

Migraine: a phase II adaptive trial with a comparator

Goal: To select dose that is as good as an active comparator in a phase II dose-ranging migraine prevention trial.

Background: This is a phase II efficacy trial in the prevention of migraine. Six doses of a new drug are tested: 14, 28, 42, 70, 98 and 140mg in a placebo-controlled, active comparator controlled trial. Primary response (PR) is decrease from baseline in mean number of migraine attacks per 28-day period.

The objective of the study is to assess the efficacy of the drug versus placebo and to find the dose that produces similar efficacy as the active comparator.

Bayesian Model: PR was assumed to be normally distributed with constant error. Mean PR was modeled as a function of the drug dose using a Normal Dynamic Linear Model (NDLM). This is a semi-parametric smoother of the dose-response profile that doesn't assume any specific pattern such as monotonicity, etc...

Priors were vague on the placebo response (intercept), initial slope (from 0 to 14mg) and residual error:

$$\text{int} \sim \text{Normal}(0, 10E9), \text{ slope} \sim \text{Normal}(5, 10E9), \text{ and } \tau \sim \text{Gamma}(0.0001, 0.0001).$$

Vague priors were also taken on the variance inflation factor for the slope:

$$W_{\text{delta}} \sim \text{uniform}(0.0001, 100),$$

where the larger W_{delta} , the less smoothing.

Discontinuities in the smoother at dose levels were not allowed, by setting strong priors on the variance inflation factor for intercept (W_{theta}) towards small values:

$$W_{\text{theta}} \sim \text{uniform}(0.0001, 0.01).$$

Adaptive design: This is a two-part trial with one interim analysis. The first cohort included 50 patients: 10 placebos, 10 actives, and 5 at each dose level. The second cohort, after the interim included 70 patients: 10 placebos and 60 spread optimally across doses. The adaptive allocation was made based on the Quantile Weighted Variance (QWV) criterion, targeting the improvement of the response variance at doses where the efficacy is similar to the active comparator.

Decision: At the interim and final analysis, the efficacy of each dose was compared to placebo by evaluating the posterior probability and comparing it to a 97.5% significance threshold:

$$\text{Pr}[\text{dose} > \text{pbo}] > 97.5\%.$$

Simulation: The following dose-response pattern was simulated to evaluate the type I error rate, power and dose allocation procedure of the study design:

Dose (mg)	Mean	Std
0	1	1.5
14	1	1.5
28	1.3	1.5
42	1.5	1.5
70	2	1.5
98	2.25	1.5
140	2.5	1.5
Active	2	1.5

In this setting, the 14mg dose is not efficacious (same as placebo) and 70 mg dose has the same efficacy as the active comparator.

Results: One thousand studies were simulated. Results from the simulations are presented below.

As expected, after the interim analysis, more subjects (N~21) were allocated to the 70 and 98mg doses, were the response was similar to the active comparator.

