

Using modeling and simulation to evaluate placebo run-in for pain studies

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Background and Objective(s)

In clinical studies investigating how pain can be reduced the effect is often measured using a numerical rating scale (NRS). This is an 11 graded scale between 0 and 10 where 10 is worst imaginable pain. This is recorded by the patient daily, starting prior to first dose intake and continuing until end of study. The primary endpoint is often the difference between baseline (5 consecutive days before start of treatment) and the last 5 days of treatment. What can be problematic in these studies is the pronounced placebo effect often observed. The objective of this investigation was to explore if a placebo run-in period could improve the information acquired in a phase IIb study.

Patients and Methods

Previous collected placebo data indicate that the individual temporal course of placebo response can be positive or negative on the NRS scale where a majority of the patients initially experience a reduction in pain. However, after 10 days of treatment the placebo response seems to have reached a plateau. Using this data, a longitudinal placebo model was developed including inter individual variability (IIV) in the direction of NRS response. IIV was also included on baseline, maximum placebo response and time to reach plateau. The model predicted the data well. Three typical individuals are shown in Figure 1.

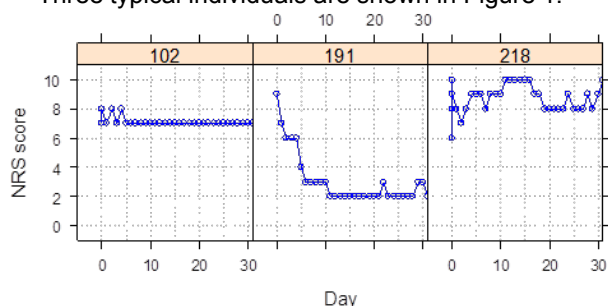


Figure 1. The NRS vs time for three typical placebo treated patients.

A design including placebo treatment for all patients during the first 10 days was suggested (Figure 2). Datasets with placebo and 3 different dose levels and different number of individuals were used for simulations in NONMEM. 1000 studies with and without placebo run-in with a drug effect which follows a linear exposure response with delta NRS of 1.2 at the highest simulated dose was simulated. The results from the two different designs were thereafter compared.

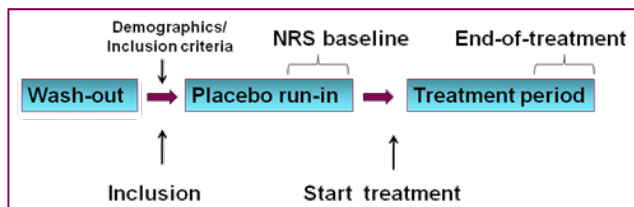


Figure 2. New suggested study design.

Results

When comparing the new and previous designs, a higher power to detect an exposure response relationship was obtained and the dose suggested to be used in phase III will be predicted with higher precision.

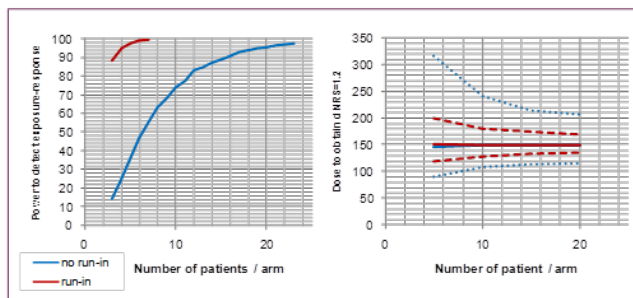


Figure 3. Left is power to detect an exposure-response relationship vs. number of patients. Right is the precision in the estimated dose suggested to phase III vs. number of patients. Dotted line is 80% confidence interval and solid line is median.

Discussion and Conclusion

This investigation indicates that a study design where all patients in a phase II pain study are treated with placebo initially and thereafter randomized to treatment, generates data that is substantially more informative for selection of dose regimen for phase III, as compared to a study design without placebo run-in period.

Using such a design may result in reduced cost and time needed for the Phase IIb study and/or increased probability of a successful phase III study