Promoting Statistical Insight

01 – 02 March 2017

Hilton Garden Inn Hotel
Heathrow Airport

A PSI Training Course in

Dose Finding in Drug Development using MCP-Mod

presented by

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Statistical Methodology and Consulting, Novartis Pharma

including regulatory perspectives from

Rob Hemmings

Statistics and Pharmacokinetics Unit Manager, MHRA, UK

This course will introduce and discuss methods for Phase II dose finding studies, including a review of basic multiple comparisons and modelling methods, as traditionally used in these studies. A unified strategy for designing and analysing dose finding trials denoted MCP-Mod, combining multiple comparisons and modelling, will be the focus of the course.

Day 1

The first day will provide an overview of dose finding in drug development. The application of multiple comparison procedures (MCP) and modelling approaches (Mod) will then be covered, including a review of contrast tests as well as nonlinear regression methods for dose response and target dose estimation. Then a step-by-step description of MCP-Mod will be provided, including a detailed discussion of its five main steps across the design and analysis stages:

1. Identification of candidate parametric models, which are likely to represent the underlying dose response shape.
2. Derivation of optimum contrast coefficients, such that the marginal power to detect a specific dose response shape associated with the respective candidate model is maximized.
3. Evaluation of the significance of the individual models in terms of a multiple contrast test based on the previously derived optimal contrast coefficients.
4. Model selection or model averaging, provided statistical significance has been shown in the previous step.
5. Use the selected model(s) to produce inferences on adequate doses, employing a model-based approach.

MCP-Mod will first be introduced in its originally published version for a single, normally distributed efficacy endpoint. The extension of this framework will be described for count data and time-to-event endpoints as well as situations involving generalized non-linear models, linear and non-linear mixed effects models, and Cox proportional hazards models.

Day 2

On day two, considerations will be given to practical aspects around the design and analysis of dose finding trials using MCP-Mod. This includes importantly a discussion of its design aspects, in particular sample size derivations. As MCP-Mod is a hybrid procedure, focusing on hypothesis testing and estimation, sample size calculation procedures for both objectives will be presented and their

application on the design illustrated with a real dose finding study. A variety of further practical considerations will be discussed that summarizes the collective experience over the past 10 years in using MCP-Mod in Phase II dose finding trials. The application of the DoseFinding R package will be demonstrated in detail, including a description of functions for the design and analysis of dose finding trials using MCP, Mod or MCP-Mod. Hands-on exercises allow the course attendees to the experience the capabilities of the DoseFinding R package and how to use its functions to implement the MCP-Mod methodology. The course ends with a review of regulatory considerations.

About the presenters:

Frank Bretz joined Novartis in 2004, where he is currently Global Head of the Statistical Methodology and Consulting group. He has supported the methodological development in various areas of drug development, including dose-finding, multiple comparisons, and adaptive designs. He is a co-founding editor of the Springer Series in Pharmaceutical Statistics and the incoming editor of Statistics in Biopharmaceutical Research. He has authored or co-authored more than 120 articles in peer-reviewed journals and four books.

Björn Bornkamp works as a Senior Expert Statistical Methodologist in the Statistical Methodology group at Novartis Pharmaceuticals. He has research and practical experience in the design and analysis of dose-finding studies and the interface of pharmacometrics and statistics. He joined Novartis in 2010 after obtaining a PhD in Statistics from the Dortmund University of Technology in Germany.

Rob Hemmings has been with the Medicines and Healthcare products Regulatory Agency for 16 years and heads the group of medical statisticians and pharmacokineticists. Much of Rob's time is spent educating medical colleagues in the importance and artistry of clinical trial statistics; their use in proof and in obfuscation. Rob is a member of the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) and the chair of the CHMP's Scientific Advice Working Party. These positions, and involvement at the Biostatistics Working Party of CHMP and the EMA's extrapolation and modelling and simulation groups, have presented the opportunity for pursue a particular interest in understanding 'dose' and he has been actively involved in recent EMA initiatives in this area.

Course runs from: 10:00 – 17:00 (registration from 09:30) on Day 1 and
09:00 – 16:30 on Day 2.

Registration Please register online at www.psiweb.org and click on Events; payment now available online. Registration costs (includes lunch and refreshments) PSI are holding a limited number of hotel rooms until the 31st January which will be allocated on a first come first served basis
Fees PSI Members: £495 plus vat Non-members: £570 plus vat (includes PSI membership for 1 year)

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