Optimal Design of a Population Pharmacodynamic Experiment for Ivabradine

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Purpose. To design a parsimonious population pharmacodynamic experiment that has the same or greater efficiency than that provided by two phase I studies.

Methods. The design was based on optimization of the population Fisher information matrix. Options for optimization were (1) determination of the optimal sampling times for each group ("group" represents a group of subjects that have identical design characteristics), (2) determination of the optimal doses for each group, and (3) determination of the optimal group structure.

Results. (1) Optimizing the sampling times, while retaining only four unique times per group, provided a more parsimonious experiment with the same efficiency as the original "study" that involved on average 10 samples per subject. Splitting sampling times between the first dose and a steady-state dose gave the most informative design. (2) The optimal dose was the same in all groups and was the upper bound of the dose range. (3) The optimal population design consisted of only one group with four unique sampling times that are the same for all subjects.

Conclusion. A population pharmacodynamic trial design is presented that is more parsimonious than the original study and would be appropriate for inclusion in a premarketing clinical study.

KEY WORDS: pharmacodynamics; ivabradine; optimal design; population analysis; Fisher information matrix.

INTRODUCTION

Ivabradine is a novel negative chronotropic agent that has been developed for the prevention of myocardial ischaemia. Both the parent and the N-dealkylated metabolite, S-18982, have been shown to decrease heart rate (1). Further details and the chemical structure have been described previously (1). The pharmacokinetics of ivabradine and S-18982 have been described by two linked two-compartment models with first-order absorption, first-pass loss, and first-order elimination (2). The effect of ivabradine and S-18982 on exercise-induced tachycardia was found to be described best by a multiple ligand model (3). The pharmacokinetic and pharmacodynamic data were obtained from two phase I trials that included 78 healthy male volunteers.

There are several recent articles addressing optimal population design issues without the use of extensive simulations (4–6). The methods for determining the population Fisher information matrix (PF) for nonlinear mixed effects models are described in those papers and are not discussed here. The method used here, proposed by Mentré et al. (4), requires that the model be linearized using a first-order Taylor series expansion about the random effects terms. Choosing design points from the design space (including the possible sampling times, doses, and number of patients) that maximizes some measure of PF will yield an optimal population design. Given that the measure of PF is proportional to the number of patients and indirectly proportional to the number of samples per patient, an upper constraint is invoked to avoid designs that become impractical clinically (6).

This paper focuses on the design of a population pharmacodynamic experiment where it is desirable to obtain accurate parameter estimates for both the fixed effects and random effects components (including residual variance) for a nonlinear pharmacodynamic model. To achieve this, a D-optimal design criteria was chosen where the goal is to maximize the determinant of the information matrix (7). Because the inverse of the Fisher information matrix is the lower bound of the estimation variance matrix, this is equivalent to minimizing the determinant of the variance matrix (8).

The aim of this study was to design a more parsimonious clinical trial for the estimation of the pharmacodynamic parameters that is at least as efficient as the combined two original phase I trials (termed "baseline trial design"). Others have shown, although not using optimal design criteria, that many early phase population trial designs can be simplified without significant loss of information (see Cosson and Fuseau (9) for a recent example). It was our intention to examine this process using optimality criteria.

METHODS

Pharmacodynamic Model

The pharmacokinetic and pharmacodynamic models for ivabradine and S-18982 have been described previously (2,3). The pharmacodynamic model that best described the heart rate effects of ivabradine and S-18982 from two phase I trials was a multiple ligand model.

$$E = \frac{C_I \cdot E\max_I}{EC_{50I}(1 + C_S/EC_{50S}) + C_I} + \frac{C_S \cdot E\max_S}{EC_{50S}(1 + C_I/EC_{50I}) + C_S}$$

where Emax is the maximum effect, EC_{50} is the concentration at which 50% of the maximum effect is achieved, C is the concentration of either ivabradine or S-18982 in the biophase provided from the pharmacokinetic model, and the subscripts I and S represent ivabradine or S-18982, respectively. The sigmoidicity parameter (γ) was fixed at 1 and is therefore not shown in the model.

