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Draft Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

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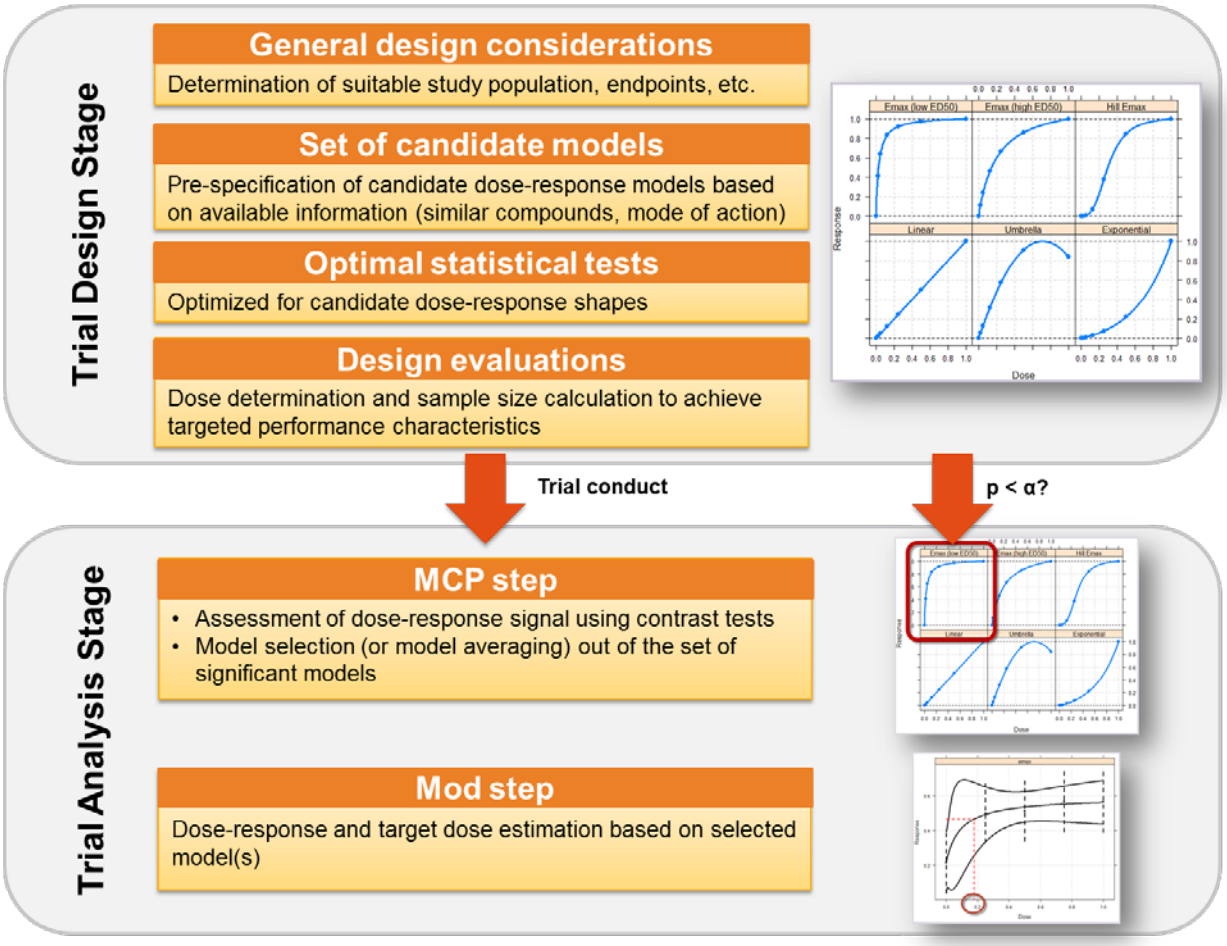
Introduction

Estimating dose-response and selection of a dose for confirmatory Phase III trials and potential market authorisation is among the most difficult elements of the whole development process. Dose finding studies are commonly designed using a small number of doses and a narrow dose-range, often focused on the upper end of the dose response relationship. In recent years there is some shift towards investigating the full dose response relationship and estimating the so-called minimum effective dose (MED). The Applicant presents the MCP-Mod (Multiple Comparison Procedure – Modelling) approach for dose response testing and estimation intended to enable more informative Phase II study designs to provide a more solid basis for all subsequent dose selection strategies and decisions.

