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A two-stage dose-response adaptive design method for establishing a Proof of Concept

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In exploratory clinical trials of drug development, searching for the true dose-response curve of a treatment agent is a challenging task due to ethnical and logistic reasons. Often using a full spectrum of doses is not initially feasible in a trial. One solution to such a problem is a two-stage dose-response adaptive design where both adding and dropping treatment arms are possible between the stages. By implementing such a procedure, one must establish evidence of dose-response or a Proof of Concept (PoC) first, then, determine a best dose-response model and an optimal treatment dose while preserving the family-wise error rate (FWER). To accommodate these requirements, we propose a method of extending the Multiple Comparison Procedures-Modeling Approach (MCP-Mod) originally developed by Bretz, et al. (2005) into a two-stage design. The MCP-Mod method combines both modeling approaches 4 and multiple comparison procedures in establishing a PoC. Our research focuses on the first objective of the MCP-Mod, which aims to establish a 'global' PoC in the two-stage adaptive design. To start our procedure, we must first prespecify the candidate dose-response models and the potential levels of the doses. A placebo (no active drug) must be included. In the first stage, the placebo group and a subset of the prespecified dose levels are used. In the second stage, the placebo and a set of doses are selected according to a pre-specified Adding and/or Dropping Treatment Adaptation Rule (ADTAR). The function defining the ADTAR maps the set of all the possible preliminary PoC results in Stage 1 to a set of adaptation choices in Stage 2. In both stages, we test preliminary hypotheses to establish whether or not dose-response relationships exist. In each stage, data are assumed to be normal and independent both within and across groups. Hence, the model-associated multiple contrast test statistics follow a multivariate t-distribution under the null hypothesis of no dose-response. Note that the model-associated contrast test statistics uses optimal contrasts which are obtained by maximizing the non-centrality parameter of the multivariate t-distribution. With the optimal contrasts, power of the null hypothesis tests is maximized. Then the correlation matrix in each multivariate t-distribution is estimated using optimal contrast vectors. In addition, weights corresponding to the dose adaptation choices are computed via the ADTAR function in order to adjust contrast test statistics in Stage 2. The weights are derived by characterizing the missing data mechanism in Stage 2 caused by adding and/or dropping dose groups as Missing At Random (MAR). The assumption of MAR allows us to use a weighted estimator for a mean response of each group. Note that the estimates of the correlation matrices are constrained by the optimal contrasts and the weights. The doses in Stage 1 and the adaptation choices in Stage 2 should be prespecified so that the estimated correlation matrices in both stages are positive definite. The preliminary test results of both stages are combined to establish a global PoC by use of a Conditional Error Function (CEF). The CEF is Bauer and Kiser's procedure (1999), a common method to combine p-values of adaptive two-stage designs. The CEF embeds a function of p-values called a combination test. Among many function forms proposed for combining the tests across the two stages, we chose the Fisher's test for combining p-values as the combination test. This test assumes that p-values are stochastically greater or equal to the standard uniform distribution. One advantage of using Fisher's test is its flexibility in allowing sample sizes to adaptively vary across the stages of the trial. Hence, a pre-specified decision rule utilizes the p-values associated with the multiple

contrast statistics obtained from the two stages and the CEF. Using simulations based on 10,000 trials, the ADTAR approach is evaluated by assessing the probability of detecting a dose-response curve, Proof of Activity (PoA), under three different response shapes: Emax, quadratic, and logistic curves; and four different total sample sizes: 80, 200, 400, and 600. In both stages, equal sample sizes per group are assumed. Furthermore, the total sample size in Stage 1 is the same as the total sample size in Stage 2. In order to evaluate the FWER, we also use a constant model or no dose-response data. The ADTAR approach is compared to a one-stage design and four combinations of possible Stage 2 designs which were used in a fixed rather than adaptive manner. In the fixed studies, we first start with a design which is identical to Stage 1 of ADTAR. Each of the four fixed studies then uses a previously determined design which is identical to one of the adaptive choices of Stage 2 in ADTAR. Stage 1 and Stage 2 designs in the fixed studies are chosen independently of each other. Comparisons between ADTAR and each of the fixed two-stage studies as well as the one-stage design yielded similar simulation results for all sample sizes considered. All of the designs including ADTAR preserved the FWER roughly at a 5% level under the constant dose-response in sample sizes. For the Emax dose-response, the PoA value of the ADTAR approach, the one-stage design, and the maximum value of the fixed two-stage studies were similar. However, for the quadratic dose-response, the ADTAR approach showed PoA values between the maximum and minimum PoA values of the fixed two-stage studies while the one-stage design resulted in lower PoA values than the minimum PoA values of the fixed two-stage studies. For the logistic dose-response, both ADTAR approach and one-stage design showed higher PoA values than the maximum PoA values of the fixed two-stage studies. In conclusion, the ADTAR approach performed relatively well and showed robust global PoA with less variability compared to both one-stage and fixed two-stage studies. Considering the flexibility of dose choices within one protocol, the ADTAR approach seemed advantageous in establishing a PoC. The established global PoC serves as the first step prior to determining a best dose-response curve and an optimal dose which will be used in the confirmatory studies of clinical development on a treatment agent.