The effect E computed from the above expression represents a change from baseline, and the model to describe the expected heart rate at a given time is computed as $E_0 - E$. In a more general sense, the heart rate for the ith individual for the jth measurement is given by:

$$HR_{ij} = f(\mathbf{\Psi_i}, \boldsymbol{\theta}, \mathbf{x_{ij}}) + \varepsilon_{ij}$$

where Ψ_i denotes the vector of pharmacodynamic parameters

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for the ith individual, $\boldsymbol{\theta}$ is a vector of population pharmacokinetic parameters, $\mathbf{x}_{ij}$ is a vector of independent variables such as dose and time, and ε is an i.i.d. error term with a distribution given by $N(0,\sigma^2)$.

For the experimental designs that were investigated, the pharmacokinetic parameters were fixed at their mean population values estimated previously (2) and considered as known independent variables. This reduces the population model to a pharmacodynamic problem of 15 population parameters; 7 fixed effect parameters, E_0, $E\text{max}_I$, $E\text{max}_S$, EC_{50I}, EC_{50S}, and the rate constants for elimination of drug and metabolite from the effect site Keo_I and Keo_S; 7 variances of between-subject random effects parameters (corresponding to the above fixed effect parameters); and the variance of the residual error. In the original study it was found that Emax and EC_{50} could not be estimated both for ivabradine and S-18982 (3). Hence, $E\text{max}_S$ was fixed to be equal to $E\text{max}_I$ and EC_{50S} was to $1.2 \times EC_{50I}$ (3). The model was reduced further by fixing Keo_S to 10 h^{-1} and the between-subject variance of Keo_S to zero (previously estimated to be <3%). The final population pharmacodynamic model had nine parameters. The population pharmacokinetic and pharmacodynamic parameter values are given in Table 1.

Table 1. Population Pharmacokinetic and Pharmacodynamic Parameter Values Used for the Design

Parameter (units)	Fixed effects	Between-subject variance	Population distribution
CL_I ($L \cdot h^{-1}$)	27.4	Fixed	n/a
V_{1I} (L)	216	Fixed	n/a
CLD_I ($L \cdot h^{-1}$)	73.5	Fixed	n/a
V_{2I} (L)	644	Fixed	n/a
Ka (h^{-1})	2.1	Fixed	n/a
F_I	0.82	Fixed	n/a
T_{LAG} (h)	0.22	Fixed	n/a
CL_S ($L \cdot h^{-1}$)	136	Fixed	n/a
V_{1S} (L)	92.4	Fixed	n/a
CLD_S ($L \cdot h^{-1}$)	230	Fixed	n/a
V_{2S} (L)	635	Fixed	n/a
E_0 (bpm)	169	73.4	Normal
$E\text{max}_I$ (bpm)	77.4	0.0346	Log normal
EC_{50I} ($mcg \cdot L^{-1}$)	71.4	0.0525	Log normal
$E\text{max}_S$ (bpm)	77.4[a]	n/a	n/a
EC_{50S} ($mcg \cdot L^{-1}$)	85.7[b]	n/a	n/a
Keo_I (h^{-1})	0.172	0.165	Log normal
Keo_S (h^{-1})	10[c]	0	n/a
σ^2	5.40	0	Normal[d]

n/a: Not applicable.
CL: Clearance.
V_1: Volume of distribution of the central compartment.
CLD: Distributional clearance.
V_2: Volume of distribution of the peripheral compartment.
Ka: Absorption rate constant.
F_I: Fraction of ivabradine that reaches the systemic circulation intact.
T_{LAG}: Lag-time of absorption.
[a] Fixed to $E\text{max}_I$.
[b] Fixed to $1.2 \times EC_{50I}$.
[c] Fixed value with no variability.
[d] The residual error was considered to be additive and normally distributed with variance given by σ^2. Subscripts I and S represent ivabradine and S-18982, respectively.

Resolution and Clustering

The concept of resolution and clustering has been discussed previously (10). Resolution is defined in this study as the maximum difference between two design points that is considered *a priori* to be nonsignificant. Clustering refers to a cluster of design points that occur within an acceptable level of resolution. For pharmacokinetic experiments the effect of clustering is often ignored (11). This is not possible for many pharmacodynamic experiments where the duration of taking the sample may be prolonged. Cluster identification was considered after the minimization process was terminated (except where stated otherwise).

Design Optimization Features

A population design is composed of a number of groups, each group composed of a number of individuals. In this setting the term group is used to describe a collection of subjects that have identical design characteristics given by the number and timing of samples and the dose. This makes determination of optimal designs for mixed effect models necessarily more complex than standard regression model designs. We consider the problem within the framework of three design options: (*a*) determination of the optimal sampling times for each group, (*b*) determination of optimal doses for each group, and (*c*) determination of the optimal group structure. These are discussed below.

