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Research Article

Models, Optimal Sampling and Bioequivalence-A New Paradigm Case Study for a Drug with Complex Absorption Modified Release Methylphenidate

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ABSTRACT

Purpose: The purpose of the investigation was to compare the performance of ordinary sampling *versus* optimal sampling in Bioequivalence (BE) studies for an Extended-Release (ER) oral Methylphenidate (MP) tablet with complex absorption Concerta®.

Methods: For approval of generic versions of Concerta®, the FDA recommends a replicated crossover BE study design be used to define subject-by-formulation interaction variance and inclusion of pAUC (partial Area-Under-the-Curve metrics), in addition to standard metrics. Comparisons between ordinary and optimal sampling for the metrics was determined by the calculation of 90% Confidence Intervals (CIs) for selected Test/Reference (T/R) ratios (0.8, 0.9,0.95,1.0,1.10, and 1.25) for K0fast (zero-order fast absorption rate constant) and KAslow (first-order slow absorption rate constant). The effects of varying the values for FA (Fraction Absorbed) T/R ratios were also studied. Simulations were done using the recommended BE study methods above using a literature-sourced MP model. In addition, optimal sampling was measured against ordinary sampling obtained from a generic MP drug product *vs.* Concerta® in a human volunteers BE study.

Results: The ordinary and optimal sampling schemes resulted in comparable performance of the 90% CIs for the BE metrics pAUC: 03 hrs, pAUC: 37 hrs, pAUC: 712 hrs, and the standard metrics C_{max}, $AUC_{0\text{-}t}$ for the simulations and the experimental MP data.

Conclusion: These results indicate that optimal sampling and ordinary sampling give essentially the same BE results for a MP ER drug product with complex absorption.

Keywords: Models; Optimal sampling; 90% confidence intervals; Bioequivalence; Modified release methylphenidate

INTRODUCTION

With passage of the Drug Price Competition and Patent Term Restoration Act in 1984 [1], the design of Bioequivalence (BE) studies for generic drug products *vs.* approved reference drug products for orally-administered drug dosage forms required standardization of study design for purpose. Study designs recommended by the FDA to address BE-specific issues depended on properties of the specific drug under test. The types of recommended study designs and their statistical analyses were instituted to address average, individual, population, and referenced-scaled average BE [2]. FDA BE guidances have recommended variously performing: A) Two-period, two-sequence, two-treatment, single-dose, crossover studies, B) parallel-design studies, and/or C) replicated-design studies [3-5] as needed to address various types of BE-related concerns. These study designs have been developed to address oral drug products that have first-order, zero-order, and/or complex absorption, as well as oral drugs with highly-variable absorption patterns. These designs have also been used to establish BE for some long-term injectable drug products. All of the designs have generally required that plasma samples be collected for approximately three terminal elimination half-lives to determine exposure [4].

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There have been some published studies discussing modification of the number of samples specified for collection in the currently recommended designs. One study reference in a publication used an optimal-sampling approach for a novel adaptive sequential design which would allow for re-estimation of the second-stage sample size based upon first-stage results [6]. The author's main emphasis was to define the intra-subject Coefficient of Variation (COV) to better define sample size. Another publication looked specifically at using optimal times for sample collection, with the main emphasis being the estimation of (AUC) using a one-compartment model. The authors of the Kong FH and Gonin R, publication concluded from simulation studies that the trapezoidal approximation for AUCs up to 24 hrs post-dose under an optimal sampling design is an improvement over the ordinary sampling time design when the number of samples was reduced from ten to six [7]. In particular, the ordinary design has a non-negligible bias while the optimal design appeared to reduce such bias. The publication by Jackson [8] employed limited sampling (based upon the drug's pharmacokinetics) used training and test data sets with various levels of intrasubject error and concluded these procedures were useful only for formulations with test product/reference product (T/R) ratios for Fraction Absorbed (FA) within the range of 0.90-1.10 for drugs with highly variable absorption characteristics [8].

The aim of the current study was to focus on the effects on BE determination when using optimal sampling in BE studies for oral ER MP drug products with complex absorption characteristics. This was done by determining if use of optimal sampling will result in similar BE metrics (e.g., 90% CIs for AUC: 0-3 hrs, AUC: 3-7 hrs, AUC: 7-12 hrs, AUC_{0-t}, and C_{max}) compared with ordinary sampling for Concerta® and a generic MP product with both having complex absorption characterized by zero and first-order PK [9-10].

MATERIALS AND METHODS

Pharmacokinetic model

Concerta®: The parameters, sampling times and PK model for Concerta® were described in prior publications [9-11]. The model has two parallel inputs with the first being a fast, zero-order immediate-release phase and the second being a slow, first-order delayed-release phase.

Replicate experimental be fasting study for generic MP ER oral drug product *vs.* Concerta®

Ethics: This study was conducted in compliance with FDA Good Clinical Practice (GCP), and all applicable regulations, including the Federal Food, Drug and Cosmetic Act., U.S. Code of Federal Regulations (Title 21), ICH Guidelines, and IRB requirements relative to clinical studies [12].