The analysis of dose finding studies can be classified into two major strategies: multiple comparison procedures (Bretz et al., 2010) and modeling techniques (Pinheiro et al., 2006a) but none of these alone represent a comprehensive approach. The MCP-Mod approach impacts both the design and the analysis of dose finding studies; see Figure for details. At the trial design stage, a suitable set of candidate models is identified in repeated clinical team discussions, which also impacts decisions on the number of doses, required sample sizes, patient allocations, etc. At the trial analysis stage, dose response is tested using suitable trend tests deduced from the set of candidate models. Once a dose response signal is established, the best model(s) out of the set of pre-specified candidate models is (are) then used for dose response and target dose estimation.



To better illustrate the scenarios in which MCP-Mod is best used, the following is re-produced from the Applicant submission.

In its currently available version, the MCP-Mod methodology is best used in trials satisfying certain characteristics. In-scope:

- Drug development stage: Phase II dose finding studies to support dose selection for Phase III.
- Response: Univariate (efficacy or safety/tolerability) variable. For efficacy, the response variable is ideally predictive to the clinical Phase III efficacy outcome. Could be a binary, count, continuous or time-to-event endpoint. Observations could be cross-sectional (i.e. from a single time point) or longitudinal.
- Dose: Typically, the dose levels utilized in the actual trial are used for the design and analysis. However, more broadly "dose" could be any univariate, continuous, quantitative measurement, as long as an ordering of the measurements is possible and the differences between measurements are interpretable. For example, sometimes it is possible to convert b.i.d. and o.d. regimen to a common univariate scale.
- Number of doses: For the Mod step, a minimum of four distinct doses (including placebo) is required, ideally distributed over the effective range. For the MCP step (e.g. for dose response signal testing or identifying the type of plausible dose response shapes), at least three distinct doses (including placebo) are needed.

A formal technical validation of the software proposed for implementation, i.e. the DoseFinding R package, is outside the scope of this procedure.

The objective of the current submission is to seek qualification of the MCP-Mod approach, as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. The MCP-Mod approach is efficient in the sense that it uses the available data better than traditional pairwise comparisons.

Scientific discussion

It is readily agreed that the design and analysis of clinical trials that investigate dose-response is important and that current practice is repeatedly sub-optimal and inefficient. The Applicant motivates the search for improved methodology based on the consequences of poor design and analysis of dose finding trials on confirmatory development reflecting on the high failure rate in Phase III, need for label changes after approval, etc. Even if difficult to quantify, these arguments have compelling 'face validity' and indeed the same concerns are enshrined in ICH E4 on Dose Response Information to Support Drug Registration. Indeed many of the 'best-practice' approaches described by the authors, for example the inclusion of multiple dose levels and attempting to quantify dose-response curves are explicit in this regulatory document and despite not being widely practiced, are welcomed and regarded as uncontroversial.

It is agreed, in terms of both design and analysis, that these trials are frequently performed less than optimally in terms of the dose range included, the number of doses included and the use of pairwise comparisons (to placebo and between dose levels) that are performed and presented as the basis for determining study success or failure. With this in mind, it is rather obvious that a strategy based on a modelling approach that attempts to quantify a dose-response relationship may offer an improved basis for decision making and it is arguable therefore that to qualify MCP-Mod as an improvement over the commonly used approach is uncontroversial from a regulatory perspective. Nevertheless, the fact

that these sub-optimal approaches persist makes this a relevant topic for a CHMP opinion. It is noted by the Applicant that a number of alternative approaches might be considered, of which MCP-Mod is only one. This Qualification Opinion does not seek to compare between these alternative approaches.