Baseline Trial Design

The baseline trial design (BTD)—a concatenation of 2 phase I trials (2,3)—consisted of a total of 768 exercise-induced heart rate observations (N_{tot} = 768) on 78 subjects over a 156-h period. Most observations were sampled on the first and last dose. There were nine groups. For each group the total number of samples per subject was 12, 16, 16, 8, 8, 8, 8, 8, and 8, the number of subjects was 12, 9, 9, 8, 8, 8, 8, 8, and 8, and dose rate was 0, 10, 20, 8, 16, 20, 24, 28, and 32 mg every 12 h. This baseline trial design was evaluated both for the final population pharmacodynamic model with 9 population parameters (BTD-9), which all optimal designs were subsequently compared to, and for the full model with 15 population parameters (BTD-15) with the lognormal variance of $E\text{max}_S$ and EC_{50S} arbitrarily set to 0.1.

Option 1: Optimal Sampling Times

The design variables were the sampling times for the groups and the design space was continuous over the potential range of the study period, i.e., 0–156 h. Those sampling times that maximized the determinant of PF were considered optimal conditional on all the other features of the baseline trial design (i.e., number of groups, the dose amount for each group, and the number of subjects per group). The sampling times were set to be the same for all subjects within each group, but were allowed to vary between groups.

The total number of samples per subject was fixed to 4, the same as the number of fixed effect parameters (i.e., N_{tot} = 312). Design strategies that were tried included: (*i*) all samples were taken off the first dose, (*ii*) all samples were taken off the last dose, and (*iii*) samples were split between the first and last dose. In the last strategy, three splits were

possible: split 1/3, 2/2, and 3/1 denoting 1, 2, or 3 samples from the first dose and 3, 2, or 1 from the last dose, respectively. The resolution for the design points was set to 0.5 h, based on the smallest time difference between any two measurements in the baseline trial design.

Option 2: Optimal Dose Levels

The design variables were the dose for each of the groups and the design space was given by the range of discrete dose levels used in the baseline trial design, i.e., 0, 8, 10, 16, 20, 24, 28, and 32 mg every 12 h. The dose interval was fixed and not subject to optimization. In addition to the doses, all other features of the baseline trial design were maintained the same so that $N_{tot} = 768$. Consideration of resolution was unnecessary.

Option 3: Optimal Group Structure

This option involves locating the optimal group structure, i.e., the number of groups, the number of subjects in each group, and the corresponding sampling times. The maximum number of groups was set to 4 (equal to the number of fixed effect parameters). Groups were "lumped" if the dose levels were the same and the sampling times where within acceptable resolution. The sample time of each observation was optimized in the procedure, although the fractional split of samples between the first and last dose was fixed at the best split found in option 1. The design constraint was given by the total number of heart-rate observations ($N_{tot} = 312$). The number of samples per subject n_i and subjects per group N_k was allowed to vary from 1 to 8 and 9 to 78, respectively, such that: $N_k \times n_i \times 4 = N_{tot} = 312$.

Optimization Method

The maximization procedure used here is based on a *local exact* design optimization. The design is said to be *local* because it depends on the pharmacodynamic parameter value, compared to the *robust* designs where prior distributions of the parameter values are given (5,12). It is called an *exact* design because the optimization is performed with respect to the variables designing the experiment, compared to *approximate* or *statistical* design (4,8), where a distribution of the experimental effort is assumed.

Optimization was performed using a two-stage process to find the minimum of the inverse of the determinant of PF. The software was written within the framework provided by MATLAB (version 5.3). The MATLAB code (PFIM) for evaluating PF has been described previously (13). For stage 1, a nonadaptive random search was performed to locate the design points that yield a global minimum; see Tod and Rocchisani (14) for a description, and D'Argenio (12) for an example. For stage 2, a simplex algorithm was used to find the optimal design where one of the vertices of the simplex was set to the best design points from stage 1. Two runs were performed for each of the final optimization procedures for options 1–3. If this produced the same result, then the two stage method was considered to have found at least a local minimum. In all cases it remains unknown whether a true minimum was found in any of the following optimization results.