Informed consent: An Informed Consent Form (ICF) that includes all relevant elements currently required by FDA or state regulations was provided to each prospective study subject at screening and before enrollment into the study.

Study design and patients

This study was designed based on the known PK of Concerta® ER oral tablets based upon FDA Draft Guidance [5], and generally accepted standards for the conduct of BE/BA studies under fasted conditions. The study was an open-label randomized, two-treatment, two-sequences, four-period, single-dose, four-way crossover replicate design bioequivalence and bioavailability study conducted in adult male and female healthy subjects (18-45) in a fasting state: 44 subjects completed at least wo periods of the study, one of which included the reference product. Each subject received a single 54 mg dose of the reference tablet (Concerta®) on two occasions and a single dose of the test tablet (MP HCL ER) on two occasions with a 7-day washout period.

Analytical methods

Pre-dose samples were collected within 60 minutes before dosing. Samples were taken pre-dose (0-hour) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 11.0, 12.0, 16.0, 20.0, 24.0 and 30.0 hrs post-dose. Plasma levels of MP enantiomers were quantified using a fully-validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The method was linear over a concentration range of 0.105 ng/mL to 50.000 ng/mL, and the lower limit of quantitation was 0.105 ng/mL.

Optimal sampling-methods

Optimal plasma sampling times for the primary simulated BE study and for the experimental BE study were selected based on optimal experimental design using a D-optimality method [13]. Employing a priori information based on a previously-published Concerta® Model [9], Fisher information was obtained using the Concerta® Model's final estimates. A minimum of five sampling time points was pre-specified (the number of total samples per individual, N-i) to produce reasonable concentration time-profiles for the estimation of the BE parameters. For the given simulated population-replicated PK model, the BE parameter estimates and the effects of between-subject variation and within-subject variation on the 90% CIs for pAUC: 0-3 hrs, pAUC: 3-7 hrs, pAUC: 7-12 hrs, C_{max} and AUC_{0-t} were investigated.

Primary simulation study-design and statistics

Simulated BE studies were performed using NONMEM version 7.5.0 (ICON Development Solutions, Dublin, Ireland) with GNU Fortran (GNU Compiler Collection version 4.7.2; Free Software Foundation, Boston, MA).

The studies were conducted using a "replicated" design—a two-formulation, two-sequence, four-period, replicated, crossover design as represented in (Table 1).

Table 1: Two sequence four period, and two formulation replicated design used for the simulations.

Sequence	Period			
	1	2	3	4
1	T	R	T	R
2	R	T	R	T

The between-subject-variability and within-subject variability was set at 15% for all simulations. These values were chosen based upon preliminary simulations to keep the least square means values below 30% (i.e., the threshold for highly variable drugs) and σD (i.e., subject-by-formulation standard deviation) less than 0.17, the upper-level value cited in the FDA guidance [5]. Ordinary sampling times were: Pre-dose (0 hr), and 0.25 hrs, 0.5 hrs, 1 hr, 1.5 hrs, 2

hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 6.5 hrs, 7 hrs, 7.5 hrs, 8 hrs, 10 hrs, 12 hrs, 16 hrs, and 24 hrs post-dose. Optimal sampling times were pre-dose (0 hr), and 0.1 hrs, 1.5 hrs, 3 hrs, 7 hrs, 12 hrs, and 24 hrs post-dose. The standard BE statistical analysis recommended by FDA [5] was performed on the resulting simulated data. The individual BE parameters pAUC: 0-3 hrs, pAUC: 3-7 hrs, pAUC: 7-12 hrs, AUC: 0-24 hrs (i.e., AUC_{0-t}), and C_{max} were log-transformed and analyzed. $AUC_{0-\infty}$ was not analyzed since the T/R ratio and 90% CIs were similar to those for AUC_{0-t} due to the drug's very short half-life of 3.5 hr [9]. A single 40-subject study (generic test product *vs.* Concerta®) was simulated 1000 times. A linear mixed-effects model was used for the study analysis. The mixed model generalizes the standard linear model as:

$$Y = X\beta + Z\gamma + \varepsilon$$

Where γ is an unknown vector of random effects parameters with known design matrix Z and ε is an unknown random error vector whose elements may not be independent and homogeneous. It is also assumed that γ and ε are Gaussian random variables that are uncorrelated and have expectations 0 and variances G and R, respectively.

All parameters were fixed to the reference published values except for K0fast (test) and KAslow (test). Simulations were done by observing changes in one absorption rate constant while the other was fixed at the published reference value. Each individual K0fast (test) and KAslow (test) value was increased or decreased from the published reference value to give the desired individual K0fast (test)/K0fast (reference) and KAslow (test)/KAslow (reference) ratio. Subsequent changes in the T/R ratios for K0fast (test) and KAslow (test) were done to determine how close were the 90% Cis for BE parameter values between simulations using ordinary sampling times *vs.* those using optimal sampling times with the above referenced changes in the absorption rate constants made for both sampling schemes.

