AptivSolutions®

Accelerating the Possibilities

ADDPLAN® DF

AN ADVANCED TOOL FOR OPTIMIZING DOSE SELECTION IN EXPLORATORY DRUG DEVELOPMENT

An Aptiv Solutions White Paper

EXECUTIVE SUMMARY

Driven by high attrition rates in Phase 2 and Phase 3[1], the pharmaceutical industry has set itself the major objective of dramatically improving R&D efficiency and productivity. A key determinant of this high level of failure is poor dose selection in exploratory development. Two key processes underpin Pharma's ability to reduce product attrition. The first is the accurate assessment of Proof of Concept and the second is robust determination of the target dose to be taken forward into confirmatory Phase 3 trials.

Determining an optimal dose level for a drug and characterizing its dose response relationship are key objectives for any new medicine. Drug developers are concerned with safety and tolerability when the dose is too high and inadequate efficacy if the dose is too low. Accurately defining this risk/benefit ratio is a key step in the clinical development process and failure to achieve this can lead to patients missing out on ground-breaking medications and the pharmaceutical industry failing to achieve key product approvals. Thus, selection of the dose to be taken forward into confirmatory studies is a critical decision which has important ethical and financial consequences.[2]

Proof of Concept and dose selection can be achieved through use of a Multiple Comparison Procedure and a modeling approach. When used alone both techniques have limitations. The Multiple Comparison Procedure can be used to determine Proof of Concept using few assumptions on the underlying dose-response relationship and taking the dose as a qualitative factor. In the modeling approach, assumptions on functional relationships are used for estimating the target dose. The dose is taken as a quantitative factor allowing greater flexibility and accuracy in the dose selection process.[3]

More recently a hybrid methodology (MCP-Mod)[4] has been described that combines the approaches of the Multiple Comparison Procedure (MCP) with modeling (Mod) enabling a much more robust determination of the optimal dose for a drug, and its dose-response relationship. In collaboration with the authors of the hybrid methodology, Aptiv Solutions has developed a fully-validated software package ADDPLAN® DF, that implements the MCP-Mod dose-finding methodology. This methodology will enable drug developers to determine more accurately the effective dose to take forward into confirmatory Phase 3 studies.

THE CRITICAL IMPORTANCE OF DOSE FINDING TRIALS

The pharmaceutical industry is facing unprecedented challenges to increase R&D efficiency and effectiveness. The average cost to bring a new molecular entity to market is now estimated to be approximately $1.8 billion.[1] Both the FDA and Industry acknowledge that the processes used to define dose and dosing regimen in Phase 2 are not robust however, are a major contributing factor to late phase attrition. Thus, the consequences of improving dose selection in Phase 2 should be measured in terms of the success rate of subsequent confirmatory trials. In this case, the business value of improving dose selection can amount to billions of dollars across a product portfolio and perhaps more importantly, deliver an increased number of novel medicines to patients.

The objectives of Phase 2 trials have been succinctly described:[5]

- Detect dose response and establish Proof of Concept: evaluate if there is evidence of activity associated with the drug, represented by a change in clinical response resulting from a change in dose
- Identify clinical relevance: if Proof of Concept is established, determine if a pre-defined clinically relevant response (compared to placebo) can be obtained within the observed dose range
- Estimate the dose-response profile within the observed dose range
- Select the target dose: when the previous goal is met, select the target dose to be studied in confirmatory trials

Studying these objectives efficiently in a Phase 2 trial is a major challenge and one that can be significantly improved through the development and application of novel dose-finding methodologies. The criticality of this phase of development cannot be understated as it directly impacts the probability of success in Phase 3 trials.

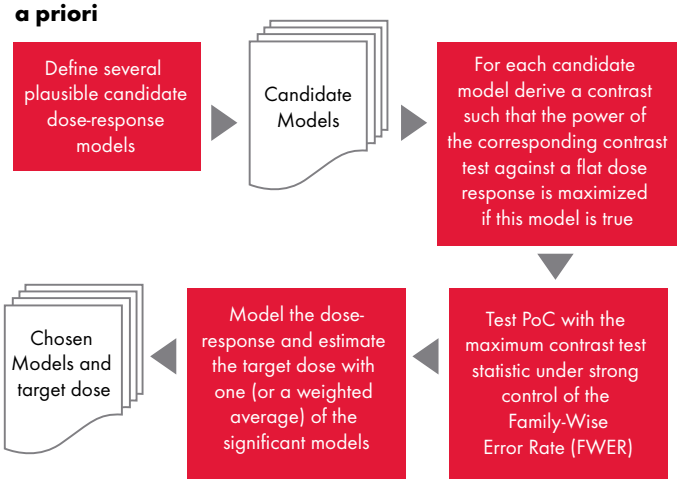
MCP-MOD: AN INNOVATIVE APPROACH TO DOSE-FINDING

