Operating Characteristics of a Partial-Block Randomized Crossover Bioequivalence Study for Dutasteride, a Drug With a Long Half-Life: Investigation Through Simulation and Comparison With Final Results

Gengqian Cai, PhD, Jake J. Thiessen, PhD, Charlotte A. Baidoo, MMath, and Michael J. Fossler, PharmD, PhD, FCP

Studies to establish bioequivalence (BE) of a drug are important elements in support of drug applications. A typical BE study is conducted as a single dose, randomized, 2-period crossover design. For drugs with long half lives (> 48 hours) and evaluation of multiple BE objectives in 1 trial, this design may not be adequate. A parallel design may then be a more appropriate choice. However, parallel designs require increased sample size, which can become substantial.

One option that is a compromise between the complete randomized block design and the parallel design is a partial-block crossover design. This approach came about during the development of a combination of dutasteride and tamsulosin. Previous experience with performing single-dose dutasteride studies suggested that 28 days of washout is needed between treatments because of its half-life of 7-9 days.

Simulations were performed to assess the operating characteristics of this design using a previously developed PK model. Four scenarios were developed, and each scenario was simulated 500 times. The results showed that this design demonstrated acceptable consumer and producer risk. Partial-block crossover designs should be considered for studies when the half-life of the drug is long and there are more than 2 periods.

**Keywords:** Bioequivalence; modeling and simulation; partial-block crossover design

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Bioequivalence (BE) is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Studies to establish BE of a product are important elements in support of drug applications. In BE studies, the systemic exposure profile of a test drug product is compared to that of a reference drug product. For 2 orally administered drug products to be bioequivalent, the active drug ingredients or active moieties in the test product must exhibit the same rate and extent of absorption as the reference drug product. Usually, 1 or more pilot studies in a small number of subjects will be carried out before proceeding with a full BE study. The pilot studies can be used to validate analytical methodology, assess variability, optimize sample collection time intervals, and provide other information useful for the design of the pivotal BE study.

The definition of BE, expressed in terms of rate and extent of absorption of the active ingredient or moiety to the site of action, emphasizes the use of pharmacokinetic measures in an accessible biological matrix such as blood, plasma, and/or serum to indicate release of the drug substance from the drug product into the systemic circulation. This approach rests on the assumption that measuring the active moiety at the site
of action is generally not possible and, furthermore, that some relationship exists between the efficacy and safety of the compound and its concentration in the systemic circulation. To establish BE, reliance on pharmacokinetic measurements may be viewed as a bioassay that assesses release of the drug substance from the drug product into the systemic circulation. For studies of single-dose design, the primary pharmacokinetic parameters used to assess BE will be total exposure (as measured by area under the curve [AUC]) and peak exposure (as measured by the maximum concentration [Cmax]). The appropriate AUC parameters for assessment of equivalence of extent of bioavailability will generally be $\text{AUC}(0-\infty)$ and $\text{AUC}(0-t)$, where $t$ is the time of the last measurable concentration. In addition, a partial area may be used to assess the extent of early exposure when this information is useful on the basis of appropriate clinical efficacy or safety trials.

The traditional BE criteria (limit) is 0.80 to 1.25, that is, the 90% confidence interval for the ratio of test vs reference should be completely within the limit (0.80, 1.25). There are small but significant differences in how these criteria are applied around the world. The Food and Drug Administration (FDA) and European Medicines Agency (EMEA) require that the confidence intervals of both AUC and Cmax should fall in this limit in order to claim BE.\textsuperscript{2,3} Health Canada requires only that the 90% confidence interval of AUC fall completely within this limit. For Cmax, Health Canada only requires that the point estimate of the test vs reference ratio fall between 0.80-1.25.\textsuperscript{4} However, the FDA and the EMEA usually require BE to be demonstrated only in the fasted state. In contrast, Health Canada requires BE to be demonstrated in both fasted and fed states. For modified-release products, Health Canada also requires the assessment of BE under steady-state conditions.

A typical BE study is conducted as a single-dose, randomized, 2-period crossover design. The washout between periods should be at least 5 half-lives to ensure no carry-over of the previous dose to the next treatment. Sampling should be carried out until at least 80% of the AUC is represented. This method minimizes the percentage of total exposure that is estimated by extrapolation. A BE study to satisfy multiple regulatory requirements would generally be conducted as a single-dose, randomized, 4-period crossover design to evaluate the PK under both fed and fasted conditions.

For drugs with very long half-lives (≥ 48 h) this study design may pose some problems. Prolonged sampling over many days or weeks may lead to dropouts, with loss of data and power. Gaudreault and colleagues showed through simulation,\textsuperscript{5} as well as through re-analysis of a large number of BE studies, that truncating sampling to 72 hours after the dose yields results that are similar to those from traditional sampling. These findings were later confirmed through simulation by another group.\textsuperscript{6} However, the washout between treatment arms is not changed by decreased sampling and may contribute to the dropout problem. In some cases, a parallel design may be a more appropriate design choice. However, the price to be paid for this design is increased sample size, which can become quite significant, especially if there are more than 2 treatment arms in the study.