The Fa was fixed to 1.00 for all simulations except those that investigated Fa at T/R levels of 0.8. 0.90, 0.95, and 1.00. The simulations for Fa were done under the assumption that the BA was more likely to decrease rather than increase, other than for dose dumping.

Power and type 1 error

Power and type 1 error were determined as in a prior published study [11], except the comparisons were for results using ordinary sampling times *vs.* simulated optimal sampling times for generic product *vs.* Concerta®.

Additional studies 1 and 2-experimental be data and simulations

Two additional studies were done as described below to add further proof of applicability of an optimal sampling design to that of an ordinary sampling design for use in BE studies (proof of concept).

Study 1 was done by comparing results from the experimental replicated BE study of the generic drug product *vs.* Concerta® performed using ordinary sampling with results that would have been obtained from the clinical study if optimal sampling had been used instead.

Study 2 was a separate simulated study done to challenge the validity of the Primary Simulated Study results by conducting additional BE study simulations comparing BE results obtained using lower and higher PK model parameter T/R ratio values for test MP of (0.95 Fa, 0.85 KAfast, 0.85 KAslow) and (0.95 Fa, 1.15 KAfast, 1.15 KAslow).

RESULTS

Primary simulation study

(Figure 1), (upper plot) shows the generic test product *vs.* Concerta® reference product mean plasma levels for sequence 1- (period 1 (T) *vs.* period 2 (R) and period 3 (T) *vs.* period 4 (R)). Figure 1 (lower plot) shows T *vs.* R mean plasma levels for sequence 2- (period 1 (R) *vs.* period 2 (T) and period 3 (R) *vs.* period 4 (T)). The graphs clearly show the overlap of the test and reference product mean plasma levels.

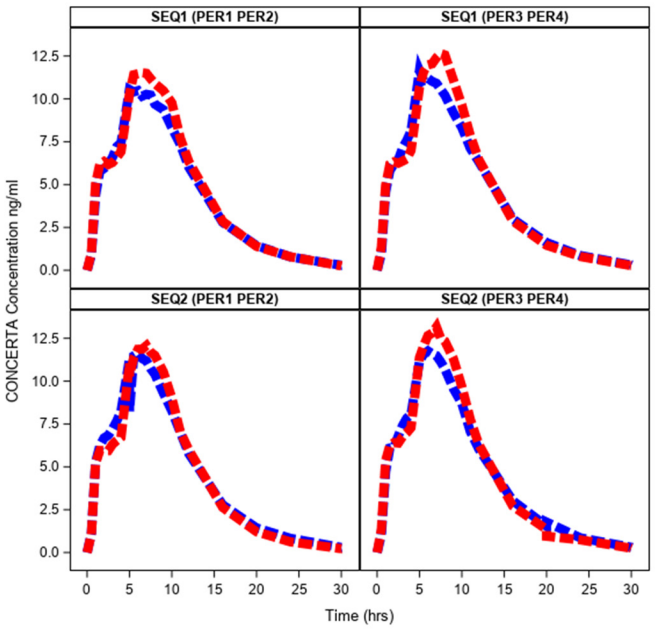

Figure 1: Mean graphs for the sequences and periods for the generic methylphenidate *vs.* Concerta®. **Note:** (▬): Generic_MP; (▬): Concerta.

(Figure 2) shows the impact of changes in KAfast T/R ratios at values of 0.8, 1, 1.10, and 1.25 on the BE metrics of pAUC: 0-3 hrs, pAUC: 3-7 hrs, pAUC: 7-12 hrs, and AUC: 0-24 hrs for ordinary *vs.* optimal sampling. All studied KA ratios resulted in pAUC parameters within the 0.8-1.25 acceptable 90% CI limits except for pAUC: 0-3 hrs at the 0.8 KA ratio. At the 0.8 ratio, the lower limit value for ordinary sampling was 0.78 while that for optimal sampling was 0.79, both outside the acceptable BE criteria. The other occasion when the CIs exceeded the limit was at the 1.25 KAfast T/R ratio for pAUC: 0-3 hrs which resulted in upper 90% CI values of 1.25 for ordinary sampling and 1.24 for optimal sampling. In both cases the CIs did not exceed the BE upper limit of 1.25. Other CIs that showed a notable difference between ordinary and optimal sampling were those for pAUC: 7-12 hrs. Although neither the ordinary or optimal sampling 90% CI values were near the upper or lower BE limits for failure, ordinary sampling resulted in a wider CI range compared with optimal sampling as the KAfast T/R ratios moved closer to 0.8. In contrast, optimal sampling had a narrower range for the 90% CIs than did original sampling and was more responsive to increases in the T/R ratio at 1.25. This may be related to the increase in intersubject variability from 10% in a prior published simulation to 15% in the current simulations [11].

