

Title: Applying Optimal Design Techniques to a Drug-Drug Interaction Study for a Triple Combination Therapy

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Objectives Novartis is developing a new triple fixed-dose combination product. As part of the clinical pharmacology program, pharmacokinetic (PK) drug-drug interaction (DDI) potential must be examined at the highest triple combination dose. The current proposal is to develop a three way combination, in a clinical trial involving arms with combinations of drugs A-B, A-C, B-C, and A-B-C. The goal of the accompanying DDI study is to assess the difference in exposure of components A, B and C in the double and triple combinations. The study must:

- Use a logistically feasible design for patients in an out-patient setting.
- Determine differences in exposure and maximum concentration between components in triple and double combinations.
- Apply Schuirmann's two one-sided tests for assessing drug-drug interaction.
- Calculate number of patients per treatment arm to adequately power the study.

This paper describes our design process of a DDI clinical trial meeting the complex medical, logistical and financial constraints associated with developing this triple dose combination.

Our main objectives in this trial design process are twofold. First, for ethical reasons, we must ensure that our new design is fully informed by our current and extensive knowledge of the pharmacokinetics of drugs A, B, and C in double combination [1,2]. Second, we must use constrained optimization to capture the practical clinical constraints of visit times, dosing schedules, number of treatment arms, number of samples per individual, and overall cost of incorporating a triple combination DDI study into a pivotal multifactorial clinical trial [3]. In particular, for our therapeutic area and this multiple dose study, patients are necessary instead of healthy volunteers to avoid dangerous long term exposure to high dose regimens. Unfortunately, use of patients in an out-patient setting limits the practicality of traditional dense sampling designs.

To accomplish these two objectives, we will conduct this confirmatory study using a population PK analysis, with the model identified prospectively based on our earlier clinical trial data sets. Starting with a nominal estimate of PK model structure and parameters from these earlier trials, we pursue a locally optimized trial design, applying the D-optimality criterion while incorporating our practical clinical constraints [4Our goal is to power the trial design so that if the actual ratio of geometric means of exposure is unity (no DDI), then we have an 80% probability that the 90% confidence interval for this ratio is contained entirely in the interval (0.56,1.8). This is the classic Schuirmann's two one-sided tests with size of 0.1. Our choice of the (0.56,1.8) interval is motivated by earlier discussions with the health authorities. Each exposure of component A, B and C will be compared using NONMEM in triple and double combinations separately, with no multiple comparisons correction.

Methods: The trial design methodology followed four basic steps: 1) use the model parameter estimates (fixed and random effects) for drug (A or B or C) in dual-combination (AB, BC, CA).; 2) use these nominal modes to derive an optimal sparse sampling time strategy; 3) develop a statistical model for testing DDI; and 4) scale trial size to achieve desired power.

Incorporating early knowledge, our PK models are all two-compartment linear models with first order absorption parameterized in terms of K_A and apparent CL , V_2 , Q , and V_3 . Dependence on whether the drug was used alone or in combination, inter-subject random effects, and residual variability are modeled PK under combination dosing is coded with a categorical variable. Ideally, from the three double-combinations, six PK models would be developed. Unfortunately, only single dose data was available for one of the double combinations. Four PK models, based on NONMEM analysis of two earlier double-combination DDI trials, are applied.

Earlier PK studies provide the nominal models for the DDI study. Using the sets of nominal PK parameters for each of the three compounds, we use the POPT software package to design D-optimal sampling strategies, which choose sampling times to maximize the determinant of the expected Fisher information matrix [5]. POPT

determines a sampling design given trial size and model parameters (together with inter- and intra-subject variance parameters). Also, given a trial design, POPT provides the Fisher information matrix and corresponding error covariance matrix of estimates of model parameter that would be obtained in trials using the trial design.

Three patient-grouping strategies were considered, including a traditional dense design; a design with early, middle, and late measurement groups; and a design in which each patient is sampled only twice. A number of different group balances and interval constraints were considered along with the sample timing optimization. After optimization with POPT, the sampling times were adjusted slightly to simplify design implementation, at no cost in overall power. To complete the trial design, we choose the number of subjects per treatment arm, N. We use the error variance for clearance from the diagonal of the error covariance matrix, taken from the inverse of the Fisher information matrix generated by POPT. The minimum number of subjects per treatment arm is then chosen to meet our 80% power requirement.

Results: Figure 1 and Table 1 show the power as a function of study size for the case of two samples per subject. For each treatment arm, 5 subjects would be assigned to each one of eight groups. With time=0 the time of daily dose, the sampling time (in hours) for each of the eight groups would be [0, 0.5], [0.5, 1], [1, 1.5], [2, 2.5], [3, 3.5], [5, 5.5], [8, 8.5], and [11.5, 12]. Each patient is minimally inconvenienced, since the waiting time between blood samples is only ½ hour. This would allow completion of the DDI study as part of the larger clinical trial, instead of requiring a separate facility and protocol. Similar results are developed for the other two candidate designs.

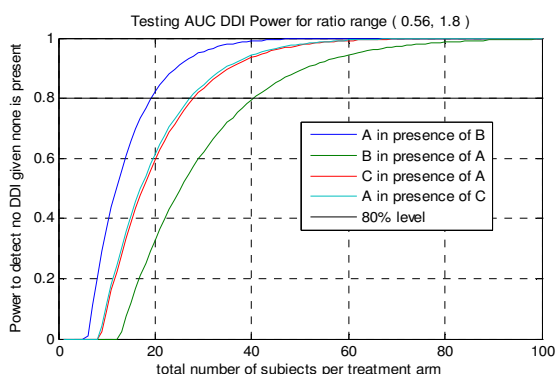


Figure 1: The tradeoff between trial size and power to detect no DDI.

(Q.D dosing with sampling at steady state)	POPT optimized sampling times (hr)	Sample Size
8 elementary designs, each with same number of patients:	Time=0 is time of daily dose	minimum 40 subjects/treatment arm for 80% power
Each patient is measured twice, with a ½ hour separation between samples	8 groups with sampling times: [0, 0.5] [0.5, 1] [1, 1.5] [2, 2.5]	
Total spread of measurements in trial is from 0-12 hours from dose time	[3, 3.5] [5, 5.5] [8, 8.5] [11.5, 12]	80 total samples per treatment arm

Table 1: Optimized sampling schedule for a design with two samples per subject

Conclusions: With the use of optimization, we have formulated several candidate designs for a clinical trial meeting the complex constraints of a DDI study for a triple combination therapy. The design process incorporates our prior knowledge while allowing a tradeoff between practical considerations of clinical implementation, subject recruitment and cost, while maintaining safety. These candidate designs have been presented to the clinical team for further discussion and reduction to practice as part of a pivotal clinical trial.

References:

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