrolled in the present study exerted PPRs in response to IPS during placebo treatment, although the majority of the patients were on chronic treatment with ASMs (LEV, valproate [VPA], lamotrigine [LTG]) known to suppress PPR in photosensitive epilepsy patients (Binnie, 2001; [23]. This may indicate that the PPR in these patients was resistant to treatment with steady-state doses of ASMs such as LEV, VPA, and LTG and that this resistance could be overcome by add-on treatment with SEL. This raises the hope that SEL might also be more effective than these ASMs in clinical settings, an interesting aspect that needs further investigation.

4.4. Pharmacokinetics and safety of SEL

The pharmacokinetics of SEL in the epilepsy patients enrolled in this study were similar to those observed previously in healthy subjects[2]. Following oral administration of radiocarbon-labeled SEL, 3 % and 92 % of the dose were recovered in the feces and urine, respectively, reflecting near complete absorption of the drug; in the urine, the unchanged compound (25 %) and the acid metabolite (53 %) represented 78 % of the dose. In plasma, up to 72 h post-dose, >90 % of the circulating material was the parent compound. SEL appears neither to inhibit nor to induce the major human drug metabolizing enzymes, and it demonstrated low plasma protein binding (<10 %), which suggests a low potential for drug-drug interactions[2]. As also shown here, the linear, time-independent pharmacokinetics of the drug combined with a rapid and almost complete absorption indicate that SEL has a straightforward pharmacokinetic profile.

All the single SEL doses administered were safe and well tolerated. Adverse effects reported after SEL were mild to moderate. No evident association was observed between the incidence of adverse effects and dose level. No relevant changes in mood were observed after SEL, although a small increase in sedation was noticed 3 h after SEL administration.

4.5. Interpretation of POP data in the photosensitivity model

During the development of a novel ASM, the photosensitivity model used here, where epilepsy patients with known photosensitivity serve as test subjects, is an important first POP option to determine whether a potential therapy can eliminate or attenuate a photosensitive response [6]. Photosensitive POP trials are a useful tool to quantitatively predict efficacy in different types of epilepsy and can be useful as early and informative indicators in ASM discovery and development[23]. The clear advantage of the model is real-time testing in epilepsy patients, as early as possible in drug development. For instance, the widely used SV2A ligands, LEV and BRV, were developed in part because of their

efficacy in the Phase II photosensitivity model[12,11]. Importantly, PPR is not only a model of generalized seizures but can also be used to identify or prove the efficacy of new ASMs for patients with focal epilepsy[8]. Over time, various novel drugs with different chemical structures and mechanisms of action have been tested in the photosensitivity model, including the partial $GABA_A$ receptor agonist abecarnil[9], the $GABA_A$ receptor subtype-selective positive allosteric modulator darigabat[7], and the recently approved dual-mechanism ASM cenobamate [10]. Based on the promising data in the photosensitivity model reported for SEL here, several open-label and two multicenter Phase IIb trials with SEL add-on treatment in patients with drug-resistant focal-onset seizures were performed but detailed outcomes of these trials are not yet in the public domain. Available results support a potent antiseizure activity of SEL at 10–80 mg BID (NCT00152503 and NCT00152451; ClinTrials.gov).

4.6. The high potency of SEL makes this drug a candidate for seizure rescue therapy

Among all drugs tested so far in the photosensitivity model [3,23,8,6], including BDZs such as diazepam, lorazepam, and alprazolam, SEL is by far the most potent compound. This makes SEL a suitable candidate for seizure rescue therapy using appropriate formulations (e.g., intranasal or buccal/sublingual), where currently the only treatment options are BDZs [15]. Nasal or buccal formulations require that the ASM is potent enough to achieve effective seizure control using a small volume of the formulation. SEL is more potent than most BDZs in suppressing seizures but it is much less sedative than BDZs, does not induce respiratory depression, and has no addictive or misuse potential[2], which is a major advantage over BDZs. Seizure rescue therapies given outside the hospital are useful for treating acute repetitive seizures (ARS; also called “seizure clusters”) and are frequently used to interrupt prolonged seizures[15]. Another emerging indication for seizure rescue formulations is rapid epileptic seizure termination (REST) in the 30–40 % of epilepsy patients who continue to experience breakthrough seizures despite ASM treatment [1]. REST intends to abort an ongoing seizure following patient or caregiver home administration of therapy at the first clinical sign of seizure onset. Such treatment requires rapid systemic absorption without intravenous access, and evidence of seizure cessation within minutes of administration[1]. Although we do not know yet whether SEL suppresses seizures within minutes after mucosal (e.g., transnasal) administration, the high lipophilicity of this drug argues in favor of rapid mucosal absorption. Based on the promising clinical effects reported here, PrevEp, Inc., is currently developing an intranal formulation of SEL as the first non-BDZ ARS rescue therapy.