(Figure 3) is the plot for KAslow at the same T/R ratios as for KAfast in Figure 2. There were similar 90% CI ranges for ordinary *vs.* optimal sampling; none were above or below the BE CI limits of 0.80-1.25. The only CI range that showed major differences between the sampling schemes was for pAUC: 7-12 hrs with the range for ordinary sampling always wider; however, both were still well within the acceptable CI BE range at all studied T/R ratios.

(Figure 4) shows pAUC results for Fa T/R ratios of 0.80, 0.90, 0.95, and 1.00 for ordinary *vs.* optimal sampling. The T/R ratios of 0.80 and 0.90 resulted in all pAUC BE metric CI ranges being at or below the acceptable lower BE limit of 0.80. CI ranges were similar for all BE metrics except for pAUC: 7-12 hrs where ordinary sampling had a noticeably wider range than did optimal sampling. A result of the increased range for the pAUC: 7-12 hrs CI resulted in all T/R ratios being either at or below 0.8 except for ratio=1. The upper CI for pAUC: 7-12 hrs never exceeded the upper acceptance limit of 1.25. (Figure 5) shows what effect changes in the T/R ratios (from 0.8-1.0) for KAfast, Kaslow, and Fa have on C_{max}. Only when the Fa T/R ratio was 0.80 did the lower 90% CI for C_{max} go below the lower acceptable BE limit of 0.80.

(Figure 6) shows what effect changes in the T/R ratios (from 1.10-1.25) for KAfast and KAslow have on C_{max}. All the resulting CIs for C_{max} were within the 90% CI acceptable BE limits. Fa was not investigated for T/R above 1.00.

Type 1 error

The results for type 1 error determined using experimental data for ordinary sampling *vs.* simulated sampling for generic product *vs.* Concerta® are presented in (Table 2). The results for ordinary *vs.* optimal sampling times were comparable in most cases and all were below the nominal 5% value.

Additional studies 1 and 2 (proof of concept)

The results from Study 1 compared the use of (experimental study data) for ordinary sampling *vs.* simulated data for optimal sampling for the replicated BE study are given in (Table 3). The results indicate that the 90% CIs and T/R ratios were indistinguishable between experimental ordinary sampling and simulated optimal sampling.

The results from Study 2, a simulated BE study comparing a generic drug product *vs.* Concerta® using ordinary *vs.* optimal sampling are given in (Table 4).

In Study 2, the T/R ratios for K0fast, KAslow, and Fa were raised and lowered to investigate what effect, if any, this would have on BE findings for ordinary *vs.* optimal sampling. The results indicated that the BE results for ordinary *vs.* optimal sampling were essentially the same despite the changes in the PK plasma sampling times