Design Efficiency

Population designs for the pharmacodynamic experiment were compared based on two criteria. First, the efficiency (7) of the design, and second, comparison of the standard errors of the population parameters. The relative efficiency (E_f) of design ξ_1 with respect to the baseline trial design ξ_0 is defined as

$$E_f = \left(\frac{\det[\mathbf{PF}^{\Psi}(\boldsymbol{\xi}_1)]}{\det[\mathbf{PF}^{\Psi}(\boldsymbol{\xi}_0)]} \right)^{1/p}$$

where p is the number of population parameters and hence the dimension of $\mathbf{PF}^{\Psi}$.

We also compared the expected standard errors of the parameters. These were computed as the square root of the diagonal elements of the inverse of PF.

Sensitivity Analysis and Sampling Windows

The marginal sensitivity of the optimal population design from option 3 to specification of the fixed effect pharmacokinetic population mean parameter values was examined. To do this, the value of the normalized determinant of PF was evaluated for several values of each of the pharmacokinetic mean parameters over the range given by 50% and 200% of its mean value used in these analyses. An important change in the normalized determinant was arbitrarily chosen to be a reduction of 5%.

Using the optimal sampling times from the best result of the option 3 analysis, we estimated the marginal window associated with each optimal sampling time point. The marginal sampling windows were estimated by fixing all sampling times except the time of interest and then varying this time until the normalized determinant was reduced by 5%.

RESULTS

Baseline Trial Design

The determinant of PF for the design where there were 15 parameters (BTD-15) was very small and the matrix was close to singular. As described previously, the model was reparameterized to include only 9 parameters (BTD-9). The standard errors of this and subsequent designs are given in Table 2.

The relative efficiency of BTD-15 was 0.011 compared to BTD-9. The fixed effect population parameters and the between-subject variance of $E\max_S$ and EC_{50S} were estimated poorly (shown in Table 2). This suggests that the full pharmacodynamic model (BTD-15) was deterministically unidentifiable.

Optimization of Sampling Times (Option 1)

The results of the different design strategies based on four sampling times are given in Tables 2 and 3. It is seen that the most efficient sampling strategy is one in which the samples were split between the first and last dose. For each design, the projected number of samples (equivalent N_{tot}) and subjects (equivalent N) required to give the same efficiency as BTD-9 was computed by maintaining the same sampling strategy per group but increasing the number of subjects in each group (Table 3).

Table 2. Predicted Coefficient of Variation (%) of the Estimation Error of the Population Pharmacodynamic Parameters for the Various Designs

	Study designs				
	BTD 15 N_{tot} = 768	BTD 9 N_{tot} = 768	Option 1 N_{tot} = 312	Option 2 N_{tot} = 768	Option 3 N_{tot} = 312
Fixed effect parameters					
E_0	0.67	0.65	0.71	0.66	0.68
$E\max_I$	0.14	0.095	0.12	0.070	0.064
EC_{50I}	1.7	0.20	0.25	0.15	0.16
$E\max_S$	70.4	NE	NE	NE	NE
EC_{50S}	92.4	NE	NE	NE	NE
Keo_I	100	56.7	67.2	48.8	52.4
Keo_S	1.1	NE	NE	NE	NE
Random effect parameters					
ω_{E0}	18.5	18.6	20.1	19.2	20.1
$\omega_{E\max_I}$	53.8	52.9	78.7	38.2	40.0
$\omega_{EC_{50I}}$	128	127	180	102	119
$\omega_{E\max_S}$	>1000	NE	NE	NE	NE
$\omega_{EC_{50S}}$	>1000	NE	NE	NE	NE
ω_{Keo_I}	55.0	54.9	71.1	41.3	57.5
ω_{Keo_S}	>1000	NE	NE	NE	NE
Residual error					
σ^2	7.8	5.9	12.2	6.01	15.6

NE: Not estimated.

Optimization of Doses (Option 2)

Optimization of dose while retaining the original group structure yielded the same dose for all groups. The optimal dose was the highest available dose (32 mg) and gave a relative efficiency of 143% (see Tables 2 and 3).