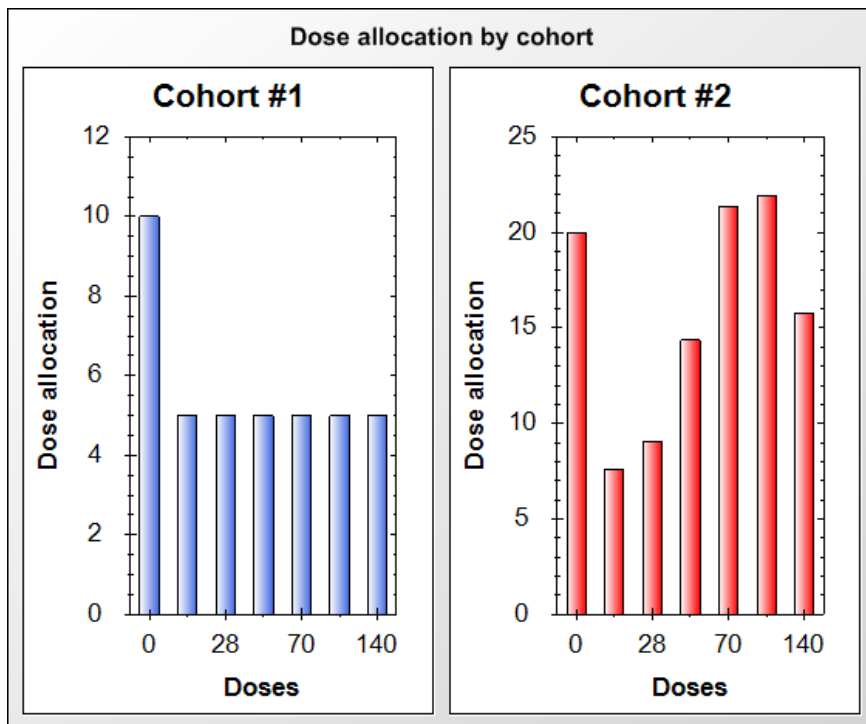


Figure 1. Mean dose allocation before and after the interim analysis.

End-of study power for the pairwise comparison of doses to placebo were 61, 79 and 81% for the 70, 98 and 140mg doses, respectively. Type I error rate as assessed at 14mg was well controlled at end of trial. It was only 4%. To control the type I error rate

at 5%, the threshold x for the posterior probability: $\Pr[\text{dose} > \text{pbo}] > x\%$ may be updated from 97.5 to 96% in the decision rules.

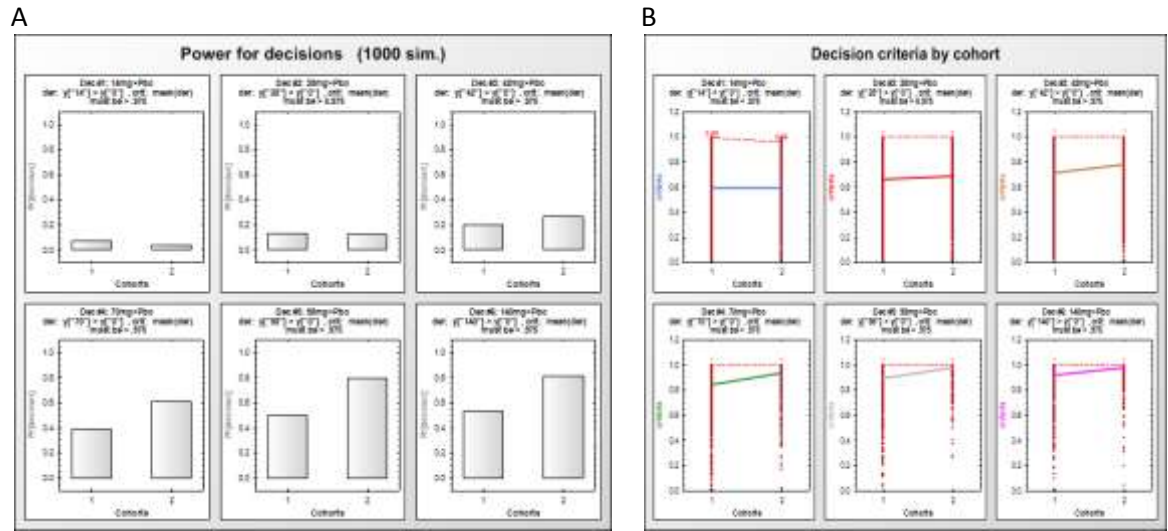


Figure 2. A. Power for the pairwise comparisons of doses to placebo at interim and final analyses. B. Individual probabilities: $\Pr[\text{dose} > \text{pbo}]$ estimates from simulation with means (colour lines) and 95% quantile (dashed red line).

Decimaker: The corresponding Decimaker study project may be found [here](#). It includes the simulation results as presented above.

References:

- Stephen D. Silberstein; Walter Neto; Jennifer Schmitt; David Jacobs. Topiramate in Migraine Prevention: Results of a Large Controlled Trial. Arch Neurol. 2004;61(4):490-495.