PROSPECTIVE APPLICATION OF A MULTIVARIATE POPULATION OPTIMAL DESIGN TO DETERMINE PARENT AND METABOLITE PHARMACOKINETIC SAMPLING TIMES IN A PHASE II STUDY

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SETTING THE SCENE

- A sparse pharmacokinetic sampling strategy is often applied to studies in Phase II due to logistical and practical considerations in study implementation requiring that a minimum number of samples are taken per patient. Practical factors, such as range of doses being studied, timing of samples during the day, potential for BQL concentrations, numbers of concurrent procedures have to be included.
- It is imperative that enough samples are taken and that these samples are at optimal times. This will ensure the data collected are informative for identifying pharmacokinetic parameters in model development.
- A number of statistical criteria for model oriented experiments, which maximize the information content of the data, are available. Criteria, based on the Fisher information matrix, whose inverse according to the Rao-Cramer inequality is the lower bound of the variance-covariance matrix of any unbiased estimator of the parameters, have previously been developed for population univariate and recently multivariate responses [1, 2]. There are very few, mainly retrospective, applications of population multivariate designs. We made use of a software program that was designed specifically to implement these methods [3].

OBJECTIVES

- Propose a sparse pharmacokinetic sampling strategy for incorporation into a dose ranging Phase IIb study based upon a previously developed population pharmacokinetic model that allowed simultaneous estimation of parent and metabolite pharmacokinetic parameters.
- Suggest clinically relevant sampling windows to balance optimality with practical and logistical considerations of study conduct.

METHODOLOGY

Parent drug and metabolite population PK model

A population multiresponse (parent and metabolite) pharmacokinetic model was developed based on a previous study in the same targeted population.

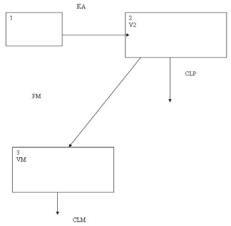

Figure 1. Population parent drug and metabolite pharmacokinetic model.

The model is expressed by $y_{jmi} = f_m(\theta_i, t_{ji}) + \varepsilon_{jmi}(\sigma_{m1}^2, \sigma_{m2}^2)$

where

m=1,2: two responses;
i=1,..,N subjects;
j=1,..,n measurements;
θ_i=g(θ,b_i) p-vector pf parameters;
$b_i \sim N(0,\Omega)$, Ω: pxp covariance matrix

$$\varepsilon_{jmi}(\sigma_{m1}^2, \sigma_{m2}^2) = \varepsilon_{jmi}(\sigma_{m1}^2 + \sigma_{m2}^2 f_m^2(\theta_i, t_{ij}))$$

$\Omega =$

	KA	CLP	V2	CLM	V3	FM
KA	0.45	0	0	0	0	0
CLP	0	0.26	0.12	0.16	0.08	0
V2	0	0.12	0.10	0.08	0.02	0
CLM	0	0.16	0.08	0.12	0.01	0
V3	0	0.08	0.02	0.01	0.17	0
FM	0	0	0	0	0	0

The residual error terms for the two different response, parent and metabolite, are measured at the same time and are correlated with a 2x2 correlation matrix. It is assumed that $\varepsilon_i \sim MVN(0, R)$, where MVN is multiresponse normal distribution and R is an Mn x Mn given by:

where $R = \begin{bmatrix} R_{11} & R_{12} & \cdots & R_{1M} \\ R_{21} & R_{22} & \cdots & R_{2M} \\ \vdots & \vdots & \ddots & \vdots \\ R_{M1} & R_{M2} & \cdots & R_{MM} \end{bmatrix}$

$$R_{qm}(j,l) = \tau_{qm}\sqrt{\left[\sigma_{q1}^2 + \sigma_{q2}^2 f_q^2(\theta_i, t_{ij})\right]\left[\sigma_{m1}^2 + \sigma_{m2}^2 f_m^2(\theta_i, t_{il})\right]} \quad j = l$$

$$R_{qm}(j,l) = 0 \qquad j \neq l$$

$\tau_{qm} = 0.8$

$\sigma_{q1} = 0.1; \sigma_{q2} = 0.18$

$\sigma_{q1} = 0.2; \sigma_{q2} = 0.2$

R is the residual variance covariance matrix, which includes the correlation between responses measured at the same time.