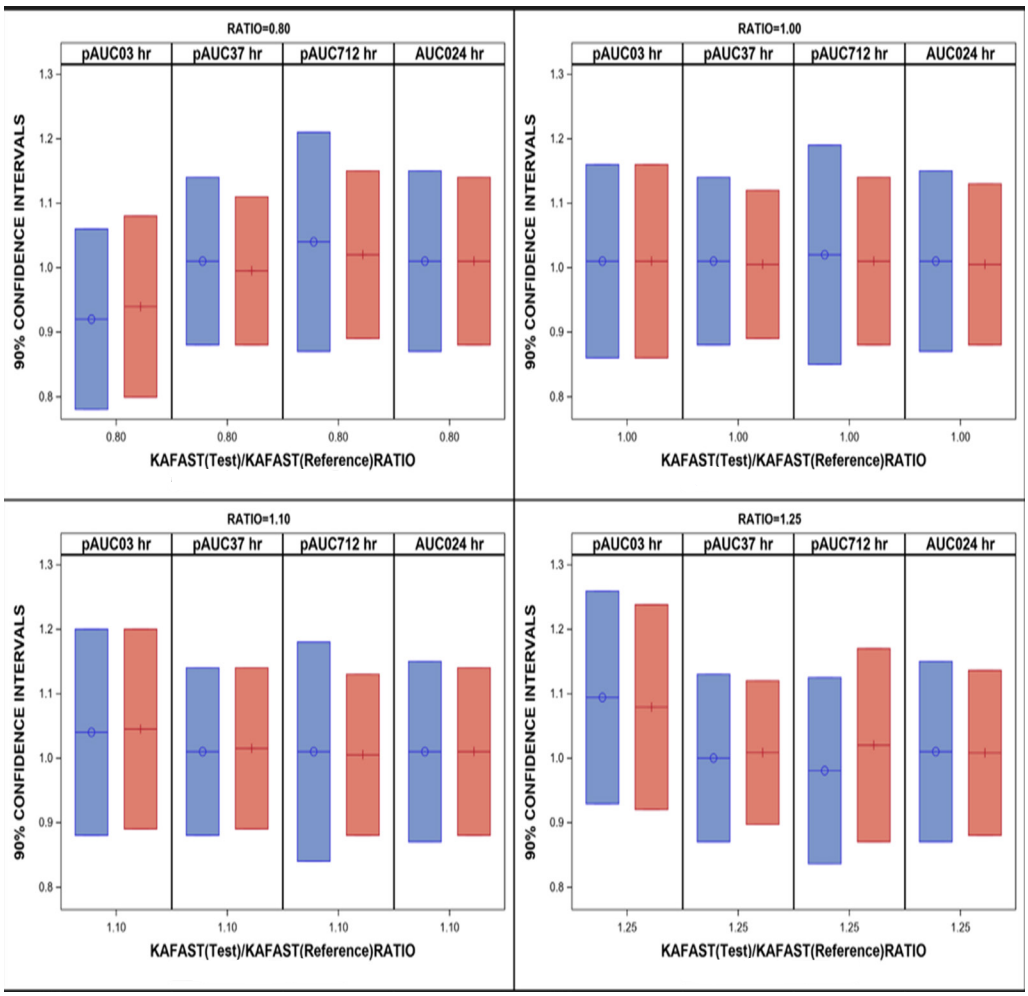

Figure 2: 90% confidence intervals for Concerta® simulations where KAslow and Fa were held constant at the reference values (0.40 and 0.32 respectively) while the KAfast (test) values were increased from a Test/Reference ratio of 0.8 to 1.25. The confidence intervals are for the bioequivalence parameters pAUC: 03 hrs, pAUC: 37 hrs, pAUC: 712 hrs, and AUC: 024 hrs. The blue graph represents ordinary sampling while the red graph is for optimal sampling. **Note:** (■): CI_Ordinary; (■): CI_Optimal.

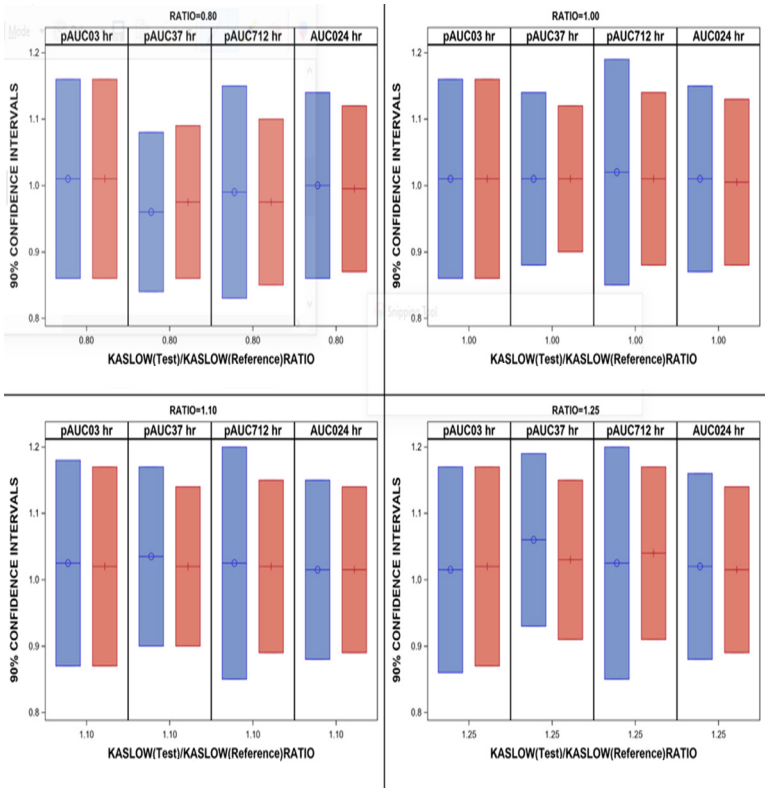

Figure 3: 90% confidence intervals for Concerta® simulations where KAfast and Fa were held constant at the reference values (1.11 and 0.32 respectively) while the KAslow (test) values were increased from a Test/Reference ratio of 0.8 to 1.25. The confidence interval designations are the same as for Figure 3. **Note:** (■): CI_Ordinary; (■): CI_Optimal.

