

ORAL PRESENTATION

Open Access

A Bayesian dose-finding procedure applied to a seamless phase I/II trial in rheumatoid arthritis

Anne Whitehead^{1*}, Helene Thygesen¹, Vladimir Dragalin², John Whitehead¹

From Clinical Trials Methodology Conference 2011
Bristol, UK. 4-5 October 2011

There is a growing interest amongst clinical investigators in the conduct of single trials combining the safety exploration of phase I with the initial investigations of efficacy usually made during phase II. This is being made increasingly possible through the use of biomarkers that show early signs of physiological changes that are associated with a therapeutic effect. Such a combined study calls for complex statistical models, able to capture the joint distribution of the safety and efficacy outcomes. Bayesian models are particularly attractive in such early phase studies because in interpreting small data sets, judicious use of investigators' opinions becomes worthwhile.

We will describe a dose escalation procedure for a combined phase I/II clinical trial, based on a Bayesian model for the joint distribution of toxicity and efficacy (both considered binary variables) making no assumptions other than monotonicity: that is the risk of toxicity and the chance of benefit are both assumed to be non-decreasing as functions of dose level. The procedure will be discussed in the context of a placebo-controlled, sequential trial in rheumatoid arthritis, in which patients, in each stage, are randomized across all doses levels that appear safe and non-futile at the time of recruitment. The primary efficacy outcome is a binary response at 16 weeks related to an assessment known as the ACR20, but an earlier efficacy assessment based on the ACR20 assessment and reduction in C-reactive protein at 4 weeks is used during the dose escalation phase for making decisions on doses for the next cohort. The measure of safety is the occurrence of a dose limiting toxicity within 4 weeks of treatment. Based on data

from a pilot study, we constructed five different scenarios for the dose-response relationships for which we simulated the trial and assessed the performance of the procedure. The new method appears to have satisfactory operational characteristics, and is flexible in that it can be adapted to the logistics of a particular trial and incorporate a placebo arm.

Author details

¹Medical and Pharmaceutical Statistics Research Unit, Department of Mathematics and Statistics, Lancaster University, Lancaster, Lancashire, LA1 4YF, UK. ²Aptiv Solutions, Morrisville, North Carolina, 27560, USA.

Published: 13 December 2011

doi:10.1186/1745-6215-12-S1-A90

Cite this article as: Whitehead et al.: A Bayesian dose-finding procedure applied to a seamless phase I/II trial in rheumatoid arthritis. *Trials* 2011 12(Suppl 1):A90.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit



* Correspondence: p.a.whitehead@lancaster.ac.uk

¹Medical and Pharmaceutical Statistics Research Unit, Department of Mathematics and Statistics, Lancaster University, Lancaster, Lancashire, LA1 4YF, UK

Full list of author information is available at the end of the article