Population multiresponse Fisher Information Matrix

The population multiresponse Fisher Information Matrix is as defined in [3]. Briefly,

$$y_{mi} = f_m(g(\theta, b_i), \xi_i) + \varepsilon_{mi}(\sigma_{m1}^2, \sigma_{m2}^2) \cong f_m(g(\theta,0), \xi_i) + \left.\frac{\partial f_m^T(g(\theta, b_i), \xi_i)}{\partial b_i}\right|_{b_i=0} b_i +$$

$$+ \sigma_{m1} + \sigma_{m2}\left[f_m(g(\theta,0), \xi_i) + \left.\frac{\partial f_m^T(g(\theta, b_i), \xi_i)}{\partial b_i}\right|_{b_i=0} b_i\right]$$

$$E = E(y_i) \cong \left[f_1(g(\theta,0), \xi_i)^T, \ldots\ldots\ldots, f_M(g(\theta,0), \xi_i)^T\right]^T \qquad V = Var(y_i) \cong U^T \Omega U + R$$

$$F(\Psi, \xi_i)_{rs} = J_r^T V^{-1} J_s + \frac{1}{2} tr\left(\frac{\partial V}{\partial \Psi_r} V^{-1} \frac{\partial V}{\partial \Psi_s} V^{-1}\right) \qquad J_r = \left[J_{r1}^T, J_{r2}^T, \ldots\ldots\ldots, J_{rM}^T\right] \quad J_{rm} = \frac{\partial f_m(\Psi, \xi_i)}{\partial \Psi_r}$$

$$PF(\Psi, \Xi) = \sum_{i=1}^{N} F(\Psi, \xi_i)$$

Efficiency and clinical sampling windows

$$eff_D = \left[\frac{|F(\Psi, \Xi)|}{|F(\Psi, \Xi_D)|}\right]^{1/\dim(\Psi)}$$

Optimal sampling windows with pre-determined level of efficiency

Windows are determined by allowing the sampling window design to result in a specified level of efficiency when compared to the fixed times D-optimal design. A uniform distribution was used to generate sampling times from the sampling windows. Algorithm as given in [4], where three steps are followed: 1) Determine the local population D-optimal design; 2) For a given sampling window length $|F(\Psi, \Xi^W)|^{1/\dim(\Psi)} \approx \frac{1}{H}\sum_{h=1}^{H} |F(\Psi, \Xi^{W(h)})|^{1/\dim(\Psi)}$

3) Determine the optimal window length for efficiency level $eff0$ as $\delta^* = \arg\left\{\min_{\delta \in \Delta}\left[\left(\left(\frac{|F(\Psi, \Xi^W(\delta))|}{|F(\Psi, \Xi^D)|}\right)^{1/\dim(\Psi)} - eff_0\right)^2\right]\right\}$

where Δ is the space for window length δ.

Sampling windows evaluation with user supplied windows:

Samples were obtained from the user supplied windows using a normal distribution and efficiency calculated as:

$$|F(\Psi, \Xi^W)|^{1/\dim(\Psi)} \approx \frac{1}{H}\sum_{h=1}^{H} |F(\Psi, \Xi^{W(h)})|^{1/\dim(\Psi)} \qquad eff_D = \left[\frac{|F(\Psi, \Xi)|}{|F(\Psi, \Xi_D)|}\right]^{1/\dim(\Psi)}$$

RESULTS

D-Optimal sampling times

D-optimal sampling times for the parent drug and metabolite separately were found. As the data is planned to be collected and analysed simultaneously a population multivariate design was found. Initially an earlier time was allowed as a lower bound in the optimisation, but then due to the number of doses investigated and the potential for BQL plasma samples a later time of 30 min was set as a lower bound.

Table 1. D-optimal times for drug X study. In all cases exchange algorithm with step size 0.1 was used.