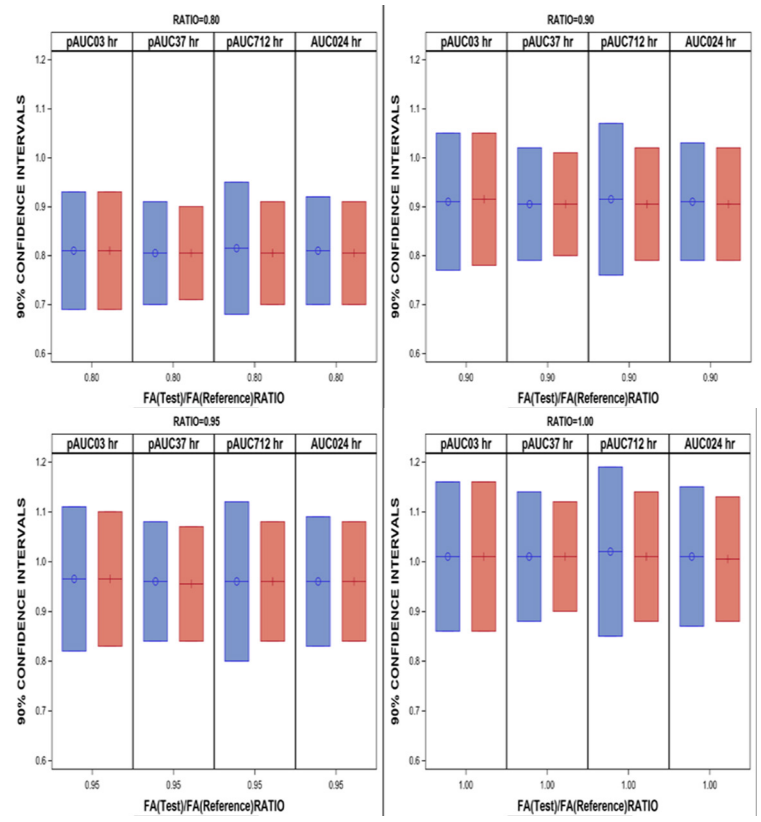

Figure 4: 90% confidence intervals for Concerta® simulations where Kafast and Kaslow were held constant at the reference values while the Fa(test) values were increased from a Test/Reference ratio of 0.8 to 1.0. The confidence intervals are for the bioequivalence parameters pAUC: 03 hrs, pAUC: 37 hrs, pAUC: 712 hrs, and AUC: 024 hrs. The blue graph represents ordinary sampling while the red graph is for optimal sampling. **Note:** (■): CI_Ordinary; (■): CI_Optimal.

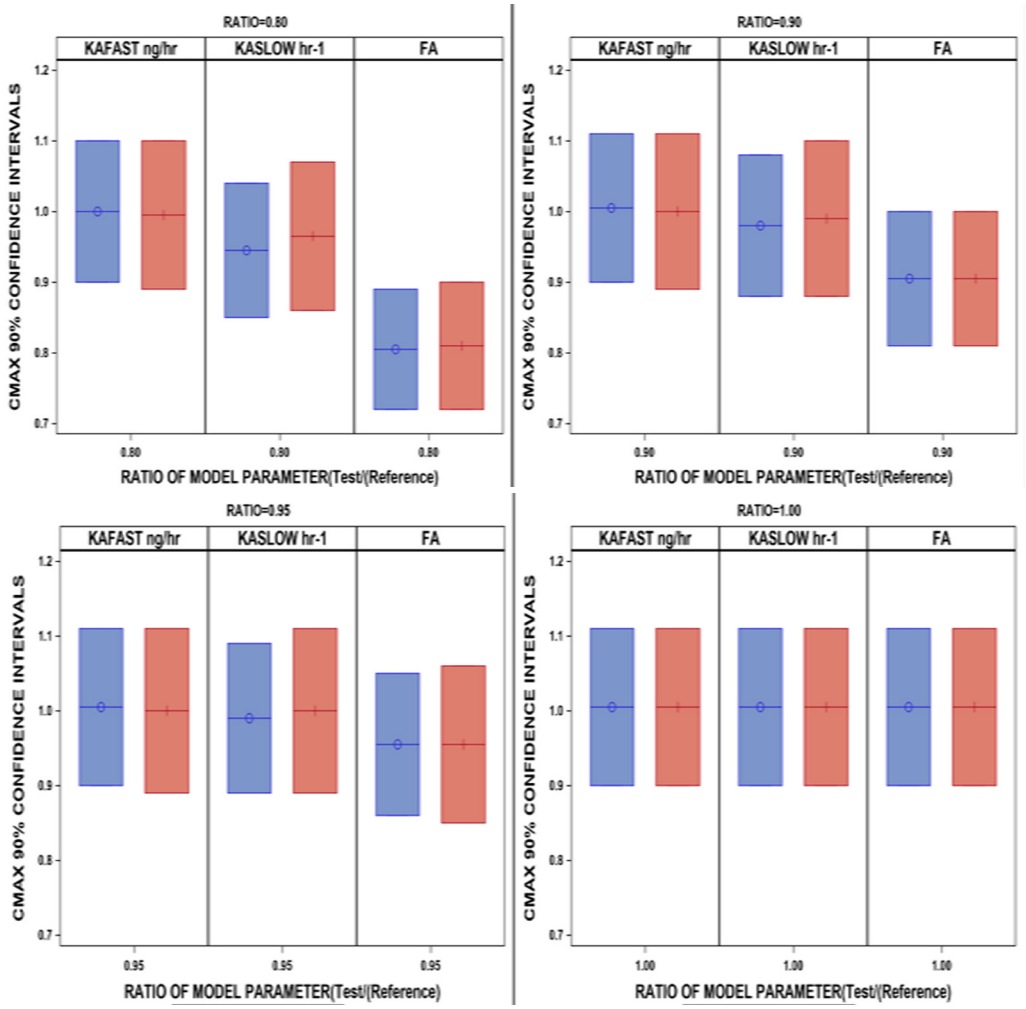

Figure 5: 90% confidence intervals for Concerta® for the BE parameter C_{max} while KAfast (Test), Kaslow (Test) to reference ratios were allowed to vary between 0.8 to 1.0 and Fa (test) being varied between 0.8 to 1.0. References values for these parameters were held constant at the reference values. The blue graphs represents ordinary sampling while the red graph is for optimal sampling. **Note:** (▬): CI_Ordinary; (▬): CI_Optimal.