For studies in which there are greater than 2 treatment arms, 1 option that is a compromise between the complete randomized block design and the parallel design is a partial-block crossover design. Using this design, each subject receives a subset of the total treatments, thus limiting the number of treatment washouts experienced by each subject. Another advantage is that within-subject comparisons and variability may be estimated in this design. In general, the sample size required for such studies is larger than what is required for complete crossover studies, but less than that required for parallel designs. Despite the obvious advantages of these designs, they have not been used to a large extent in the BE literature.

The present approach came about during the development of a fixed-dose combination capsule (FDC) of dutasteride (a 5α-reductase inhibitor) and tamsulosin (an α₁ antagonist). These 2 compounds have markedly different half-lives. The half-life of tamsulosin is 9-11 hours and poses no barrier to performing single-dose complete crossover BE studies.\textsuperscript{7} However, dutasteride has a half-life (after single-dose administration of 0.5 mg) of 7-9 days. Previous experience with performing single-dose dutasteride studies suggested that at least 28 days of washout is needed between treatments.\textsuperscript{8}

Previously published clinical data demonstrate the effectiveness of the combination of dutasteride and tamsulosin when given as the separate marketed formulations in men with a diagnosis of enlarged prostate.\textsuperscript{9} Differing BE requirements (demonstration of BE under both fasting and fed conditions) across North America and Europe resulted in a development plan that included several very large BE trials that would have been expensive to conduct as individual studies. Conducted as a single 4-way crossover study, there was concern that the 3 long washout periods required would result in an excessively long study (~ 5 mo) and excessive dropouts. The partial-block design was selected so as to minimize the time spent on study for the subjects. Simulations were performed to evaluate the operating characteristics of this design, with the
Table I. Pharmacokinetic Variability Data for Dutasteride and Tamsulosin From Pilot Studies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Within-subject CV (%)</th>
<th>Between-subject CV (%)</th>
<th>Point Estimate of Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutasteride: fed state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td>24.77</td>
<td>38.22</td>
<td>0.90</td>
</tr>
<tr>
<td>AUC(0-t)</td>
<td>19.52</td>
<td>102.69</td>
<td>0.95</td>
</tr>
<tr>
<td>Tamsulosin: fed state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td>20.10</td>
<td>24.04</td>
<td>1.06</td>
</tr>
<tr>
<td>AUC(0-t)</td>
<td>16.88</td>
<td>33.98</td>
<td>0.98</td>
</tr>
<tr>
<td>Tamsulosin: fasted state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax(0-t)</td>
<td>13.48</td>
<td>18.84</td>
<td>0.95</td>
</tr>
<tr>
<td>AUC(0-t)</td>
<td>13.74</td>
<td>23.60</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; CV, coefficient of variation.

METHODS

Data from Pilot Study

Point estimates of ratios and variability estimates of pharmacokinetic parameters were available from pilot studies for both dutasteride and tamsulosin, as shown in Table I. Based on the information from these pilot studies, dutasteride has higher within-subject variability than tamsulosin for either AUC or Cmax. Dutasteride also has point estimates further away from unity than tamsulosin for either AUC or Cmax. Therefore, the power/sample size of the study design would be completely driven by dutasteride.

Study Design

The treatments for the proposed study are depicted in Table II. The design was a multicenter, open-label, single-dose, randomized, 3-way partial crossover design study in healthy males. Each subject participated in 3 sessions and received 3 of the 4 regimens listed in Table II. Subjects were randomized to 1 of the following sequences: ABC, ACB, BAC, BCA, CAB, CBA, ABD, ADB, BAD, BDA, DAB, or DBA. Dosing was separated by a washout period of approximately 28 days, as stated previously.

According to FDA and EMEA BE criteria, the 90% confidence intervals for both AUC and Cmax have to be within the specified range of 0.80-1.25. Health Canada requires that only the AUC meet this requirement. So the overall sample size (N = 78) is driven by the FDA/EMEA requirement for Cmax, assuming the point estimate of Cmax ratio is 0.90, as in the pilot study. Only 26 subjects would be needed if the study were powered based on dutasteride AUC in a 2-period crossover design. This difference in regulatory requirements is the main reason Treatments A and B appear in every subject, whereas C and D do not. However, it will be shown below that this design gives the same precision/power as a traditional 2-period crossover design for the C and D comparison using AUC. Using the partial-block design, it is more efficient to balance the treatments within each treatment comparison rather than balancing all 4 treatments. At the same time, there must be ≥90% power for the B:A comparison for dutasteride Cmax.

