

## Chapter 16. Epilepsies and Convulsive Disorders

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## **I. INTRODUCTORY REMARKS**

With an overall prevalence in the order of 0.5 to 1%, epilepsy is a very frequent serious neurological disorder, and almost invariably requires long-term pharmacological management. Over the past 15 years, several new antiepileptic drugs (AEDs), including felbamate, fosphenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin and zonisamide, have appeared in the market with the objective of improving efficacy, tolerability, and ease of use compared with the classical AEDs (carbamazepine, valproic acid, phenytoin, phenobarbital, primidone, ethosuximide and benzodiazepines). These objectives, however, have not been completely fulfilled. Most importantly, the introduction of the new AEDs has had little impact towards the goal of achieving seizure freedom in the many patients (about one third of a typical unselected epilepsy population) who remain refractory to conventional medications.

There are many areas where clinical research is needed. The comparative efficacy and tolerability of the newer AEDs is not yet clearly defined and there is a paucity of trials comparing head-to-head these agents. Even direct comparisons between newer and older AEDs have been relatively scarce and limited to selected epilepsy syndromes (mostly patients with partial seizures with or without secondary generalization, and patients with primarily generalized tonic-clonic seizures). Moreover, most of these trials had questionable designs in terms of low sample size, suboptimal dosing regimens (often favoring the sponsor's product), and limited duration of follow-up. Studies in generalized epilepsy syndromes and in special populations such as infants, children and the elderly have been particularly scarce.

Despite the relative abundance of different AEDs, clinicians feel that there are still unmet needs in the pharmacological treatment of epilepsy. First, over a third of the patients with epilepsy are not controlled with the current options. Second, up to a quarter of the patients exposed to a first AED will have adverse effects severe enough to require the drug's withdrawal, and many more will suffer from chronic adverse effects limiting their quality of life. Thirdly, several epilepsy syndromes remain resistant to standard therapies. Examples include the Lennox-Gastaut syndrome and mesial temporal sclerosis. Newer drugs with improved efficacy and tolerability profiles are surely needed.

Despite the relatively "crowded" market, pharmaceutical companies should be interested in further development of newer antiepileptic compounds. Not only is epilepsy frequent and will increase further in frequency as the elderly population enlarges, but also many AEDs have found additional indications for other CNS disorders (e.g., migraine prophylaxis, neuropathic pain, anxiety, and bipolar disorder) that amplify the rewards of this line of research.

As seizures are potentially dangerous events, placebo as the only treatment has generally not been accepted in AED research. Therefore, AEDs are investigated initially as adjunctive therapy in patients with partial seizures refractory to available medications. However, due to the fact that newly diagnosed epilepsy is treated with a single AED, a monotherapy license is highly desirable and ultimately monotherapy trials also need to be conducted. These are usually done prior to licensing (conversion to monotherapy) or after a license for adjunctive therapy use has been obtained (monotherapy trials in patients with newly diagnosed partial and/or generalized seizures).

Clinical trials in epilepsy are largely geared towards registration in the US by the Food and Drug Administration (FDA) and in Europe by the European Medicines Evaluation Agency (EMA). Unfortunately, registration trials leave many questions unanswered. For example, most studies are performed in either newly diagnosed patients or those with severe, refractory epilepsy, but few if any are performed in patients with less severe but established epilepsy. Certain common epilepsy syndromes, such as absence and juvenile myoclonic epilepsy are difficult to study in a randomized controlled way, and as a result there is very little useful data on the efficacy of the new AEDs in these populations. Also, certain populations, such

as the developmentally disabled, or those with psychiatric and medical comorbidities are often excluded from randomized trials, again leading to a paucity of data about safety concerns, if any, in these groups.

## **II. PHASE II STUDIES FOR REGISTRATION OF NEW ANTIEPILEPTIC DRUGS**

### **II.1. Outline of a typical development plan**

This phase usually begins with open label exploratory studies to assess titration rates, maximally tolerated dosages, pharmacokinetics and drug interactions. Results of these studies are critical for the appropriate design of pivotal studies. Determining the influence of other antiepileptic drugs on the study drug is particularly important, and should be investigated using well designed interaction studies. Many standard AEDs will either induce or inhibit the metabolism of a study drug, if it is cleared via hepatic microsomal enzymes. Failure to discover such an interaction in early phase II could lead to substantial underdosing or overdosing in the pivotal trial. Similarly, if the study drug inhibits the metabolism of a commonly used background AED such as phenytoin or carbamazepine, interpretation of efficacy outcome in a randomized trial could be severely confounded. Subsequently, the drug candidate is assessed against placebo as adjunctive treatment in patients refractory to standard therapies. As a rule, these studies are carried out in patients with partial seizures, because these patients are easier to recruit. Studies seek to enroll patients with a relatively high frequency of seizures, to permit evaluation of clinical response over a relatively short time scale.

Two types of randomized controlled designs have been used: cross-over and parallel. Due to difficulties in carrying out cross-over trials and problems with interpretation of results, a parallel-group design is preferred.

The typical pivotal trial will utilize a multicenter, double-blind placebo-controlled randomized, adjunctive therapy, parallel group design. At least 2 or 3 dose levels should be explored, preferably within the same trial. Early proof-of-concept monotherapy studies (presurgical design) may occasionally be included as part of the phase II development program (see section 3). Patients included in short-term studies should be allowed to enter long-term open-label follow-up.