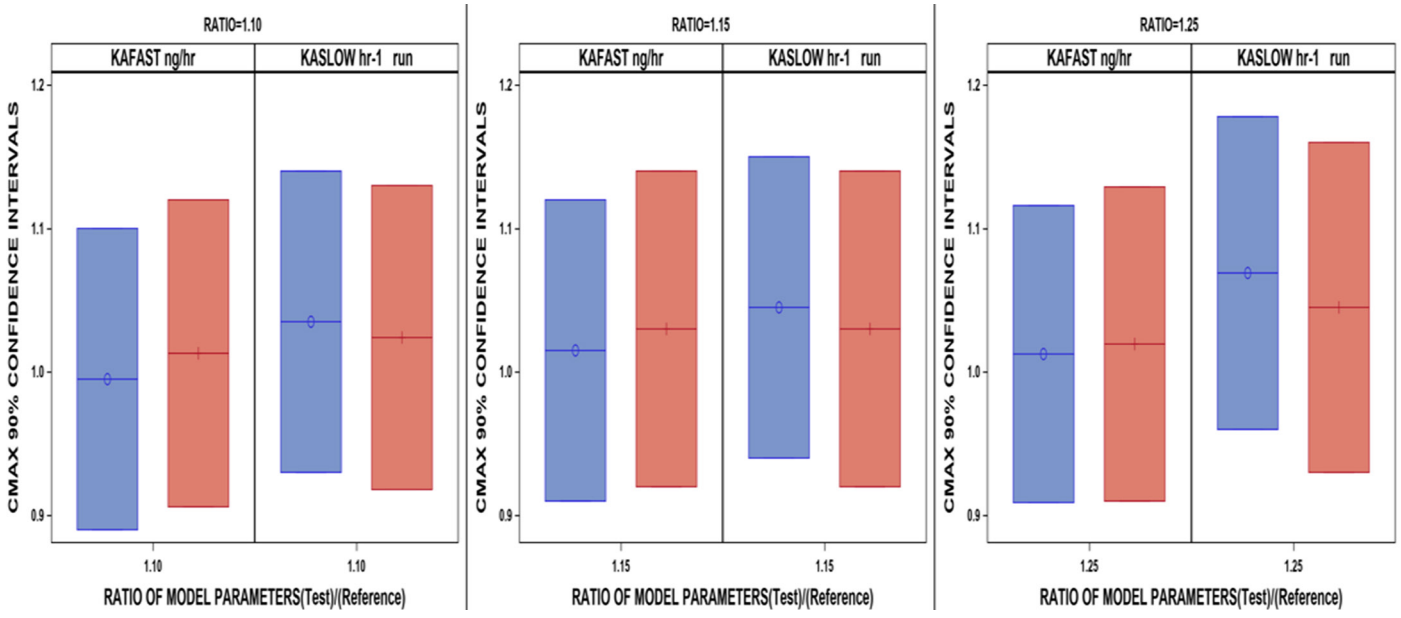

Figure 6: 90% confidence intervals for Concerta® for the BE parameter C_{max} while KAfast (Test), Kaslow (Test) to reference ratios were allowed to vary between 0.8 to 1.0 and Fa (test) being varied between 0.8 to 1.0. References values for these parameters were held constant at the reference values. The blue graphs represents ordinary sampling while the red graph is for optimal sampling. **Note:** (▬): CI_Ordinary; (▬): CI_Optimal.

Table 2: K0fastT/K0fastR (Test/Reference) and KaslowT/KaslowR (Test/Reference) Ratios which were changed for Concerta® and the resulting Type 1 Error Rates at H0; 80% for the Designated BE parameters for ordinary and optimal times. N=1000 simulations.

BE parameter	Ordinary sampling	σD	Optimal sampling	σD
	Type 1 error		Type 1 error	
K0fastT/K0fastR (Test/Reference)				
pAUC: 0-3 hrs	4.30%	0.16	4.80%	0.16
KaslowT/KaslowR (Test/Reference)				
pAUC: 37 hrs	4.80%	0.13	4.80%	0.12
pAUC: 712 hrs	2.60%	0.13	2.00%	0.12
C_{max}	3.60%	0.12	4.90%	0.12
AUC: 0-24 hrs	1.40%	0.16	1.50%	0.11

Table 3: Replicated fasting study BE study results for a fasting bioequivalence study between a Concerta® generic drug X and Concerta® with ordinary sampling *vs.* optimal sampling.

