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Designing a new proof-of-principle trial for treatment of partial seizures to demonstrate efficacy with minimal sample size and duration—A case study

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Summary The ideal proof-of-principle study design provides a strong efficacy signal over the shortest duration, while exposing the fewest patients possible. Data from a large database (Pfizer Inc) which studied add-on pregabalin for the treatment of partial seizures was used to model how duration of baseline, post-randomization treatment period, and number of subjects impact the likelihood of an interpretable efficacy signal. Data from four double-blind, randomized, placebo-controlled, phase III studies that had at least one 600 mg/day treatment arm were combined. The common 6-week baseline period was divided into weekly intervals, as was the 12-week post-randomization period. Two methods of analysis were used: logistic regression performed on 50% responder rate and the Hodges—Lehmann estimate on percentage reduction from baseline seizure rate. A simulation-based re-sampling approach was used to determine sufficient sample size. Four weeks of baseline with 3 weeks of treatment were determined to be clinically and statistically sufficient. A reasonable sample size was estimated to be 40—50 patients per group, if a highly efficacious drug was used. These modeling results indicate that the efficacy of an antiepileptic drug can be demonstrated in a relatively short period of time with a reasonable sample size.

Abbreviations: AED, antiepileptic drug; CI, confidence interval; HLE, Hodges—Lehmann estimate; OR, odds ratio; PoP, proof-of-principle; SD, standard deviation.

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Introduction

In clinical drug development, after phase I healthy volunteer studies have been completed, the next step usually involves performing a ''proof-of-principle'' (PoP) study. The intent of such a study is to determine, in the most efficient way possible, whether the drug has the potential to be efficacious in treating a particular disease. Often when new chemical entities are being developed, PoP studies are performed to make ''go-no-go decisions'' or, if the treatment is being developed by a small startup company, positive results may be used to obtain further funding for development. A positive PoP study adds some certainty to the very uncertain process of drug development. Furthermore, therapeutic areas in which such a study design exists will attract more potential therapies.

The ideal PoP study provides a strong efficacy signal over the shortest amount of time. In addition, since the drug is at an early phase of development, when little is known about safety, it is prudent to expose the fewest patients possible. A number of different PoP designs have been used to determine whether drugs have antiepileptic capabilities. In one design, a single dose of medication is administered to patients with photosensitive epilepsy to determine whether the drug will attenuate epileptiform activity elicited by flashing lights (Kasteleijn-Nolst Trenite et al., 1996). However, this design has been criticized because it does not assess efficacy in the population of interest, namely patients with refractory partial-onset seizures. Observational/uncontrolled studies have also been employed, but in some cases this has led to an indication of apparent efficacy that has not been borne out in subsequent trials (The Group for the Evaluation of Cinromide in the Lennox-Gastaut Syndrome, 1989). Another potential PoP design mimics the standard randomized, placebo-controlled, adjunctive trial, but uses the shortest duration possible and the fewest number of patients. However, there is always concern that if trial duration and subject number are not selected prudently, a PoP study could inappropriately reject a new compound by failing to demonstrate efficacy.

We looked for collaborators using the following requirements: several add-on placebo-controlled studies of an antiepileptic drug (AED) using the same dose, and studies of sufficient duration. Upon query of a number of companies, Pfizer Inc opened their database of pregabalin trials.

Pregabalin is an anticonvulsant and analgesic medication developed by Pfizer Inc. The development plan for pregabalin included several large randomized, placebo-controlled, parallel studies in patients with refractory partial-onset seizures. The manufacturer (Pfizer Inc) holds a large database of patients enrolled in these AED trials. Such a database can provide an invaluable resource for modeling the behavior of patients, such that novel trial designs can be ''tested'' virtually to determine their likelihood of success. This is particularly important in a disease such as epilepsy in which the variability of seizure frequency, as well as the size of the placebo effect, can have a major impact on the likelihood of observing a drug effect.

We therefore used the pregabalin database to model how duration of baseline, post-randomization treatment period, and number of subjects impact the likelihood of an interpretable efficacy signal. Our objectives were to determine an optimal study period and sample size for a PoP phase II study design in refractory partial seizure patients. Although both pregabalin 300 and 600 mg/day are known to be effective dosages, the number of trials including a 300 mg/day arm was less than the number of trials including a 600 mg/day arm and therefore for this analysis we are only presenting the analysis from the 600 mg/day arm. This study was not intended to address the relative efficacy of pregabalin in comparison to other AEDs. Rather, the data are being used to address future methodology for AED PoP studies. However, it should be noted that we used the highest pregabalin dose, which was quite efficacious. This should be kept in mind when considering the results below. If lower or less efficacious doses are used, a larger sample size will likely be needed.

Methods

Research design

Data from four double-blind, randomized, parallel-group, placebo-controlled, phase III, add-on pregabalin trials in patients with partial-onset seizures were pooled for analysis. This included data from standard design studies and their primary analyses (pregabalin epilepsy studies: titration to 600 mg/day (Arroyo et al., 2004; Beydoun et al., 2005); immediate 600 mg/day (Elger et al., 2005; French et al., 2003)). Total numbers of patients were 367 in the placebo group and 532 in the 600 mg/day group (Table 1). Additional details on the design and patient populations in the four studies included in the analysis are summarized in a prior publication (Gil-Nagel et al., 2009).

Patients were men or nonpregnant, nonlactating women 18 years of age or older, of any race, weighing between 50 and 135 kg (110—298 lbs), and with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic). Patients must have failed adequate seizure control in the past while on standard AEDs and must have been receiving one to three standard AEDs at doses within an acceptable therapeutic range. See Gil-Nagel et al., 2009 for full exclusion/inclusion criteria.

For each study, the principal criterion to establish efficacy of pregabalin was reduction in frequency of all partial seizures from baseline in the pregabalin group versus the placebo group, which was evaluated using endpoint — the response ratio (Rratio) (see Gil-Nagel et al., 2009 for further details). However, Rratio transformation is not an easily understood measure; thus, for the present analysis, the percentage change from baseline seizure rate was used.

Statistical methods

The common 6-week baseline period was divided into weekly intervals, −6 to −1 weeks prior to randomization. The 12-week post-randomization period was also divided into weekly periods from week 1 to week 12. Two methods of analysis were used: (Model A) logistic regression performed on responder rate (50% reduction in seizure rate), and (Model B) Hodges—Lehmann estimate (Hollander and Wolfe, 1973) comparing treatment and placebo groups on percentage change from baseline seizure rate. The Hodges—Lehmann method consists of the median