Optimization of Group Structure (Option 3)

The results of option 3 are presented in Tables 2 and 4. It should be recalled that the dose is that provided by option 2 and the maximum number of groups was set to 4. The optimal design was one where there were 4 samples per subject and 19 subjects in two groups and 20 subjects in two groups. Increasing or decreasing the number of observations per subject was associated with lower efficiency. The sampling times for the optimal design were the same for all groups and were 0.2, 2.8, 12.0, and 148.0 h (the 148-h sampling time representing a sample taken at 4 h after the last dose). The design was therefore simplified to a single group of 78 subjects. Increasing the number of observations to 340 (i.e., 7 extra subjects) for the optimal design from this option afforded an equally efficient while more parsimonious design.

Most parameters were estimated with good precision except the population mean value of Keo_I and the between-subject variance of EC_{50I} and Keo_I (Table 2). On the basis of the optimal design from option 3, about 350 subjects (1400 heart rate observations) would be needed in order to reduce the standard errors of Keo_I and the between-subject variance of EC_{50I} to 25 and 55%, respectively.

Table 3. Optimal Design Using Options 1 and 2

Design	Relative efficiency[a] (%)	Total number of observations (N_{tot})	Equivalent N_{tot} (equivalent N)
Baseline trial	100	768	768 (N/A)
Option 1: sampling times (n_i = 4; doses, N_k and k same as the baseline trial design)			
First dose study	22	312	1418 (355)
Last dose study	17	312	1835 (459)
Split 1/3[b]	45	312	693 (174)
Split 2/2[b]	59	312	529 (132)
Split 3/1[b]	60	312	524 (131)
Option 2: doses (n_i, N_k, k same as the baseline trial design)			
All groups receive 32 mg	143	768	537 (54)

n_i: Number of observations per subject; N_k: number of subjects per group; k: number of groups; N: total number of subjects in the trial.

[a] All designs are compared to the baseline trial design.

[b] The samples were split between the first dose and last dose, e.g., split 2/2 indicates that two samples were taken off the first dose and two were taken off the last dose.

Table 4. Optimal Designs Using Option 3 Where Dose is 32 mg for All Subjects and There Are Four Groups ($k = 4$)

Design		Relative efficiency[a]	Total number of observations	Equivalent N_{tot}
n_i	N_k	%	N_{tot}	(equivalent N)
1	78	<1%	312	47,200 (47,200)
2	39	53	312	592 (296)
3	26	84	312	370 (124)
4[b]	**19.5[c]**	**92**	**312**	**340 (85)**
6	13	81	312	385 (64)
8	9.75[c]	76	312	412 (52)

n_i: Number of observations per subject; N_k: number of subjects per group; k: number of groups, N: total number of subjects in the trial.
[a] All designs are compared to the baseline trial design.
[b] Best design with option 3.
[c] Uneven group sizes, e.g., $N_k = 19.5$ were split among the four groups as 19, 19, 20 and 20.

Sensitivity Analysis and Optimal Sampling Windows

The sensitivity of the efficiency of the optimal design from option 3 with respect to variation of each of the 11 mean population pharmacokinetic parameters was evaluated. The change in the normalized determinant of PF for the range of fixed effect pharmacokinetic parameter values is shown for three representative parameters CL_I, CLD_I, and V_{2I} (Fig. 1). For the parameters V_{2I}, Ka, CL_S,V_{1S}, CLD_S, V_{2S}, F_I, and T_{LAG}, the normalized determinant of PF was relatively insensitive over the range of 50–200% of their mean value. For V_{1I} and CLD_I the normalized determinant was slightly more sensitive with a 33% and 50% increase in these parameter values causing a 5% reduction and a 67% and 200% increase resulting in a 10% reduction, respectively. In contrast, the design was rather sensitive to the choice of CL_I, whereby a decrease in the value of CL_I increased the normalized determinant of the design dramatically, whereas an increase in its value by 17% and 33% caused a decrease by 5% and 10%, respectively. At the extreme value of CL_I tested (a 200% increase), the value of the normalized determinant dropped by 30%. The optimization procedure was repeated with CL_I fixed to 58.4 $L \cdot h^{-1}$ (200% of the population mean value) to test whether (*a*) the optimization of option 3 remained optimal but just provided less information about the pharmacodynamic parameter estimates, or (*b*) whether there was a more optimal design. It was found that the optimal sampling times remained virtually unchanged (0.0, 2.8, 12.0, 147.5 h), despite the larger value of CL_I. Hence, the design of option 3 remained optimal but less efficient.