### **II.2. Short-term studies**

#### **Adjunctive therapy trial in patients with refractory partial epilepsy**

##### **II.2.A. Objectives**

To evaluate short-term efficacy and tolerability during adjunctive therapy use

##### **II.2.B. Primary endpoints**

- a. Percentage change in seizure frequency during the treatment phase (double-blind phase, including or excluding the dose titration period) compared to baseline.
- b. Responder rate (percentage of patients with a greater than 50% reduction in seizures compared to baseline).

##### **II.2.C. Secondary endpoints**

- a. Percentage change in seizure frequency per seizure type (simple partial, complex partial or secondarily generalized).
- b. Percentage of patients with seizure worsening (increase in seizures by 25% or more).
- c. Percentage of seizure-free patients.
- d. Distribution of responders (seizure reduction of 25 to 50%, 50 to 75% and >75%).
- e. Completer rate (measuring the combination of failed efficacy and tolerability).

- f. In trials using different dosages, change in seizure frequency and responder rate per dosage group are to be analyzed. Usually, each dose is compared to placebo, but doses are not compared to each other.
- g. Incidence and prevalence of adverse events.

#### **II.2.D. Exploratory endpoints**

- a. Relationship between plasma drug concentration and dose, efficacy, and adverse effects. Drug withdrawal and rebound effects.

#### **II.2.E. Study design**

A multicenter, randomized, placebo-controlled, parallel-group design is generally used. Inclusion criteria usually require stable background treatment with one to three AEDs, a seizure frequency of at least three to four partial seizures per month, and no 28 day periods seizure free. A retrospective screening phase is used to determine the patient's refractory status, followed by a prospective baseline during which baseline AEDs are held constant and the patient's seizure diaries are kept. This phase should be of sufficient length to detect fluctuations in seizure frequency (usually 8 to 12 weeks). Shorter baseline periods are preferred, as longer ones retard patient recruitment. Patients are then randomized to placebo and to active treatment (with one or up to three different doses of the study medication). A titration phase of variable length is usually included depending on the characteristics of the drug (this may be crucial because many AEDs are poorly tolerated when started at full maintenance dosages). Titration flexibility might be allowed, i.e. dose may be individually down titrated in cases of poor tolerability with up to two pre-defined lower doses. A maintenance period of 8-16 weeks is then implemented during which treatment remains stable. Concomitant medications are kept stable throughout the trial. If the added agent is expected to modify plasma concentrations of concomitant AEDs, the dosages of the latter may need to be adjusted to maintain constant plasma concentrations. At the end of the trial, the patient is either withdrawn according to a pre-defined withdrawal schedule, or is changed to a predetermined dose of the study medication before unblinding in order to enter an open-label extension trial.

#### **II.2.F. Planned sample**

Assuming a two-group comparison, a sample size of about 50 to 90 patients per treatment group (depending on the population standard deviation) should permit detection of a difference of 25% between treatment groups in improvement from baseline with 80% power and a type 1 error (two-sided) of 5%.

#### **II.2.G. Study population**

Adults with refractory partial seizures, with or without secondary generalization, receiving one to three background AEDs

#### **II.2.H. Specific inclusion criteria**

- a. Adults (ages 16 to 65) with partial seizures (simple, complex and secondary generalized tonic-clonic), defined according to the International League Against Epilepsy (ILAE) classification.
- b. Patients should have non-controlled seizures despite a stable regimen with 1-3 established appropriate AEDs (the vagal nerve stimulator is sometimes considered as a drug).
- c. A defined minimum number of seizures in the baseline phase (e.g., more than 6 observable partial seizures in 8 weeks and at least one seizure in any 4-week period during the baseline).
- d. Women of childbearing potential must be using a medically acceptable method of birth control and have a negative serum HCG pregnancy test result at the initial screening visit. Oral contraceptives alone may not be considered adequate because of the potential effect of AEDs on their metabolism.

#### **II.2.I. Specific exclusion criteria**

- a. Patients with generalized epilepsy syndromes.

- b. Patients with a history of convulsive status epilepticus in the past year.
- c. Patients with non-epileptic attacks (syncope, pseudoseizures).
- d. Patients with a clinically relevant medical illness or a significant psychiatric disorder.
- e. Patients with progressive CNS disorders (vascular malformations, high grade tumors, etc.).
- f. Drug or alcohol abuse.
- g. Previous poor compliance with therapy.
- h. Pregnant or breastfeeding women.
- i. Need for rescue benzodiazepines more frequently than once in the baseline period.
- j. Uncountable seizures as a result of seizure clustering, or inadequate supervision if the patient cannot count their own seizures.

## **II.2.J. Tools for assessing primary endpoints**

Seizure diary

## **II.2.K. Specific criteria for early withdrawal and discontinuation**

The investigator will discontinue a patient before completion of the study if consent is withdrawn, if the double-blind code is broken, if it is medically unacceptable to continue treatment due to adverse events, seizure exacerbation, or other reasons, or if pregnancy occurs.

## **II.2.L. Data analysis method**

The analysis of efficacy variables is based on the intention-to-treat (ITT) population (including all randomized patients who have received at least one dose of medication). All statistical tests are two-sided and p values  $\leq 0.05$  are considered statistically significant. Multiple statistical methods can be used for the primary and secondary endpoints (analysis of variance, analysis of covariance, logistic regression, Cochran-Mantel-Haenszel statistics, etc).