Population Design for	Optimal sampling times (h)						Computational time [h]
parent only	0.5	6.9	12.0				0.0167
metabolite only	0.5	7.9	12.0				0.0167
combined model (lower bound 0.083h)	0.083	0.28	4.7	6.7	11.98	12.0	96
combined model (lower bound 0.5h)	0.5	2.4	6.8	6.8	12.0	12.0	2

	CVSE* [%]												
	ka	CL	V	ω^2_{KA}	ω^2_{CL}	ω^2_V	σ^2_{PROP}	σ^2_{ADD}					
parent only	12.2	7.9	9.2	45.4	31.8	108.2	57.7	989					
metabolite only	5.4	6.9	11.2	35.6	173.6	525	120	477					
	ka	CLp	Vp	CLm	Vm	ω^2_{KA}	ω^2_{CLP}	$\omega^2_{CLp,CLM}$	ω^2_{Vp}	ω^2_{CLM}	$\sigma^2_{P\_PROP}$	$\sigma^2_{P\_ADD}$	$\sigma^2_{M\_PROP}$	$\sigma^2_{M\_ADD}$
combined model (lower bound 0.083h)	6.3	5.3	5.4	6.6	8.1	27.6	22.5	31.5	44.3	48.5	14.7	15.6	384	31.2
combined model (lower bound 0.5h)	6.2	5.2	5.2	6.6	8.7	29.6	22.6	30.9	41.9	45.7	14.6	15.8	434.9	5694

Simulated pharmacokinetic profiles

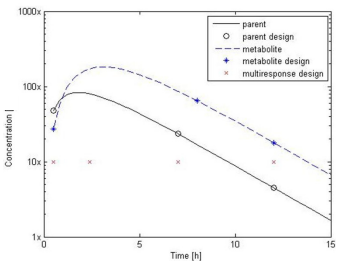

Fig.2 Simulated PK profiles for parent drug (solid line) and metabolite (dotted line), their corresponding D-optimal designs and the multivariate design.

Table 2. PK parameter CVSE(%) and efficiency for three practically feasible designs with four sampling windows (COMBINED MODEL).

Practical windows designs	CVSE* [%]													Efficiency [%]
	ka	CLp	Vp	CLm	Vm	ω^2_{KA}	ω^2_{CLP}	$\omega^2_{CLp,CLM}$	ω^2_{Vp}	ω^2_{CLM}	$\sigma^2_{P\_PROP}$	$\sigma^2_{P\_ADD}$	$\sigma^2_{M\_PROP}$	$\sigma^2_{M\_ADD}$	
[0.5-1] [2-4] [6-7] [11-12]	7.1	5.3	5.3	6.6	9.3	31.5	22.6	30.9	42.2	45.6	14.7	15.8	624	8481	85.6
[0.5-1] [3-4] [6-7] [11-12]	**7.4**	**5.3**	**5.2**	**6.7**	**9.5**	**31.9**	**22.7**	**30.8**	**41.7**	**45.2**	**14.8**	**15.8**	**611**	**8321**	**85.7**
[0.5-1.5] [3-4] [6-7] [11-12]	7.7	5.3	5.3	6.7	9.9	33.6	22.8	31.0	41.5	45.3	14.8	15.9	623.9	8666	83.0

* Coefficient of variation around the standard error;

CONCLUSIONS

- A four windows rather than original three windows design was implemented;
- Sampling times from combined model did not exactly replicate optimal times from the two separate unireponse models;
  - D-optimal unireponse times b/n parent and metabolite similar except for midpoint, which primarily determines V2 and Vm respectively;
  - Difference b/n lower and higher lower bound: need to take one sample at the bound and another prior to 0.5h;
  - CVSE for fixed effects less than 10%; for random effects acceptable less than 50%, except proportional and additive residual variances poorly defined when higher lower bound used.
- Optimal sampling windows with pre-determined level of efficiency:
  - all windows of equal length only;
  - not successful in applying the method: time consuming;
- User specified sampling windows:
  better suited for this evaluation as different window length possible;
  balanced the practical and logistical considerations of conducting the study and took into account factors such as concurrent procedures, potential for BQL concentrations, timing of samples during the day, etc.

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