

## CLINICAL TRIAL PROTOCOL OUTLINE

A multicentre, double-blind, randomized, phase IV clinical trial comparing the safety, tolerability and efficacy of levetiracetam versus lamotrigine and carbamazepine in the oral antiepileptic therapy of newly diagnosed elderly patients with focal epilepsy.

**Short Title: STEP ONE** –trial (Study on the Treatment of Elderly Patients with Older and Newer antiepileptic drugs).

Clinical trial code: STEPONE05

EudraCT Number: 2005-003324-19

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\*according to §4 para. 25 German Drug Law (AMG)

**Title:** A multicentre, double-blind, randomized, phase IV clinical trial comparing the safety, tolerability and efficacy of levetiracetam versus lamotrigine and carbamazepine in oral antiepileptic therapy of newly diagnosed elderly patients with focal epilepsy.

**Short Title:** STEP ONE –trial (Study on the Treatment of Elderly Patients with Older and Newer antiepileptic drugs)

**Clinical trial code:** STEPONE05

**Phase:** IV

**Indication:** Focal Epilepsy

**Objectives:** To evaluate the tolerability and efficacy of levetiracetam (LEV) in newly diagnosed elderly patients (aged 60 yrs or above) with focal epilepsy compared to lamotrigine (LTG) or carbamazepine slow release (CBZ).

**Primary Outcome:** The primary outcome will be the 58-week retention rate measured by the number of drop outs due to adverse events or seizures from day 1 of treatment.

**Secondary Outcome:** Proportion of patients remaining seizure-free at week 30 (Visit 4); proportion of patients remaining seizure free at week 58 (Visit 6); the time (in days) to first break-through seizure (from day 1 of treatment); the absolute seizure frequency during the maintenance (over 52 weeks) phase; proportion of seizure-free days during the maintenance phase for subjects who enter the maintenance phase; the frequency of adverse events (from day 1 of treatment); QOLIE-31 results at V6; Portland Neurotoxicity scale at V6; results of cognitive testing (EpiTrack© by UCB).

**Trial Design:** This is a randomized, double-blind, multicenter Phase IV study using a parallel group design with three treatment groups. The study will consist of a 6-week titration-phase and a 52-week maintenance phase. Patients who successfully complete the trial (final visit, V6) will be unblinded and offered either to continue on their current drug or be changed to an alternative antiepileptic drug (AED) treatment of choice.

**Population:** Patients aged 60 years or above with new onset focal epilepsy i.e. either at least one epileptic seizure in the last 6 months and focal epileptiform discharges on EEG or a relevant lesion on CT/MRI or a total of 2 epileptic seizures, one of which occurring in the last 6 months prior inclusion. Patients with acute (< 2 weeks) symptomatic epileptic seizures due to acute brain abnormalities (i.e. haemorrhage or cerebral infarct), or contraindications against any of the drugs in trial will be excluded.

## Inclusion Criteria

Subjects meeting all of the following criteria will be considered for admission to the trial:

- Age 60 yrs or above.
- New onset focal epilepsy (adjusted to the definition of the International League Against Epilepsy (ILAE) published in Fisher RS et al. 2005, *Epilepsia* 46(4):470-72) i.e. either at least one epileptic seizure in the last 6 months and focal epileptiform discharges on EEG or a relevant lesion on CT/MRI or at least 2 epileptic seizures, one of which occurring in the last 6 months prior inclusion.
- No previous AED treatment, except for a period not longer than 4 weeks prior to inclusion (V0).
- Ability of subject to understand verbal and written instructions, to comply with all study requirements, and to comprehend character and individual consequences of the clinical trial.
- Written informed consent before enrolment in the trial.

## Exclusion Criteria

Subjects presenting with any of the following criteria will not be included in the trial:

- Acute symptomatic epileptic seizures occurring acutely within a 2 week period after the onset of an acute illness such as cerebral haemorrhage, cerebral infarct, rapid progressive malignancy or other acute brain abnormalities (i.e. encephalitis, hypoxic brain damage, trauma, metabolic derangement, following brain surgery).
- Dementia (as defined by history)
- Renal insufficiency as defined by GFR < 50 mL/min.
- Increased liver enzymes (GOT, GPT, gGT) or increased bilirubin  $\geq$  2-fold the upper limit of normal (ULN).
- Pre-treatment with valproic acid within the four weeks prior inclusion (V0).
- Contraindication against or history of hypersensitivity to any of the investigational medicinal products or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal products.
- Participation in other clinical trials and observation period of competing trials within the last 2 months, respectively.
- History of drug or alcohol abuse within the last 2 years.
- Medical condition which interferes with the participation in the trial according to the opinion of the investigator.
- Patients with life expectancy < 1 year due to malignant disease
- Psychiatric morbidity requiring legal guardianship.

## Prior and Concomitant Treatments

Relevant additional treatments administered to the subjects on trial entry or at any time during the trial are regarded as concomitant treatments and must be documented in the medical record and appropriate pages of the CRF.

### - Permitted medication:

1) *Prior treatment with any AED* is allowed for a maximum of 4 weeks prior inclusion (V0). Participants who received AEDs prior inclusion (V0) for 4 weeks or less need to be tapered of within the first 4 weeks of titration (w1-4) by reducing the dose of the previous AED by 25% (of the total daily dose at V0) every week for 4 weeks.

2) The use of *benzodiazepines* as background AED is permitted as long as the dose is kept constant for at least one month before study inclusion and throughout the study. During the titration phase (w1-6) the investigator may decide to prescribe benzodiazepines for up to 4 weeks to compensate for

under-treatment due to slow titration in the first 5 weeks of the trial in subjects at high risk for recurrence. In these cases subjects should have stopped benzodiazepines one week before reaching the target dose i.e. entering maintenance phase.