## **II.3. Long-term studies**

It is customary for patients completing short-term studies to be allowed to enter long-term open-label follow-up studies. The primary objective of these studies is to provide data on tolerability and safety during long-term use and to obtain descriptive information concerning potential loss of therapeutic benefit. Typically, patients entering long-term extension trials may have the dosage of study drug and concomitant medications adjusted on the basis of clinical response. Evaluation will include an overall assessment of tolerability and seizure frequency. The study drug may be continued for as long as it is felt to be clinically beneficial, and retention of patients on the drug may be used as a crude measure of effectiveness. Additionally, extension trials may offer the opportunity to discontinue concomitant medication in order to obtain a preliminary assessment of the study drug under monotherapy conditions.

## **III. PHASE III STUDIES FOR REGISTRATION OF NEW ANTIEPILEPTIC DRUGS: ADJUNCTIVE THERAPY INDICATIONS**

### **III.1. Outline of a typical development plan**

During phase III development at least one large multicenter confirmatory adjunctive therapy, double-blind, randomized, placebo-controlled, parallel group study in refractory partial seizures is performed, usually with a dose-ranging design assessing two or three different doses of the study medication. Adolescents (over 12 years of age) as well as adults may be included in this study. Additional trials in pediatric populations may be performed. These may be conducted in children with refractory partial seizures and, if appropriate based on the expected spectrum of activity of the drug, also in children with refractory generalized epilepsies, such as Lennox-Gastaut syndrome or other syndromes. Monotherapy

trials in refractory patients (conversion to monotherapy design, or presurgical monotherapy design) may also be part of a phase III program: these trials are described in a separate section below.

A clinical development plan will include several different phase III studies, some of which may address special issues (e.g. effects on cognitive function and cognitive outcome, pharmacokinetics and drug interactions, efficacy and tolerability in special groups such as children, the elderly or cognitively impaired patients). The pivotal trial for registration purposes will be an adjunctive therapy trial in refractory partial seizures. Both the FDA and the EMEA will grant approval for the adjunctive therapy indication for partial epilepsy after two adequate and well controlled trials in patients with partial seizures. A trial in Lennox Gastaut syndrome is outlined below to provide an example of a study design for a different epilepsy syndrome.

### **III.2. Short-term adjunctive therapy studies**

#### ***Adjunctive therapy trial in refractory partial epilepsy***

The design for phase III adjunctive-therapy trials in refractory partial seizures is similar to that described above for phase II trials. Often, multiple doses are explored. Different regimens may also be explored, such as BID versus TID.

#### ***Adjunctive therapy trial in Lennox-Gastaut syndrome***

##### **III.2. A. Objectives:**

To evaluate efficacy and short-term tolerability of adjunctive therapy in patients with Lennox-Gastaut syndrome

##### **III.2.B. Primary endpoints**

- a. Determination of a statistically significant between-group difference with respect to either 1) reduction in the average monthly seizure rate for all seizure types combined or 2) each component of a compound variable consisting of percentage reduction in drop attacks (tonic-atonic seizures) and the parental global evaluation of seizure severity.
- b. Reduction in the average monthly (28-day) seizure rate for all seizure types combined during the treatment phase (double-blind phase, including or excluding the dose titration period) compared to baseline.
- c. Percentage reduction in drop attacks (tonic and atonic seizures).

##### **III.2.C. Secondary endpoints**

- a. Percentages of patients considered to be treatment responders (defined as those with an equal or greater than 50% reduction from baseline for drop attacks, major seizures, and all seizures).
- b. Reduction in the average monthly (28-day) rate of major seizures (drop attacks and tonic-clonic seizures).
- c. Parental global evaluation of improvement relative to baseline.
- d. Incidence and prevalence of adverse events.

##### **III.2.D. Exploratory endpoints**

- a. Relationship of efficacy and tolerability parameters with dose and plasma drug concentrations. Quantitative EEG analysis.

##### **III.2.E. Study design**

A multicenter, randomized, adjunctive therapy, double-blind, placebo-controlled parallel-group design is used. The trial may consist of a 4-week baseline phase followed by a 12-week double-blind treatment phase (including a titration and a maintenance period). Only one dose (weight adjusted) may be explored.

Other aspects of the design are comparable to those described for phase II adjunctive therapy trials in refractory partial epilepsy.

### **III.2.F. Planned sample**

As described above for phase II adjunctive therapy trials in refractory partial epilepsy. Sample size may be moderately lower than in refractory partial epilepsy due to the fact that patients with Lennox Gastaut syndrome tend to have greater seizure frequencies, with a lesser population standard deviation.

### **III.2.G. Study population**

Male and female children (older than 4years), adolescents and adults with Lennox-Gastaut syndrome

### **III.2.H. Specific inclusion criteria**

- a. Adults and children, aged 4 to 65.
- b. History, EEG, and seizure patterns consistent with a diagnosis of Lennox-Gastaut syndrome. Seizure types will include drop attacks (i.e., tonic and atonic seizures) and either a history of or active atypical absence seizures. Other seizure types may include tonic-clonic, myoclonic, and partial-onset seizures. Seizures are classified according to the ILAE International Classification of Epilepsies and Epileptic Seizures.
- c. Patients are required to have refractory and frequent seizures during the month before entering the baseline phase while being maintained on a stable regimen with one or two standard AEDs.

