What is needed are Phase II dose finding studies that more accurately predict the appropriate therapeutic window for Phase III trial success. Multiple Comparison Procedure – Modelling (MCP-Mod) is a powerful statistical tool that greatly improves the design and analysis of dose finding studies for more accuracy on the targeted dose range. It is deemed “fit-for-purpose” by the FDA after an exhaustive qualification analysis in 2015(2).

Combined with the adaptive study design, automatic simulation and modelling capabilities of ICON’s ADDPLAN® neo, adaptive MCP-Mod may significantly enhance drug development efficacy. ADDPLAN®’s adaptive MCP-Mod designs help to reduce costs in futile developments programs, while allowing predictive insight in successful development programs, actively supporting early development preparations leading to shortened timelines. It helps skilled development staff to determine appropriate dose levels to improve dose-finding for Phase III, while taking uncertainties on the underlying dose-response during planning and analysis of the study into account.

Adaptive Analysis

MCP-Mod is a two-step approach for analysing Phase II dose-finding data, targeting two of the main Phase II objectives:

1. Establish that the drug works
2. Determine appropriate doses for Phase III testing

While these objectives could be gained using other classical methods -- such as separate classical multiple comparison procedures or simple dose-response modelling -- MCP-Mod provides the added benefit of incorporating the existing uncertainty on the underlying dose-response relation into the study design and analysis method. This results in higher efficiency and greater robustness of the analysis, as acknowledged by the EMA, which qualified MCP-Mod as an “efficient statistical methodology for the model-based design and analysis of dose-finding studies under model uncertainty in 2014.

Using standard pairwise comparison procedures for dose-finding, the number of study doses is typically small and limited to the upper end of the admissible dose range. Any additional study dose would cost additional patients, while increasing a penalty for “multiplicity”. Data is not shared between doses, such that patients allocated to ineffective doses do not fully contribute to the learning, and could hence be regarded as being wasted. To increase success probability for pairwise comparisons, it is not required to pick the most promising dose to compare to the placebo. Pairwise comparisons are designed for “confirming” instead of “learning”. Standard designs for pairwise comparison procedures often lead to inefficient patient allocation for learning on the dose-response relationship, potentially leading to failed dose-finding studies.

Modelling differs from pairwise comparison procedures in how the data are analysed. A predefined curve is fitted through the observed data, providing estimates of the response for any dose within the examined range with some quantified uncertainty. Observations on ineffective doses are not wasted with the use of modelling, but contribute to the fitted curve, thereby increasing certainty on the response at any dose level within the examined range. Data between doses are shared via the predefined dose-response model. However, any predefined dose-response model is a simplified description of the true unknown dose-response relation and could hence provide misleading information, leading to biased estimates of doses and effects.
MCP-Mod addresses these limitations using a hybrid approach. A set of dose-response curve assumptions are defined during the design process, based on team discussions, including pharmacokinetic and pharmacodynamic modelling, other clinical and non-clinical experiences with compounds having a similar mechanism of action in the targeted indication and any other information which could support the determination of likely dose-response relations. These “candidate models” then define an optimal statistical test for the existence of a drug-related effect. The underlying statistical optimization routine for the determination of the MCP-Mod test results provides an intuitive and appealing way to combine data in two steps:

1. Data from dose levels with assumed similar responses are pooled: (e.g. extremely low ineffective doses support the determination of the “Placebo effect”).
2. The pooled data are weighted; the higher the uncertainty at any dose level, the lower its weight; (e.g. the more patients are on a dose, the lower the uncertainty on the dose, the higher the weight in the test)

Finally, data from all dose levels are combined to establish that the drug works. Inclusion of sub-therapeutic dose levels will not reduce the power of the MCP-Mod test, as these doses will contribute to the information on the effect at “ineffective” doses. In addition, the number of dose levels does not lead to a multiplicity problem in MCP-Mod. This tool allows more dose-levels across more-widely spaced dose ranges to be studied without significant loss in power during Phase II.

The selection of multiple “candidate models” serves in addition as a guide for the selection of study doses and randomization rates for most efficient “dose-response modelling,” using optimal design theory (Fedorov and Leonov).

In its detailed statistical and pharmacometric reviews of MCD-Mod, the FDA found that the methodology facilitates more informative Phase II trial design by encouraging:

- Testing three or more active and well-separated doses
- Investigating doses on the ascending part of the dose-response curve
- Interpolation within data points and extrapolation beyond data points to select dose(s) for pivotal trial(s)

The agency also encouraged developing MCP-Mod beyond its current applications in univariate response studies to include multivariate responses for safety and efficacy, and exposure response.

Adaptive Design

By itself, MCP-Mod is technically considered an adaptive analysis tool rather than an adaptive design element, as the MCP drives no design change (e.g. early stop, adaptive randomization), but only serves as a filter for the models to be fitted. However, adaptive design features are in line with model-based dose-finding and will further increase the utility of MCP-Mod.

One adaptive feature is adding doses for further exploration after an interim analysis on a subset of patients. For example, a dose-response plateau might suggest that all examined doses in the first study stage were higher than necessary to achieve a clinically beneficial response. What looks nice for the success of the drug is problematic for the selection of Phase III doses: How far could you decrease the dose, without leaving the plateau? Adding lower doses after an interim analysis could help to establish the lower end of the dose-response curve and identify the minimum effective dose. Other adaptations could allow early study closure if it becomes evident that a targeted benefit may not be reached with the drug.

As with any adaptive trial design, all potential adaptive MCP-Mod design changes should be specified and examined in advance to ensure statistical validity. ADDPLAN® Neo enables this complex modelling by automating iterative, integrated simulation of a range of adaptive design features. This tool not only makes skilled staff more productive by minimising the need for manual input, it allows testing of a much broader range of adaptive designs within various response scenarios. The results are trial designs optimised to provide the required information with high probability in the most efficient way. Interim simulations based on the accumulating data allow to predict likely study results early – allowing accelerated development preparations for a sooner market entry.

To learn how to enhance your dose ranging studies using MCP-Mod and adaptive design, contact our adaptive experts for counsel.
References