3) Selective serotonin reuptake inhibitors and tricyclic antidepressants are permitted during the trial.

- **Restricted use medications:** Benzodiazepines are permitted for medical conditions other than epilepsy only if the administration is limited to maximum duration of 14 days. The use of benzodiazepines for control of seizure clusters is allowed on 2 different occasions during the maintenance phase of the trial. Each occasion may be a period of 24 hours during which up to 3 doses of benzodiazepines may be used. Subjects who do exceed these limits of use have to be withdrawn from the study (see section 5.5.1.).
- **Prohibited medications:** use of other antiepileptic agents (other than LEV, CBZ or LTG and except pre-medication and benzodiazepines during titration or if dose is kept constant (see points above). The use of valproic acid is generally prohibited.

**Sample Size:** 360 patients to be included, 120 patients per treatment arm.

**Investigational Medicinal Product(s):** levetiracetam, lamotrigine, carbamazepine-slow release

**Dose assignment:**

	LEV 250 mg capsules	LTG 25 mg capsules	CBZ 100 mg capsules	N capsules
<b>Titration Phase</b>				
Week 1 and 2	0-0-1	0-0-1	0-0-1	1
Week 3 and 4	1-0-1	1-0-1	1-0-1	2
Week 5	1-0-2	1-0-2	1-0-2	3
Week 6	2-0-2	2-0-2	2-0-2	4
<b>Maintenance Phase</b>				
Week 7 to 58	2 to 12 per day (500 – 3000 mg)	2 to 12 per day (50 – 300 mg)	2 to 12 per day (200 – 1200 mg)	2 to 12 capsules

**Statistical Analysis:** Retention-rates will be compared pairwise between treatment groups using Fisher's exact test. The method of Kaplan-Meier will be used to estimate the time to first epileptic seizure and the logrank test will be used to test differences between treatment groups.

**Trial Duration and Dates:** Duration of treatment: 6 weeks titration phase, 52 weeks maintenance phase.

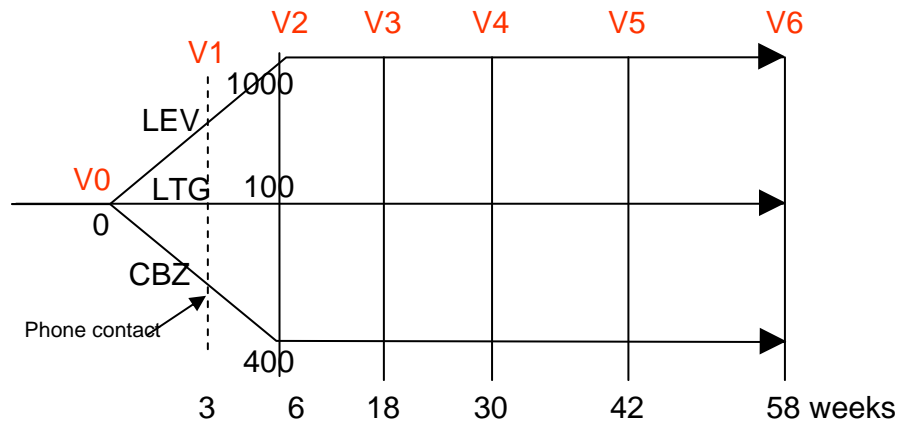
**Follow up:** At the end of trial subjects will be unblinded and may choose to continue on the medication or taper the trial medication and be treated with an alternative drug at the investigators discretion. The patient will receive a dosing schedule and a referral letter for his/her physician.

**Duration of trial:** approximately 2 years.

**Start of recruitment:** January 2007

**Projected number of centres:** 60

**Number of countries:** 3

**Flow Chart:**

LEV = Levetiracetam, LTG = Lamotrigine, CBZ = Carbamazepine-SR

**Table: Schedule of events**

Procedure	Inclusion	Titration		Maintenance/Treatment				V <sub>x</sub>
		V0	V1	V2	V3	V4	V5	
Visit	V0	V1	V2	V3	V4	V5	V6	V <sub>x</sub>
Week	0	3	6	18	30	42	58	
Informed Consent	X							
Inclusion/Exclusion	X							
Medical and Psychiatric History	X							
Seizure history and classification	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X
AED dosage		X	X	X	X	X	X	X
EEG and MRI/CCT <sup>1</sup>	X							
Physical and neurological exam <sup>2</sup>	X						X	
Brief neurological exam			X	X	X			X
Clinical Labs: Chemistry/Hematology	X		X		X		X	
PK Serum sample – drugs			X		X		X	
Seizure Diary review			X	X	X	X	X	X
Randomisation	X							
Dispensing of subject diary	X		X	X	X	X		
Dispensing of trial medication	X		X	X	X	X		
Return of trial medication			X	X	X	X	X	
Tel. Contact		X						
AE Reporting		X	X	X	X	X	X	X
QOLIE-31 <sup>3</sup>	X				X		X	
Toxicity scale <sup>4</sup>	X				X		X	
EpiTrack <sup>5</sup>	X				X		X	
Final information							X	
Post trial medication							X	

- 1 – If not done within the last 6 months prior screening
  - 2 – Including vitals signs ((RR, pulse rate) and recording of body weight in kg
  - 3 – Quality of life assessment (QOLIE-31) (see appendix 17.2)
  - 4 – Portland neurotoxicity scale (PNS) questionnaire (see appendix 17.3)
  - 5 – Standardized cognitive testing (see appendix 17.4)
- V<sub>x</sub> – additional, optional visit at the discretion of the investigator