### **III.2.I. Specific exclusion criteria**

- a. As described for phase II adjunctive therapy trials in refractory partial epilepsy except, of course, for the epilepsy type.

### **III.2.J. Tools for assessing primary endpoints**

Patient/caretaker seizure diaries, parental global evaluation scale.

### **III.2.K. Specific criteria for early withdrawal and discontinuation**

As described for phase II adjunctive therapy trials in refractory partial epilepsy.

### **III.2.L. Data analysis method**

As described for phase II adjunctive therapy trials in refractory partial epilepsy.

### **III.3. Long-term adjunctive therapy studies**

Please refer to the outline described for phase II long-term adjunctive-therapy studies.

## **IV. PHASE III STUDIES FOR REGISTRATION OF NEW ANTIEPILEPTIC DRUGS: MONOTHERAPY INDICATIONS**

### **IV.1. Outline of a typical development plan**

As monotherapy is the standard treatment for most patients with epilepsy, approval of a monotherapy indication is very important for the success of the drug in the market place. Monotherapy studies also allow evaluation of a drug's efficacy and tolerability profile, due to removal of the confounding effects of concomitant medication and associated drug-drug interactions.

Because the use of placebo as sole therapy is generally considered ethically unacceptable in epilepsy, most studies use an active control as comparator. This, however, may complicate the interpretation of the results. In fact, when administration of the investigational drug leads to a degree of seizure control which is comparable to that observed with the optimal standard treatment used as a reference (a realistic

scenario, given the remarkable effectiveness of established treatments in the newly diagnosed epilepsy population), the study may be regarded as lacking assay sensitivity, i.e. the two treatments might be equally ineffective in the specific patients' population recruited in the study. To address these concerns, a number of study designs have been developed which are aimed at demonstrating a difference in favor of the investigational agent. Such protocols involve randomization of patients to a high dosage of the investigational agent and to a suboptimal dosage of either the same agent or an established AED. The use of a suboptimal dose (sometimes referred to as "pseudoplacebo"), however, is controversial as it conflicts with the principle of equipoise which, according to the Declaration of Helsinki, should govern all clinical trials. An additional problem with trials comparing a high versus a low dosage of the investigational agent is that the design is likely to fail to identify the optimal dose range, leading to labeling specifications which may not reflect the optimal mode of use of the drug. For conversion to monotherapy trials, these problems are compounded by the fact that dosage requirements in refractory patients may not necessarily be applicable to patients with newly diagnosed epilepsy, many of whom have milder forms of the disease. With short-term trials, an additional criticism is that the endpoints used and the duration of assessment (see below) may bear little or no relevance to the therapeutic setting, where long-term seizure remission is the major objective to ensure an acceptable quality of life. For the reasons summarized above, regulatory trials which tend to rely on randomization to fixed dosages and relatively short duration of treatment do not provide the information which is required for rational prescribing. Longer duration, flexible-dosages pragmatic trials (see section 5) are suited to address these concerns.

Two different patient populations may be included in monotherapy trials: patients with refractory seizures (usually partial seizures) and patients with newly diagnosed epilepsy. The trial designs used would be different. In refractory patients two types of design are employed: the outpatient conversion to monotherapy and the in-patient presurgical withdrawal to monotherapy. Both designs involve short-term assessment aimed at demonstrating superiority over a suboptimal comparator or placebo. In newly diagnosed epilepsy two types of trials have also been applied: the superiority design, which is usually a medium-term comparison versus a suboptimal comparator or placebo, and the non-inferiority design, which typically involves a longer duration of assessment.

EMA guidelines for granting the monotherapy indication differ somewhat from those of the FDA. The EMA requires that the investigational drug should have proven efficacy and safety in newly diagnosed epilepsy, with use in other monotherapy situations being regarded as supportive. Non-inferiority monotherapy trials using an established comparator at optimized dosages are considered by the EMA as the best study design, even though supportive evidence from some kind of superiority trial (conversion to monotherapy or low-dose vs. high-dose active control) is also recommended. The FDA, on the other hand, does not accept the validity of non-inferiority trials and requires clear demonstration of superiority versus a comparator, either in refractory patients (conversion to monotherapy design) or in newly diagnosed patients. An alternative monotherapy design has been proposed. It involves using historical control data derived from the many withdrawal to monotherapy outpatient trials conducted to date. According to this approach, the investigational agent is assessed at a full dosage in a conversion to monotherapy trial (without including a suboptimal treatment arm, though some other type of control, such as an established AED at a fully effective dosage, may be included for comparative purposes) and a monotherapy license will be granted if the response rate exceeds the upper limit of the confidence interval established for historical controls. In this way, use of a suboptimal treatment and related ethical concerns would be avoided. The validity of this approach is currently being considered by regulatory agencies.

Given this background, a monotherapy development plan aimed at obtaining a worldwide license currently requires at least two separate studies: a superiority trial, conducted preferably in the U.S., and a non-inferiority trial, conducted preferably in Europe.

## **IV.2. Short-term monotherapy studies**

### **IV.2.i. Outpatient conversion to monotherapy trial in refractory partial epilepsy**

#### **IV.2.i. A. Objectives**

To evaluate the efficacy and safety of the investigational drug as monotherapy in patients with uncontrolled partial seizures.

#### **IV.2.i. B. Primary endpoints**

Time to exit due to fulfillment of one of the exit criteria (the aim is to show that patients allocated to the high dosage of the investigational agent are less likely to experience seizure worsening compared with those allocated to a low-dose suboptimal treatment).