BE Parameter	Ordinary sampling 90% confidence interval	Ordinary sampling Test/ Reference ratio	Optimal sampling 90% confidence interval	Optimal sampling Test/ Reference ratio
pAUC: 0-3 hrs	0.97-1.03	1	1.01-1.07	1.04
pAUC: 37 hsr	0.98-1.04	1.01	0.98-1.04	1
pAUC: 712 hrs	0.88-0.93	0.9	0.91-0.97	0.94
C_{max}	0.91-0.98	0.95	0.91-0.98	0.95
AUC: 0-30 hrs	0.95-1.00	0.98	0.94-1.00	0.97
AUC_{inf}	0.95-1.00	0.98	0.95-1.00	0.98

Table 4: 90% confidence intervals for proof of concept simulations at selected lower model parameter values (0.95 Fa, 0.85 Kafast, 0.85 Kaslow) and at selected upper model parameter values (0.95 Fa, 1.15 Kafast, 1.15 Kaslow) for Concerta®.

BE Parameter	Test/Reference ratio	90% confidence intervals	Test/Reference ratio	90% confidence intervals
	Ordinary Sampling	Ordinary sampling	Optimal sampling	Optimal sampling
0.95 Fa, 0.85 Kafast, 0.85 Kaslow				
pAUC: 0-3 hrs	0.88	0.76-1.03	0.89	0.77-1.03
pAUC: 37 hrs	0.92	0.81-1.04	0.91	0.81-1.03
pAUC: 712hrs	0.95	0.81-1.12	0.93	0.82-1.06
AUC: 0-24 hrs	0.94	0.83-1.08	0.94	0.83-1.07
C_{max}	0.91	0.82-1.00	0.91	0.82-1.01
0.95 Fa, 1.15 Kafast,1.15 Kaslow				
pAUC: 0-3 hrs	1	0.86-1.17	0.99	0.86-1.15
pAUC: 37 hrs	0.98	0.86-1.11	0.97	0.88-1.10
pAUC: 712 hrs	0.94	0.80-1.12	0.96	0.85-1.10
AUC: 0-24 hrs	0.95	0.83-1.09	0.95	0.84-1.08
C_{max}	0.99	0.89-1.10	0.98	0.88-1.11

DISCUSSION

Based upon the results of this and other investigations [11], it becomes apparent either through observation or use of correlations that specific pAUC BE metrics are influenced more by one PK parameter than by others. In the case of Concerta®, KAfast mainly impacts pAUC: 0-3 hrs whereas KAslow influences all other pAUC and C_{max} values. It is also apparent that Fa impacts all pAUC values. The overall effect may be related to inter and intra-subject variability.

The objective of this study was to take a closer look at the possible impact of optimal sampling on pAUC values since prior studies had shown the impact on AUC. The study by Kong FH and Gonin R [7], had concluded that, "the optimization approach for calculating optimal time designs for one-compartment models works well, but is sufficiently general for other compartmental models. It was concluded that the optimal design improves the accuracy of AUC estimation."

Our results not only support this conclusion but expand their findings to also include drugs with complex absorption (i.e., Concerta®) analyzed with a replicated-design BE study. This lends further support to the contention that optimal sampling should also be applied to BE studies for drugs having a wider range of compartmental models since the current research clearly supports its application to drugs with complex absorption.

Our study results have also shown that the point estimates and 90% CI for the BE metrics studied gave similar results for original sampling *vs.* optimal sampling. In the case of the comparison of simulated optimal sampling data to actual experimental data for ordinary sampling (e.g., the generic MP ER oral tablet drug product *vs.* Concerta® BE study described earlier) the 90% CI results were essentially the same.

A possible point of concern for utilization of optimal sampling would be that the T/R ratios for Fa should be within a specified range, perhaps 5% to 10% of the reference but that may prove to be drug and model dependent and would likely require extensive simulation study results to support the final desired T/R ratio resulting from the firm's pilot study when one wants to use optimal sampling.

The FDA Office of Generic Drugs had a meeting to discuss their Model Master File (MMF) in May 2024 [14], and the potential regulatory applications of a MMF.

Based upon the results of the current study, optimal sampling for use with specific PK models should be a part of the planned MMF.

On a practical level the findings presented here should influence BE study design and cost. Using ordinary sampling, the experimental generic *vs.* Concerta® MP study had 24 post-dose samples taken. The Primary Simulation Study had 18 ordinary samples and only 7 optimal samples.

CONCLUSION

The use of optimal sampling would result in fewer samples taken for analysis thus reducing study cost and improving the safety profile for subject volunteers. These factors would benefit not only the firm sponsoring the study and the study subjects, but the entire domain of generic drug development, including regulatory agencies and the public at large. The current study looked at a drug with complex absorption but that is not highly variable. Additional studies need to be conducted to determine the utility of optimal sampling for the highly variable class of drugs.

CONFLICT OF INTEREST

There are no conflicts of interest associated with this manuscript.

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AUTHOR CONTRIBUTIONS

1) Andre J. Jackson-Wrote the paper and prepared Figures, 2) Mutaz Jaber-Performed the optimal Sampling, 3) Henry C. Foehl-Did the statistical analysis, 4) Inder Chaudhary-Supplied the Human Data and helped edit the paper.

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