The briefing documentation presented is thorough and clear in relation to the proposed procedure, comprising a 'Statement of Need' to justify the procedure and qualitative and quantitative explanations of the proposed technique within a defined scope. Descriptions and quantification of the performance of the technique are presented through worked examples, simulations and real-life case studies and a series of references from the medical and statistical literature are presented to illustrate applicability, alternative approaches and extensions of the method to other scenarios.

In terms of technical performance, MCP-Mod is underpinned by robust statistical methodology used: (i) to identify and parameterise candidate models, (ii) to construct tests of each dose-response shape and an overall dose-response signal, and (iii) for model selection and model fitting. The proposed method leaves open a number of considerations to the user such as the selection of a nominal significance level for the MCP part, strategy for determining sample size, model selection criteria, strategies for performing trend tests etc. These aspects were discussed with the sponsor along with strategies for selection of dose range, number of doses and spaces of doses that are driven primarily by external factors.

For example, the Applicant recommend certain 'rules-of-thumb' such as 4-7 active doses across a >10-fold dose-range and 3-7 dose-response models / shapes based on achieving a balance of efficiency (too many shapes would decrease efficiency) and risk of bias (from too few shapes that cannot properly describe a dose-response relationship). In terms of sample size the objectives of the study must be reflected noting that sample sizes for detecting dose-response are usually inappropriate for dose-selection and dose-response estimation. More broadly, it is considered that the planning needed to implement MCP-Mod will be beneficial for trial design both in terms of the number of doses and the increase in the range of doses studied, and also in that the consequences and risks of selecting a particular trial objective, design and sample size will be better understood by all stakeholders. For example, Phase II trials may wish to identify evidence for a drug effect, doses that differ from a control, one or more dose-response relationships, or to select optimal dose. The optimal approach and the amount of information required for each objective will differ and this can be illustrated through careful dialogue and simulations during the planning phase. Considering dose in its proper functional form, i.e. as continuous rather than a qualitative, ordered categorical variable also offers advantages in terms of maximising the use of the available information through modelling and by allowing the interpolation of information across doses.

Another interesting part of the procedure relates to the control for multiple comparisons. Designing an experiment that permits conclusions to be drawn with control of false-positive error rate is clearly desirable for the study sponsor. It is mandated by regulators in the confirmatory phase of development, though not in the exploratory phase that is under discussion here, where factors other than strict type I error control may influence decisions regarding future clinical development. The choice of 5% used by the Applicant in their illustrations is arbitrary and could be varied based on the certainty that the Applicant wish to have for their decision-making.

In terms of contrasting the MCP-Mod approach with more commonly used approaches based on pairwise comparisons, the Applicant present data from simulations by the PhRMA ADRS working group (See as annex: Request for CHMP Qualification Opinion) which contrasted MCP-Mod with a Bayesian approach, a non-parametric approach and, of greatest interest for the purpose of this procedure, an ANOVA approach. The performance of each method was characterised in terms of probability to detect dose-response, the probability of identifying and selecting a clinically relevant effect, the bias and error

in terms of selecting a target dose and the precision with which dose-response is estimated. It is concluded that MCP-Mod controls Type I error rate and is less likely (than ANOVA) to identify a clinically relevant dose in the absence of dose-response (flat profile). It is further concluded that under active dose-response profiles the probability of identifying dose-response will be higher, though the probability of identifying a clinically relevant dose will depend on the shape of the dose-response curve. For the simulations investigated MCP-Mod appears to be better, at least on average, than an ANOVA based approach in terms of bias and absolute error. It is widely known of course that biased estimates will, on average, result when selecting a dose based on a particularly impressive pairwise comparison to control because of random highs and this phenomenon is displayed in the simulations, but controlled by MCP-Mod.