#### **IV.2.i.C. Secondary endpoints**

Percentage of patients meeting one of the exit criteria in each of the two treatment groups, incidence and prevalence of adverse events.

#### **IV.2.i.D. Exploratory endpoints**

Relationship of efficacy and tolerability parameters with dose and plasma drug concentrations.

#### **IV.2.i.E. Study design**

A randomized, double-blind, active control, parallel-group design is used. The trial involves a screening phase and an 8-week baseline phase, which is followed by a treatment phase including a transition period and a monotherapy period. The transition period allows for the treatments being compared to be titrated upwards and for the baseline AEDs to be progressively reduced and eventually discontinued. Withdrawal of background AEDs can be done either before or after randomization. In the more common design, patients are randomized to treatment or control, after which background AEDs are slowly withdrawn over 8-12 weeks. In the second design, all patients are converted to monotherapy treatment with the study drug in an open-label fashion, after which they are randomized to blinded treatment with high vs low dose. The transition phase is followed by a 12- to 16-week monotherapy period that includes an enriched population, i.e. all patients who have successfully converted to monotherapy and did not fulfill exit criteria (see below) in the previous phases. Dose flexibility has sometimes been allowed during this phase. At the end of the treatment phase or if there is a premature discontinuation, the investigational drug is either tapered down and substituted by another AED, or the patient enters an open-label extension phase.

#### **IV.2.i.F. Planned sample**

A sample size of about 50 patients per treatment group is required to detect a 35% difference between trial arms in the percentage of patients meeting one exit criteria with 90% power and a type 1 error (two-sided) of 5%.

#### **IV.2.i.G. Study population**

Adolescents and adults with refractory partial seizures.

#### **IV.2.i.H. Specific inclusion criteria**

Similar to those described for phase II adjunctive therapy trials.

#### **IV.2.I. Specific exclusion criteria**

Similar to those described for phase II adjunctive therapy trials.

#### **IV.2.i.J. Tools for assessing primary endpoints**

Patient's seizure diary.

#### **IV.2.i.K. Specific criteria for early withdrawal and discontinuation**

The following exit criteria are defined relative to the number of seizures during the baseline: doubling of average monthly seizure rate, doubling of the highest consecutive 2-day seizure rate, emergence of more severe or new seizure types (including generalized tonic-clonic convulsions), clinically significant prolongation of generalized tonic clonic seizures.

#### **IV.2.i.L. Data analysis method**

The analysis of efficacy variables is based on the intention-to-treat (ITT) population. Time to exit is analyzed using the log-rank test and Kaplan-Meier estimates.

#### **IV.2.ii. In-patient presurgical conversion to monotherapy trial in refractory partial epilepsy**

The presurgical design is currently less favored than the conversion to monotherapy design, partly because it has been argued that this design may primarily test efficacy against drug withdrawal seizures, which may involve pathophysiological mechanisms different from those of spontaneous seizures. Moreover, the time scale over which efficacy is assessed in presurgical designs trials is perceived as bearing limited relevance for long-term clinical use. At present, performance of this trial alone would not lead to an FDA indication for use of a drug as monotherapy. It is now more often performed as a proof of principle study, during phase IIa.

This trial requires rapid introduction of the investigational drug, and therefore is only appropriate for compounds that can be initiated rapidly.

#### **IV.2.ii.A. Objectives**

To evaluate the short-term efficacy and safety of the investigational drug as monotherapy for patients with uncontrolled partial seizures. To prove that a drug enters the brain and has an antiepileptic effect (as proof of principle).

#### **IV.2.ii.B. Primary endpoints**

Time to exit due to fulfillment of one of the exit criteria. The aim is to show that patients allocated to the high dosage of the investigational agent are less likely to experience worsening of seizures compared with those allocated to a low-dose (suboptimal) treatment.

#### **IV.2.ii.C. Secondary endpoints**

Percentage of patients completing the study, percentage of patients who meet one of the exit criteria, total number of partial seizures during the double-blind phase, total number of secondarily generalized seizures, incidence and prevalence of adverse events.

#### **IV.2.ii.D. Exploratory endpoints**

Safety of quick titration/drug-loading, speed of drug action.

#### **IV.2.ii.E. Study design**

A randomized, double-blind, parallel-group design is used, with a low-dose active control or, at times, a placebo control. The study is performed in patients with refractory partial epilepsy that are admitted to hospital for video-EEG monitoring for presurgical assessment and have their AEDs withdrawn to facilitate seizure recording. Once patients have been drug-free for 48 hours, they are randomized to a high dosage of the investigational drug and to a suboptimal (low-dose or placebo) treatment. To reduce risks, a benzodiazepine (lorazepam) may be permitted during the 48 hour medication-free period and sometimes during the first 24 hours after randomization. The medication or placebo are quickly loaded and the

double-blind evaluation lasts for 8-10 days. Dose flexibility in case of adverse events may be allowed. The double-blind phase may be followed by an open-label extension study.

#### **IV.2.ii.F. Planned sample**

Sample size may be calculated with respect to the ability of detecting a 30% difference between the high-dosage group and the placebo/low-dose group for the percentage of patients meeting one exit criteria. If it is assumed that 85% of the placebo-treated patients meet one of the exit criteria, given a two-sided Z-test with a significance level of 0.05 and a power of 0.85, about 50 patients per group are required.