In studies with multiple doses, the traditional approach to providing the evidence of activity associated with the drug is to use a Multiple Comparison Procedure. This procedure controls type I error, but is generally not suited for dose-estimation, as the dose for the Phase 3 trial would typically be selected from a small number of examined dose levels. This might result in doses being too low for proving efficacy, or too high, increasing the probability of unwanted safety events. Increasing the number of dose levels in the trial will have a direct impact on the total sample size, as the sample size has to be adjusted to account for increased multiple testing. On the other hand, dose-response modelling provides a more flexible approach to dose-estimation as it allows the choice of a dose anywhere within the entire continuous range from the minimum to the maximum administered dose. The choice of the working model can have a significant impact on dose estimation and uncertainty about the appropriate working model might lead to incorrect decisions about dose selection for Phase 3.

A combination of the Multiple Comparison Procedure and the modelling approach is called MCP-Mod.[4] The steps for defining the MCP-Mod methodology are as follows and described further in the flow chart below:

- Define several plausible candidate dose-response models
- For each candidate model, derive an optimal contrast against a flat dose response
- Test Proof of Concept
- Model dose-response and estimate the target dose with one (or a weighted average) of the significant models

MCP-MOD APPROACH



The MCP-Mod approach circumvents the use of pairwise comparisons for proving a dose-response effect. Optimal contrasts based on assumptions of likely dose-response shapes provide weighted scores for the different dose-levels. This allows the determination of true dose-response effects with a higher probability, compared to pairwise comparisons. Moreover, model-based optimal contrasts do not suffer from multiplicity issues. Dose-levels can therefore be added to test Proof of Concept without an additional penalty for multiplicity. These additional dose-levels then support the detection of a reliable working model for the dose-estimation.

MCP-Mod is adaptive in analysis. Based on the optimized contrast tests, a set of models will be fitted to the data and a working model is selected for estimating the targeted dose. Adaptive modelling accounts in this way for model uncertainty in dose estimation. Although relatively new, the MCP-Mod approach has already been implemented in a range of studies by large pharmaceutical companies and there is growing interest in applying this novel approach to dose-finding more widely.

ADDPLAN® DF has been developed to enable easy deployment of the MCP-Mod methodology and address the growing demand for designing and conducting Phase 2 studies that accurately determine true dose response.

ADDPLAN® DF - A TOOL TO DESIGN, SIMULATE AND ANALYZE INNOVATIVE DOSE-FINDING STUDIES

Using the **design engine** of ADDPLAN® DF, the optimal allocation rates for a robust dose-estimation can be calculated. Weighted sets of dose-response assumptions can be considered in the design engine to address the uncertainty about the true dose-response relationship when optimizing the allocation rates with respect to the generalized variance of parameter estimates (D-optimality), the asymptotic variance of dose-estimates (TD-optimality) or a combination of both criteria (D&TD-optimality).

The required sample size for rejecting a "no-dose-response-effect" can be calculated with the computed allocation rates. Model-based contrasts optimize the power of the statistical testing procedure under the assumption of the specified candidate dose-response shapes. Different scenarios on the true dose-response relationship can be taken into account in the sample size calculation in order to claim the existence of a dose-response effect with high probability.

The **simulation engine** of ADDPLAN® DF allows the verification of characteristics of the chosen design. The reliability of the dose-estimates can be verified by simulating dose-finding trials with the considered designs, different working model selection rules, as well as sets of contrasts and scenarios for the underlying true dose-response. Verifying the study design with the help of simulations is crucial for the final design selection. Ineffective designs and assumptions on models can be excluded by analyzing the simulation results. This will provide the evidence that an effective and efficient dose-finding design has been chosen.

The modeling facilities of ADDPLAN® DF allow the fitting of typical dose response models to the data using least squares techniques, Bootstrapping and Bayesian approaches. The doses delivering a targeted effect above placebo can be estimated and the dose-response can be characterized over the whole dose-range.

The MCP-Mod approach combines model-based multiple comparison techniques and modeling in a single system. ADDPLAN® DF provides parameter and dose estimates for all significant models, and the target dose can be selected based on the computed decision criterion for the model selection.

The whole design, simulation and analysis functionality of ADDPLAN® DF is available for normal, binary and count data.