The optimal sampling times from option 3 were 0.2, 2.8, 12, and 148 h, dosing every 12 hr. The upper and lower bounds for the marginal sampling windows were 0–0.5 h, 1.9–4.4 h, 9.8–12 h, and 145–154 h. Sampling within these windows will yield a design that is attainable clinically and will provide at least 95% of the information of the optimal design.

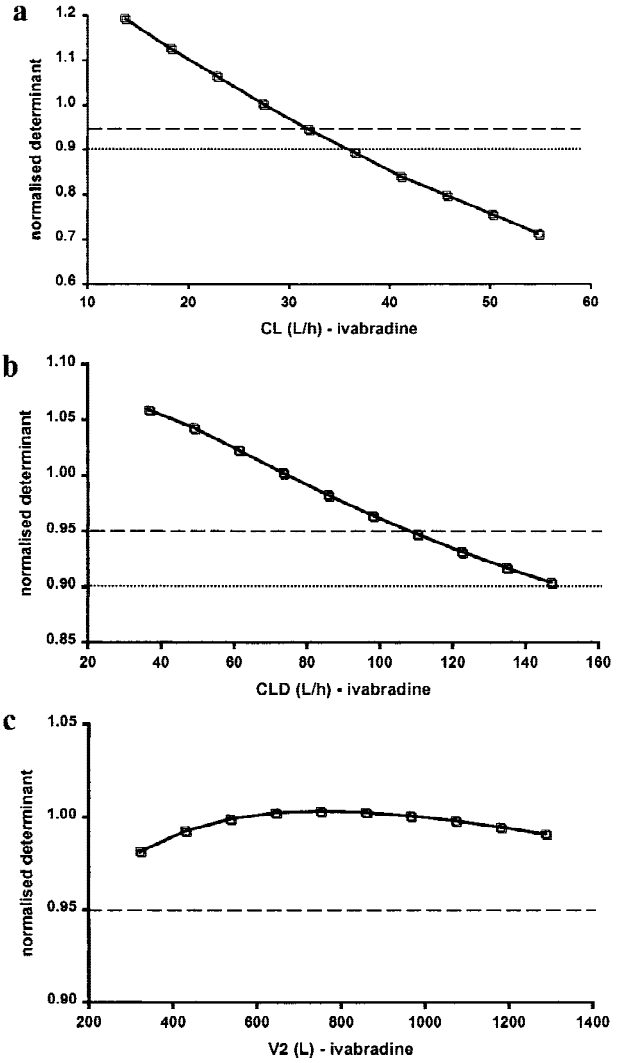

Fig. 1. Change in the normalized determinant of the design with respect to a change in the mean population pharmacokinetic parameter value for optimal design with option 3. The dashed lines represent a decrease of 5% of the normalized determinant and the dotted lines represent a decrease of 10%. The effects of changes in CL_I (1a), CLD_I (1b), and V_{2I} (1c) are shown.

DISCUSSION

This study represents, to our knowledge, the first attempt to optimize a population pharmacodynamic experiment. Optimization by any of the three options described yielded more parsimonious designs than the baseline trial design. Any one of these options would be a reasonable choice clinically, although option 3 involving optimization of group structure yielded the most parsimonious designs. For option 1, it is interesting that splitting the samples between the first and last dose provided the best design, presumably because this gives the widest range of concentrations. This is supported by option 2 where the optimal dose was found to be the largest permissible dose, again giving the widest range of concentrations. In standard nonlinear regression, the two concentrations that give an optimal design for a hyperbolic model (e.g., the *E*max model) with constant variance error are at the upper permissible boundary and at EC_{50} (16). Increasing the upper bound increases the efficiency of the design. Option 3 is a more sophisticated approach, compared to the previous options, and allows the design to include the group structure, i.e., number of subjects per group and number and timing of observations per subject. The optimal design included a sample at 0.2 h, which is less than the T_{LAG} (0.22 h), indicat-

ing that a time when the concentration is zero is required. This exercise-test could be performed predose without loss of information. Optimizing within the constraints of the maximum number of observations (N_{tot}) being equal to 312 provided a design that proved to be almost as efficient as the baseline trial design with only 40% of the number of samples. Almost all of the standard errors of the population parameters were within acceptable levels [defined as <20% for mean parameter values and <50% for variance parameter values (17)]. The efficiency of the design was maintained over a reasonable sampling window for each time. In general, the sampling windows became larger relative to time of the sample.