#### **IV.2.ii.G. Study population**

Patients with refractory partial seizures.

#### **IV.2.ii.H. Specific inclusion criteria**

Patients with refractory partial epilepsy undergoing AED withdrawal within a presurgical workup. Patients need to have between 2-10 partial seizures during baseline and be receiving no AEDs when randomized.

#### **IV.2.ii.I. Specific exclusion criteria**

Similar to those described for phase II adjunctive therapy trials in refractory partial epilepsy.

#### **IV.2.ii.J. Tools for assessing primary endpoints**

Video-EEG recorded seizures.

#### **IV.2.ii.K. Specific criteria for early withdrawal and discontinuation**

Exit criteria are predefined to ensure patient safety. These may include: 3-4 partial seizures or secondarily generalized seizures, new appearance of generalized tonic-clonic seizures, serial/prolonged seizures, or status epilepticus.

#### **IV.2.ii.L. Data analysis method**

The analysis of efficacy variables is based on the intention-to-treat (ITT) population. Time to exit may be analyzed using the log-rank test and Kaplan-Meier survival curves. Additional statistical analyses may be performed using a Cox's proportional hazards regression model. Secondary efficacy variables (percentage of patients who meet one of the exit criteria) may be analyzed using the Cochran-Mantel-Haenszel test.

### **IV.3. Long-term monotherapy studies**

#### **IV.3.i. Superiority monotherapy trial in newly diagnosed epilepsy**

##### **IV.3.i.A. Objectives**

To evaluate the comparative efficacy and tolerability of the investigational drug versus a (usually suboptimal) active control under monotherapy conditions in new onset epilepsy.

##### **IV.3.i.B. Primary endpoint**

Time to first or second seizure (seizures occurring during the titration period may or may not be censored, depending on the characteristics of the titration phase).

##### **IV.3.i.C. Secondary endpoints**

Time to treatment failure (discontinuation of treatment), percentage of seizure-free patients after 6 and 12 months of treatment.

#### **IV.3.i.D. Exploratory endpoints**

Relationship of efficacy and tolerability parameters with dose and plasma drug concentrations.

#### **IV.3.i.E. Study design**

A multicenter, randomized, double-blind, parallel-group study is performed in patients with untreated epilepsy using a dose-controlled design, i.e. comparing a low dosage with a high dosage. Target dosages may be reached after an appropriate titration period, and patients experiencing intolerable adverse effects during titration may be allowed to step back by one dose level. The aim of the study is to demonstrate that time to first or second seizure is longer in the high-dosage group than in the low-dosage group. The double-blind phase may be followed by an open-label extension study.

#### **IV.3.i.F. Planned sample**

It has been suggested that these studies be powered on the basis of number of failure events (a first seizure), not number of patients. Based on the hypothesis that the hazard ratio for time to first seizure is 0.525 and constant over time, 108 events are needed for 92.5% power to detect a statistically significant difference at the 5% (two-sided) level. Enrollment is to be stopped when 108 events have been observed. In the only trial performed using this approach and only allowing the inclusion of patients with 1 or 2 seizures during a retrospective 3-month baseline, a recruitment of about 500 patients was necessary.

#### **IV.3.i.G. Study population**

Patients with new onset epilepsy or previously diagnosed but currently untreated epilepsy. The population could include patients with partial seizures (with or without secondary generalization) and primarily generalized tonic-clonic seizures.

#### **IV.3.i.H. Specific inclusion criteria**

- a. Age of 12 to 65 years (wider age limits may be acceptable).
- b. Recently diagnosed epilepsy with two or more unprovoked seizures. It may be possible to accept one seizure plus additional unequivocal evidence supporting the diagnosis of epilepsy (epileptiform EEG activity, brain imaging evidence). Patients should have had at least one seizure within the 3 months previous to randomization (an upper limit to number of seizures during this period may be set). In addition, patients with a previous history of epilepsy that has been in remission without medications for at least 6 months and have had one seizure in the previous 3 months may be included.
- c. Patients treated with a single AED for less than 2 weeks could enter the study provided that medication is withdrawn previous to randomization.
- d. Women of childbearing potential must be using a medically acceptable method of birth control and have a negative serum HCG pregnancy test result at initial screening visit.

#### **IV.3.i.I. Specific exclusion criteria**

Non-epileptic attacks (syncope, pseudoseizures), history of status epilepticus, significant medical or psychiatric illness, drug abuse, progressive central nervous system disease. Depending on the drugs being compared, patients with specific epilepsy syndromes (for example, generalized epilepsies) may need to be excluded.

#### **IV.3.i.J. Tools for assessing primary endpoints**

Seizure diary.

#### **IV.3.i.K. Specific criteria for early withdrawal and discontinuation**

First seizure or adverse event requiring discontinuation of treatment.

#### **IV.3.i.L. Data analysis method**

The analysis of efficacy variables is based on the intention-to-treat (ITT) population. The primary efficacy variable is analyzed by Kaplan-Meier survival analysis. The log-rank test may be used to assess between-group differences. A Cox proportional hazards model may also be applied.

#### **IV.3.ii. Sequential design monotherapy trial in newly diagnosed epilepsy**

##### **IV.3.ii.A. Objectives**

To evaluate the comparative efficacy and tolerability of the investigational drug versus an active control (an established AED or a lower dose of the investigational drug) under monotherapy conditions in new onset epilepsy.