ASTHMA TRIAL EXAMPLE[2]

The primary objective of this study was the selection of a dose for a Phase 3 trial on an anti-asthmatic drug. Four active dose levels and placebo were considered for administration in the Phase 2 trial. A placebo effect of 60mL and a maximum increase over placebo of 280 mL of the change from baseline for the forced expiratory volume was assumed. The clinically relevant benefit over placebo was set at 200 mL and 5 different dose-response shapes where taken into account for addressing the uncertainty on the true underlying dose-response relationship in the design optimization step (Figure 1).

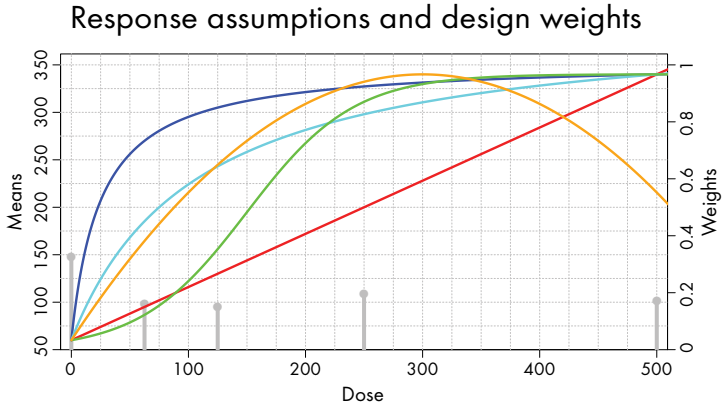


FIGURE 1: Candidate shapes and allocation weights

With the computed allocation rates and the selected dose-response shapes, the required sample size for Proof of Concept can be calculated based on different contrast types. Taking information on likely dose response-shapes into account reduces the required sample size to establish Proof of Concept. The model based contrasts need a total of 149 subjects for the assumed allocation rates. Williams-contrasts use monotonicity assumptions on the dose-response, and the sample size is slightly increased to 166. Pairwise comparisons against control (Dunnett-contrasts) do not use any assumptions on the dose-response and require the largest sample size to establish Proof of Concept (Table 1).

Contrasts	Dose					Total
	0.0	62.5	125	250	500	
Model-based	48	24	22	29	26	149
Dunnett	62	31	28	37	33	191
Williams	54	27	25	32	28	166

TABLE 1: Sample size for 90% power for different contrast tests

Simulation of the design under various scenarios provides insight into the working model selection for dose estimation. The impact of model mis-specifications can be easily studied via simulations. Figure 2 displays the effect of model selection criteria in different scenarios for the given design and candidate models.

The blue line represents the mean dose estimate of 10,000 simulations. The Akaike information criterion (AIC) penalizes additional parameters in the models. In the example provided, the model selection procedure tends to select the linear dose-response shape which leads in both scenarios to an overestimation of the Minimum Effective Dose (left-hand side). The criterion wAIC estimates the dose based on a weighted average of the dose-estimates of different models. These weights are calculated according to the AIC.[3] The model with the maximum contrast will be selected using the maxT criterion (maximum t-statistic).

The design and simulation process can be repeated to take these findings into account. Additional models can be added to the candidate set of models, assumptions on the true dose-response can be included in the simulation, or the allocation rates and sample sizes might be changed and additional dose-levels included, to examine the impact on the statistical power of Proof of Concept, and to increase the accuracy of dose estimation. ADDPLAN® DF provides the functionality to assess these different design, simulation and analysis options for dose-finding trials in a clear and validated environment.