Whilst no simulation exercise can be comprehensive, the set of simulations conducted were rather extensive and the parameters investigated were relevant. It was felt however that the simulation exercise was somewhat artificial to the extent that the most common approach to the design and analysis of Phase II dose-exploratory trials were not included. Additional investigations were requested during the course of the procedure to compare:

a. an optimised ANOVA approach, without restriction on the number of doses selected, based on a fixed sample size (n=150, 250) versus an optimised MCP-Mod approach based on the same fixed sample size. The ANCOVA approach was 'optimised' based on two designs with 4 and 8 equally spaced active doses and an allocation of patients to minimise the variance for the pairwise comparisons of active doses versus placebo.

b. a commonly applied ANOVA approach, with restriction to 2 active dose levels that varied for each different simulation exercise, based on a fixed sample size (n=150, 250) versus an MCP-Mod approach based on the same fixed sample size but optimal number of dose levels.

The main objective of the ANOVA approaches in these additional simulations was to identify a significant pairwise comparison. The Applicant presented results of these simulations and concluded that the simulations provide evidence that MCP-Mod is a robust methodology for dose response modeling (See as annex: Response to Questions). They compared MCP-Mod with a total of 5 ANOVA approaches. While some of the ANOVA approaches occasionally give comparable or even slightly better performance, no single ANOVA approach demonstrates a robust performance across all metrics and scenarios as compared to MCP-Mod. For example, some designs based on ANOVA approach perform well across all metrics if the true dose response model is linear. If the true dose response model follows an Emax shape, however, the same approach is always among the worst methods in the dose-response and dose estimation metrics. In general the performance of the ANOVA approaches is sensitive to the underlying scenario and the employed design, in particular when the used number of dose levels is small. When the number of dose levels is larger, the performance of the ANOVA approaches with respect to dose response estimation and power deteriorates. However, including a sufficiently large number of doses in a clinical dose finding study is important to reliably estimate dose response not only for the main efficacy endpoint (as studied in this simulations), but also important safety or tolerability variables, which will also influence dose selection for Phase II. Performance of MCP-Mod is demonstrably more consistent which is regarded as critical for the experimental situations in the scope of this Qualification Opinion, i.e. where there is model uncertainty.

Having completed the MCP-Mod procedure the user must still determine how to incorporate information to their decision making, along with all other factors. It is agreed with the Applicant that model uncertainty will remain after completing Phase II and that the model describing dose response may be updated as further information comes to light. In addition, multiple models may be selected for further consideration and the method is open to a model averaging approaches if the user considers

this desirable. A further advantage compared to an ANOVA approach is the possibility to more reliably interpolate between doses, and while extrapolation is not recommended by the Applicant, even this may be more reliable than with common approaches.

Further technical development may focus on investigation of criteria for suitable model selection and construction of robust design and model selection ('optimal design'). In terms of application to different experimental situations updates might consider modelling based on exposure-response relationships and it may be considered how to update the method to investigate relationships for long-acting biologics where there is no steady state and how to investigate simultaneously dose-response relationships for efficacy and safety.

CHMP qualification opinion

It is concluded that the MCP-Mod approach can be qualified as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. The MCP-Mod approach is efficient in the sense that it uses the available data better than the commonly applied pairwise comparisons. Whilst the performance of MCP-Mod against other model-based approaches has not been appraised, the anticipated benefits of a modeling approach are demonstrated by the simulations performed, and a decision to employ the methodological approach will promote better trial designs incorporating a wider dose range and increased number of dose levels. In situations where there is uncertainty around the shape of the dose-response curve, the deficiencies with commonly used approaches that include few dose levels with pairwise comparisons to a placebo are highlighted.

Statistical and modelling expertise are needed to implement the approach and the user will benefit from experience when making decisions on the input parameters (e.g. candidate models, sample size, technical approach for model selection etc.) and in terms of inference. Properly implemented however, the benefits include not only efficient data collection and more precise answers to important questions to inform decision making but should also serve to enhance discussions with stakeholders in advance of the trial comparing different strategies and explaining risks and limitations of potential designs. The further developments proposed are welcome.

Annexes

- Applicant submission – Request for CHMP Qualification Opinion
- Applicant submission – Response to Questions raised by the qualification team
- Applicant submission – Discussion Meeting for MCP-Mod Qualification Opinion Request (Slides)