##### **IV.3.ii.B. Primary endpoints**

Time to first seizure following completion of the dose titration phase.

##### **IV.3.ii.C. Secondary endpoints**

Time to treatment failure (discontinuation of treatment), percentage of seizure-free patients after 6 and 12 months of treatment. Time to second, third and fourth seizure.

##### **IV.3.ii.D. Exploratory endpoints**

Relationship of efficacy and tolerability parameters with dose and plasma drug concentrations.

##### **IV.3.ii.E. Study design**

The sequential design is a trial which allows a series of interim analyses of the emerging data so that the trial can be stopped when a predetermined difference between treatments (or lack of such a difference) has been demonstrated. These trials may require fewer patients than traditional designs of equal power, and in particular can avoid continuation when one treatment is already evidently inferior to the other. As with other trials, the design involves a multicenter, randomized, double-blind, active control, parallel-group comparison. In the only large trial where this design was used in epilepsy, patients were titrated up to a predetermined target dosage and thereafter followed up for a maximum of 162 weeks. Dose adjustments were permitted if seizure control was inadequate or adverse events were observed. The double-blind phase may be followed by an open-label extension study.

##### **IV.3.ii.F. Planned sample**

The main trial conducted to date utilized a prediction of survival curves for the reference treatment (carbamazepine, initial target dose 600 mg/day) and for the investigational drug. It was regarded as possible that the investigational drug would improve the probability of surviving without a study event for 54 weeks from 0.5 to 0.6, a difference considered clinically significant. Based on the model used, a total sample size of 450 to 700 recruited patients (depending on the true seizure rates on the two treatments) was expected to be necessary to demonstrate the target difference with a power of 0.90 and at the 5% level (two-sided). This would compare with a sample size of about 1,000 patients if a fixed (non-sequential) sample design of equal power is used.

##### **IV.3.ii.G. Study population**

Patients with new onset epilepsy or previously diagnosed but currently untreated epilepsy. The population could include patients with partial seizures (with or without secondary generalization) and with primarily generalized tonic-clonic seizures (if experimental drug is broad-spectrum).

##### **IV.3.ii.H. Specific inclusion criteria**

As described above for non-sequential design monotherapy trials in newly diagnosed epilepsy.

#### **IV.3.ii.I. Specific exclusion criteria**

As described above for non-sequential design monotherapy trials in newly diagnosed epilepsy.

#### **IV.3.ii.J. Tools for assessing primary endpoints**

Seizure diary.

#### **IV.3.ii.K. Specific criteria for early withdrawal and discontinuation**

Uncontrolled seizures at the highest dosage allowed by the protocol, or adverse event requiring discontinuation.

#### **IV.3.ii.L. Data analysis method**

Each interim analysis may comprise a comparison of the survival rates on the two treatments by means of Cox's proportional hazards regression, adjusting for seizure type and for the number of seizures during the 12 months prior to randomization. The statistics assessing the advantage of one of the treatments is denoted by the Z score, which generalizes the better known log-rank statistics to allow for any imbalance in prognostic factors. Additionally, a measure of information, denoted by V, is calculated as the null variance (approximately equal to one quarter of the total number of events). These statistics are plotted against each other at each data review, until one of the stopping boundaries of the design is crossed.

#### **IV.3.iii. Non-inferiority monotherapy trials**

##### **IV.3.iii.A. Objectives**

To evaluate the medium to long term efficacy and tolerability of an investigational drug in patients with newly onset epilepsy in comparison with an established licensed in monotherapy AED at fully effective dosages.

##### **IV.3.iii.B. Primary endpoints**

- a. Proportion of patients seizure-free for 6 months assessed in the per-protocol (PP) population.

##### **IV.3.iii.C. Secondary endpoints**

- a. Proportion of patients seizure-free for 6 months assessed in the intention-to-treat (ITT) population.
- b. Proportion of patients seizure-free for 6 months in a subset of the per-protocol (PP) population which excludes drop-out for reasons unrelated to efficacy.
- c. Percentage of patients who remain seizure-free for 12 months.
- d. Time to exit.
- e. Percentage of completers.
- f. Time to first or second seizures.
- g. Percentage of patients seizure-free at each dose.
- h. Percentage of patients withdrawn due to adverse events.

##### **IV.3.iii.D. Exploratory endpoints**

- a. Relationship of efficacy and tolerability parameters with dose and plasma drug concentrations, cognitive function measures, quality of life measures.

##### **IV.3.iii.E. Study design**

The trial may involve a multicenter, double-blind, randomized, parallel-group design comparing the investigational drug with the best reference treatment at optimized dosages. Patients are allocated to an initial target dosage of both drugs at the lower end of the expected optimal range. If the primary endpoint (6-month seizure-freedom) is not reached due to seizure recurrence after the target dose has been attained, the patient is up-titrated to a higher pre-determined dosage. If the primary endpoint (6-month seizure-freedom) is again not reached due to seizure recurrence, the patient is up-titrated to the highest dosage

level. Patients may be allowed to step back to an intermediate dosage if side effects are encountered during each of the titration phases. The double-blind phase may be followed by an open-label extension study.

#### **IV.3.iii.F. Planned sample**

Assuming a 6-month seizure-free rate of 45% with the reference comparator, a true difference of zero between treatments and a 20% rate of protocol violators, a total sample size of 580 recruited patients would be required to ensure a lower limit above –15% for the two sided 95% confidence interval for the difference in 6-month seizure-free rates, with 90% power.