A pharmacodynamic experiment is more complex to design than a pharmacokinetic experiment because the vector of input variables is not known explicitly. In phramacokinetic experiments, the input vector includes dose and sampling times, whereas for a pharmacodynamic study it is desirable for the input vector to be concentrations. In our case, we used dose and sampling times as the input vector, which in conjunction with the pharmacokinetic model are used to compute the expected concentration. It is essential, therefore, that the pharmacodynamic design is robust to specification of the pharmacokinetic model parameter values. This was shown in the sensitivity analyses where the design had low sensitivity to almost all of the pharmacokinetic parameters except CL_I (Fig. 1a). Note that perturbations in the value of this parameter both increased and decreased the information in the design. This change in information with respect to different values of CL_I is not unexpected because it has been shown that higher doses yield more information, and a low value of CL_I is tantamount to a higher dose (and vice versa). Similarly, high values of V_{1I} (resulting in lower peak concentrations) will reduce the information in the design, although the loss of information is less than for CL_I. Any loss of information due to a larger than expected value of CL_I can be accommodated for by increasing the number of subjects in the study ($A \approx 100$). However, it should be considered that the original pharmacokinetic analysis was undertaken in healthy volunteers who will be younger and fitter compared to a typical patient population likely to receive ivabradine. Therefore, CL_I in the target population may well be lower than our population estimate, thereby increasing the information in our design. It should be noted, however, that between-subject variability in the pharmacokinetic parameters was not taken into account and we did not perform a global optimization of the pharmacokinetic/pharmacodynamic problem. To our knowledge this has not been done using an approach based on PF and would require further statistical development.

There remain a number of potential limitations of the integration of optimal population designs into early phase clinical trials. Certainly from phase I to II there may be limited or no information on the effect of the study drug in the target population, and some extrapolation may be needed in order to gain inference about the new study population from the existing data. This poses some potential problems for optimal design because there may be misspecification of the population parameter values and indeed the model. Therefore, in designing a phase II trial for ivabradine to include pharmacodynamic modeling as a secondary endpoint, it would seem prudent to consider a generalization of the results presented, such as (*a*) the higher the dose, the more information in the design (note: dosing should be based on reasonable clinical judgement and the use of lower doses can be compensated in the design by investigating more patients); (*b*) samples should be taken after the first dose and at steady-state in approximately a 3:1 ratio; (*c*) timing of the sample(s) at steady-state is not critical; (*d*) a sample for which the concentration is zero is important; (*e*) decreasing the number of samples per patient below the number of fixed parameters is not desirable; and (*f*) when the number of samples per patient equals the number of fixed parameters, only a single group is needed where all sampling times can be the same for all subjects. In addition, it should be noted that the *D*-optimal sampling times given here are dependent on the current model and parameter values, and therefore, they should be considered a guide rather than a rule. It would not be unreasonable to consider a composite design whereby the optimal sampling structure is combined with additional sampling times spread across an appropriate design window. A composite design could also take into consideration likely sampling times for pharmacokinetic parameter estimation, allowing both pharmacokinetic and pharmacodynamic sampling at the same time. However, implementation of an optimal population design based on phase II for phase III would seem considerably more realistic in that information regarding use in the target population would be available and the pharmacokinetic-pharmacodynamic model would be more accurately characterized. Therefore, a more parsimonious design such as that presented here for a sparse sampling schedule in phase III would be potentially of considerable benefit. There are also concerns in phase III trials about adherence, which is usually not considered in many early phase clinical trials. The effect adherence will have on trial design is also in question. These issues are complex and have been investigated by others (18). In a very limited sense we have partially addressed the issue of compliance by assessing the sensitivity of the design to specification of the pharmacokinetic parameter values (the estimates of which will be affected by unknown poor compliance behavior). Additional limitations of the optimal design methodology used here include the use of an exact design technique and the use of a marginal sensitivity analysis. In the former case, the split of sampling times (option 1) was optimized separate from the group structure (option 3). While this will not affect the characteristics of the design found in this study, there may be a more optimal design not considered here. In the latter case, the marginal sensitivity analysis was preferred over a multivariate sensitivity analysis, which due to the convoluted nature of the surface of the determinant of PF over the joint distribution of the parameters, was considered too complex to assess in this study.

In conclusion, an optimal population pharmacodynamic design is presented. The design is explored under a number of conditions of sampling times, dose levels, and group structures, allowing both specific and general conclusions about the design to be obtained.

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