4.7. Conclusions

The present POP study in photosensitive epilepsy patients shows that SEL is a promising ASM candidate, one with a potent, broad spectrum of seizure protection and a high CNS tolerability in animal models and high potency, straightforward pharmacokinetics and good tolerability in epilepsy patients. Photosensitive POP trials are useful for quantitatively predicting efficacy in partial or generalized epilepsies. The promising efficacy and safety of SEL predicted by the present data is substantiated by the preliminary outcome of two multicenter Phase IIb trials with SEL add-on treatment in patients with drug-resistant focal-onset seizures (NCT00152503 and NCT00152451).

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CRediT authorship contribution statement

Dorothee Kasteleijn-Nolst Trenité: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Armel Stockis:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Edouard Hirsch:** Writing – review & editing, Project administration, Methodology, Investigation. **Pierre Genton:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation. **Bassel W. Abou-Khalil:** Writing – review & editing, Project administration, Methodology, Investigation. **Jacqueline A. French:** Writing – review & editing, Project administration, Methodology, Investigation. **Pascal Masnou:** Writing – review & editing, Project administration, Methodology, Investigation. **Wolfgang Löscher:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [D. Kasteleijn-Nolst Trenité has received in the past 5 years consultancy fees from UCB, Otsuka, SK, Jazz, and Praxis. Armel Stockis is a former employee of UCB Pharma and has received in the past 5 years consultancy fees from UCB, Roche, and EyeD Pharma. E. Hirsch has received consultancy fees from UCB, Angelini, and Jazz. Pierre Genton has received speaker invitations and honoraria from Sanofi-Aventis, Novartis, UCB, and Eisai and received support for teaching programs from Sanofi-Aventis and UCB. The institution of Dr. Abou-Khalil has received research support from Cerevel Therapeutics, Neuroelectrics, Otsuka America Pharmaceutical, SK-Pharma, UCB SA, and Xenon. J. French receives salary support from the Epilepsy Foundation and from Epilepsy Study Consortium for consulting work and/or attending Scientific Advisory Boards for Acadia Pharmaceuticals, Access Industries, Acuta Capital Partners, AFASCI Inc, Agrithera, Inc., Alterity Therapeutics Limited, Angelini Pharma S.p.A, Autifony Therapeutics Limited, Axonis Therapeutics, Baergic Bio, Beacon Biosignals, Inc., Biogen, Biohaven Pharmaceuticals, Bloom Science Inc., Bright Minds Biosciences, Inc., Camp4 Therapeutics Corporation, Capsida Biotherapeutics, Cerebral Therapeutics, Cerecin Inc., Cerevel, Ceribell, Cognizance Biomarkers, Cowen and Company, LLC, Crossject, EcoR1 Capital, Eisai, Encoded Therapeutics, Engrail, Epalex, EpiMinder, Epitel Inc, Equilibre BioPharmaceuticals, Genentech, Inc., Grin Therapeutics, Harmony/Epygenix, iQure Pharma Inc, IQVIA RDS Inc, Janssen Pharmaceutica, Jazz Pharmaceuticals, Korro Bio Inc., Leal Therapeutics Inc, Lipocine, LivaNova, Longboard Pharmaceuticals, Marinus, Modulight.bio, Neumirna Therapeutics, Neurelis, Neurocrine, NeuroPace, Inc., NeuroPro Therapeutics, Neuroventis, Neurona Therapeutics, Neurvati, Noema, Ono Pharmaceutical Co., Otsuka Pharmaceutical Development, Ovid Therapeutics Inc., Praxis, PureTech LTY Inc., Rapport Therapeutics, Inc., Receptor Holdings Inc., Rivervest Venture Partners, Sage Therapeutics, Inc., SK Life Sciences, Stoke, Supernus, Takeda, Taysha Gene Therapies, Third Rock Ventures LLC, UCB Inc., uniQure, Ventus Therapeutics, Vida Ventures Management, Xenon. J. French has also received research support from the Epilepsy Study Consortium (Funded by Eisai and UCB,) Epilepsy Study Consortium/Epilepsy Foundation (Funded by UCB), GW/FACES/One8Foundation and NINDS. She is on the editorial board of Lancet Neurology and Neurology Today. She is Chief Medical/Innovation Officer for the Epilepsy Foundation. She is the President and on the Board of Directors for the Epilepsy Study Consortium, Inc. Pascal Masnou has nothing to disclose. W. Löscher is cofounder and CSO of PrevEp, Inc. (Bethesda, MD, USA), which currently develops an intranasal formulation of SEL (patent submitted). He has received in the past 5 years consultancy fees from Lundbeck, Angelini, Clexio, Selene, Axonis, SynapCell, Sintetica, ND Capital, Atlas Venture, Cogent Biosolutions, Ovid, Idorsia, and Addex].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.110241.

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