#### **IV.3.iii.G. Study population**

Patients with new onset epilepsy or previously diagnosed but currently untreated epilepsy. The typical population could include patients with partial seizures (with or without secondary generalization) and with primarily generalized tonic-clonic seizures, if the investigational drug is broad-spectrum.

#### **IV.3.iii.H. Specific inclusion criteria**

As described above for non-sequential design superiority monotherapy trials in newly diagnosed epilepsy.

#### **IV.3.iii.I. Specific exclusion criteria**

As described above for non-sequential design superiority monotherapy trials in newly diagnosed epilepsy.

#### **IV.3.iii.J. Tools for assessing primary endpoints**

Seizure diary

#### **IV.3.iii.K. Specific criteria for early withdrawal and discontinuation**

Seizures uncontrolled at the highest dosage level, adverse events requiring discontinuation of treatment.

#### **IV.3.iii.L. Data analysis method**

In non-inferiority trials, analysis of the primary efficacy variable is made on the per-protocol (PP) population. Six-month seizure-free rates may be compared by a logistic regression model whose 95% confidence interval computation may include treatment and seizure types (e.g. partial vs. generalized tonic-clonic seizures without clear focal onset) as factors. Interactions between treatment group and seizure types may be excluded by applying an additional logistic regression model including treatment, seizure type and treatment by seizure type factors.

### **V. OTHER STUDIES (SPECIAL INDICATIONS, PRAGMATIC TRIALS)**

#### **V.1. Paediatric epilepsies**

Studies of AEDs in children are conducted in three main patient populations:

- a. Patients with refractory partial seizures. For this population, a multicenter, randomized, double-blind, adjunctive therapy, parallel-group, placebo-controlled trial may be performed using a design similar to that described for adults;
- b. Patients with refractory generalized epilepsy. For this population, a multicenter randomized, double-blind, adjunctive therapy, parallel-group, placebo-controlled trial similar to that described in section 3 for Lennox-Gastaut syndrome may be performed. Studies in certain syndromes may require specific protocols: for example, trials in absence epilepsy may be of shorter duration and should use EEG changes (e.g., reduction/disappearance of spike-and wave activity ) as primary efficacy endpoint;
- c. Patients with newly diagnosed partial or generalized epilepsy. These studies usually involve multicenter, randomized, double-blind, monotherapy, active control trials, which are initiated after evidence of efficacy has been obtained from adjunctive therapy trials. The range of designs is

similar to those described for monotherapy trials in adults. Not uncommonly, inclusion criteria for monotherapy trials in newly diagnosed patients allow simultaneous inclusion of children and adults. Studies in certain paediatric epilepsy syndromes, however, may require syndrome-specific protocols.

Both the FDA and the EMEA indicate that safety data in paediatric populations should be included in the registration dossier. The EMEA suggests that paediatric studies should be initiated as early as the development program allows and that a minimum of 100 children should be followed-up for at least one year. Moreover, it is recommended that short-term and long-term studies be designed to detect possible impact on learning, intelligence, growth, endocrine functions and puberty. Paediatric pharmacokinetic data are also required.

### **V.2. Epilepsies in the elderly**

Pharmacokinetic and safety data in a reasonable number of elderly patients (100 or more) should be collected during phase III. This should include an evaluation of potential effects on cognitive function and sedation, as well as interactions with medications frequently used in this age group. Randomized monotherapy trials in elderly patients may be performed to obtain information supporting the use of a new AED in this segment of the population.

### **V.3. Acute repetitive seizures and status epilepticus**

Acute repetitive seizures and status epilepticus are emergency situations where acute treatment, usually by the parenteral route, is indicated. Special trial designs are required for these indications. These involve multicenter randomized active control trials, though in some circumstances (which exclude convulsive status epilepticus) use of placebo may be justifiable. Examples of trial designs for these conditions can be found among the landmark trials listed in section 7.

### **V.4. Pragmatic trials**

Pragmatic trials are designed to reproduce conditions which more closely reflect the use of a drug in routine clinical practice. Randomized pragmatic trials may be designed to assess the relative value of different therapeutic strategies rather than individual drugs (for example, early versus deferred treatment in those situations where the indication to treat is in doubt) or to compare two or more AEDs under conditions which allow physicians to optimize dosages and other treatment modalities according to personal clinical judgement. These studies may be of little value to regulators, but they provide useful information on which to guide rational prescribing. Most of these trials follow a design similar to the randomized non-inferiority active-control monotherapy trial outlined in section 4, but they allow greater dosing flexibility and use more relevant clinical endpoints (e.g., 12-month seizure remission rates, and retention on the allocated treatment). One example of such studies is the landmark Veterans Administration trial which compared phenobarbital, primidone, carbamazepine and phenytoin in patients with partial and/or secondarily generalized tonic-clonic seizures.

## **VI. EXAMPLES OF LANDMARK WELL DESIGNED TRIALS**

### **Adjunctive therapy, partial epilepsy**

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#### **Adjunctive therapy, Lennox-Gastaut-syndrome**

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#### **Monotherapy, short-term trials**

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#### **Monotherapy, long-term trials**

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#### **Acute repetitive seizures and status epilepticus**

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### **VII. SUGGESTED READINGS**

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