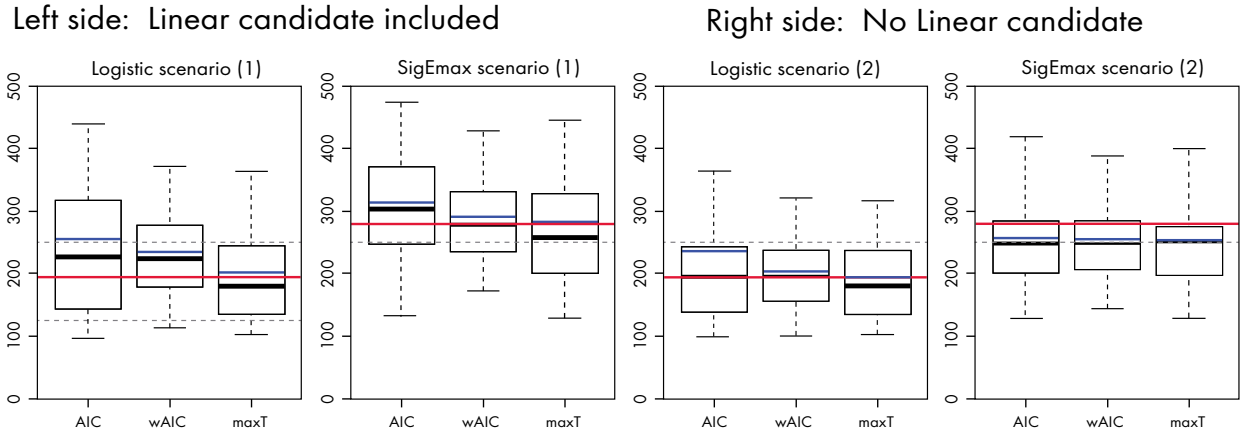


FIGURE 2: Dose-estimates and dependence on model selection

CONCLUSION

This white paper discusses the important role that MCP-Mod has to play in dose selection and describes the embodiment of this methodology in a fully validated software tool called ADDPLAN® DF. The software has been designed to address the critical need for establishing Proof of Concept and determining the optimum target dose to select for Phase 3 trials. This tool will enable drug developers to remove a number of the uncertainties inherent in Phase 2 dose-finding trials and improve critical decisions on dose-selection, which will directly impact the probability of success in Phase 3.

The Aptiv Solutions Innovation Center is working closely with international academic and industrial methodology specialists to further enhance and extend innovative and adaptive approaches to dose-finding. Future versions of ADDPLAN® DF will include adaptive design components for Multiple Comparison Procedures, Modeling and MCP-Mod, as well as standard approaches like 3+3 dose escalation and continuous reassessment methods (CRM). These will allow simulation of the adaptive aspects of trial design and demonstrate the benefits of this approach compared to standard fixed design and analysis techniques.

ABOUT THE AUTHORS

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Parvin Fardipour joined Aptiv Solutions in 2013 as Vice President, Adaptive Clinical Trials. Parvin works with clients to optimize their drug/device development process and assess opportunities to utilize adaptive design. Parvin provides consultancy on utilizing adaptive design and execution and collaborates with regulatory and industry leaders to produce best practices and procedures. Parvin has over 23 years of experience in the development of drugs spanning several therapeutic areas, with major emphasis in adaptive trial design and execution. Parvin has held several senior positions in a number of pharmaceutical companies including Wyeth, GlaxoSmithKline, Sandoz, Pfizer and more recently at Theorem. Parvin received her BSc in Mathematics from King's College London, UK and her PhD in Mathematical Modeling and Simulation from City University, London, UK. Parvin has authored many publications on the planning and execution of adaptive clinical trials, data monitoring committees and good practices for adaptive clinical trials.

DR. ANDY GRIEVE

Professor Andy Grieve joined Aptiv Solutions in 2010 and is currently Senior Vice President for Clinical Trials Methodology in the Aptiv Solutions Innovation Center. Prior to joining Aptiv Solutions, Andy spent four years as Professor of Medical Statistics at King's College London and prior to that he spent over 30 years in the pharmaceutical industry. Between 1975 and 1989 he was a statistician working for CIBA-GEIGY Pharmaceuticals both in the UK and Switzerland. From 1989 to 1994 he was the head of ICI Pharmaceuticals pre-clinical statistics group. From 1995 to 2006 he worked at Pfizer, ultimately becoming Executive Director and World-Wide Head of the Statistical Research and Consultancy Centre at Pfizer's research facility in Sandwich, UK.

Andy is a Fellow and Chartered Statistician of the Royal Statistical Society, of which he is a former President, a Fellow of the American Statistical Association and a member of Statisticians in the Pharmaceutical Industry of which he is a past-Chairman and founder-member. His research has been primarily concerned with the application of statistics to the pharmaceutical industry, and in particular the implementation of Bayesian ideas and techniques. Latterly he has been involved in the development and implementation of Bayesian Adaptive Designs. He has published over 120 articles and is the author of a book for non-statisticians involved in clinical trials: FAQs on Statistics in Clinical Trials, Brookwood Medical Publications, 1998. Andy received his MSc in Statistics from Southampton University in the UK in 1975, a PhD in Statistics from Nottingham University in the UK in 1992 and an Honorary Doctorate from Kingston University for Services to Statistics in 2006.

DR. TOBIAS MIELKE

Tobias Mielke joined Aptiv Solutions in 2012 and works as a statistical consultant in the Innovation Center. His main focus is on dose-finding and the development of statistical methodology and software for these types of trials. Before joining Aptiv Solutions, Tobias served as a Research Fellow at the Institute of Statistics at the University of Magdeburg. He was actively involved in projects on the development of optimal designs for clinical studies and on multivariate equivalence and non-inferiority testing. Tobias has 5 years of experience in statistical consulting. He holds a Master in Mathematics (2008) from the University of Dresden. Tobias received his PhD in Mathematical Statistics (2012) at the University of Magdeburg for his work on optimal experimental designs for population pharmacokinetic studies.

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