Table II. Description of Each Treatment

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Flomax 0.4 mg (sustained-release capsule commercially available in United States) and AVODART 0.5 mg in a fed state (Reference)</td>
</tr>
<tr>
<td>B</td>
<td>Dutasteride and tamsulosin hydrochloride combination capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fed state (Test)</td>
</tr>
<tr>
<td>C</td>
<td>Flomax 0.4 mg (sustained release capsule commercially available in United States) and AVODART 0.5 mg in a fasted state (Reference)</td>
</tr>
<tr>
<td>D</td>
<td>Dutasteride and tamsulosin hydrochloride combination capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fasted state (Test)</td>
</tr>
</tbody>
</table>

Estimation of Power for the Parallel (C vs D) Treatment Comparison

In the proposed 3-period partial crossover design, although no subject receives both C and D in a crossover manner, this is a connected partial crossover design for regimens C and D. Connectedness is an important property that every block design must possess if it is to provide an unbiased estimator for all elementary treatment contrasts under the usual linear additive model. In this case, the D-to-C comparison would be bridged through regimens A and B to obtain a more precise estimate than in the typical parallel design. The best linear unbiased estimator (BLUE) for D–C in the log scale is achieved through estimating

\[ D = \frac{A + B}{2} \]

from subjects receiving regimens A, B, and D and estimating...
from subjects receiving regimens A, B, and C. The average of D-[(A+B)/2] is compared to the average of C-[(A+B)/2] to obtain the D–C comparison

\[
E(D - C) = E\left( D - \frac{A + B}{2} \right) - E\left( C - \frac{A + B}{2} \right)
\]

where \( E() \) stands for expectation or mean. The standard error of the BLUE in this design depends only on intrasubject variability, as in the traditional full crossover design. We show the sample size relationship of a 2-period crossover design for regimens C and D versus our 3-period partial-block design below.

For a traditional 2-period crossover design with \( N_x \) subjects, the statistical model for an end point \( Y \) (AUC or \( C_{\text{max}} \) in this case) from treatment \( i \) and subject \( j \) can be expressed as

\[
Y_{ij} = \mu + T_i + S_j + e_{ij}
\]

where \( \mu \) is the mean fixed effect, \( T_i \) stands for the fixed treatment \( i \) (C or D) effect, and \( S_j \) is the random effect of subject \( j = 1, 2, \ldots, N_x \). \( S_j \) is assumed to be normally distributed with mean zero and variance \( \sigma^2_S \). \( e_{ij} \) is the independent random error and is normally distributed with mean zero and variance \( \sigma^2 \), where \( \sigma \) is usually referred to as the intrasubject standard deviation. The 2 random effects \( S_j \) and \( e_{ij} \) are also independent and usually \( \sigma^2_S > \sigma^2 \). Therefore, the intersubject variance is

\[
\text{Var}(Y_{ij}) = \text{Var}(S_j) + \text{Var}(e_{ij}) = \sigma^2_S + \sigma^2
\]

For this 2-period crossover design, the BLUE of the D–C effect is estimated as

\[
T_D - T_C = \frac{\sum_{i=1}^{N_x} (Y_{Dj} - Y_{Cj})}{N_x} = \frac{\sum_{j=1}^{N_x} [T_{Dj} - T_{Cj} + S_j - S_j + e_{Dj} - e_{Cj}]}{N_x}
\]

Note that the subject effect \( S_j \) is cancelled out because of the crossover feature. So the standard error for the comparison of D–C is

\[
\sqrt{\text{Var}(T_D - T_C)} = \sqrt{\text{Var}\left( \sum_{j=1}^{N_x} [Y_{Dj} - Y_{Cj}] \right) / N_x} = \sqrt{2 \cdot N_x \sigma^2 / N_x} = \sqrt{2 \sigma / \sqrt{N_x}}
\]

Similarly, in our design with 2N subjects (assuming subjects 1, 2, ..., N in the cohort getting A, B, and C and subjects \( N+1, N+2, \ldots, 2N \) in the cohort getting A, B, and D), the BLUE of D–C effect is estimated as

\[
T_D - T_C = \frac{\sum_{i=N+1}^{2N} (Y_{Dj} - (Y_{Aj} + Y_{Bj})/2) / N - \sum_{k=1}^{N} [Y_{Ck} - (Y_{Ak} + Y_{Bk})/2] / N}{2N}
\]

\[
= \frac{\sum_{i=N+1}^{2N} [\mu + T_{Dj} + S_j + e_{Dj} - (\mu + T_{Aj} + S_j + e_{Bj})/2]/N - \sum_{k=1}^{N} (\mu + T_{Ck} + S_k + e_{Ck} - (\mu + T_{Ak} + S_k + e_{Bk})/2)/N - \sum_{k=1}^{N} [T_{Dj} - (T_{Aj} + T_{Bj})/2 + e_{Dj} - (\epsilon_{Aj} + \epsilon_{Bj})]/N - \sum_{k=1}^{N} [T_{Ck} - (T_{Ak} + T_{Bk})/2 + e_{Ck} - (\epsilon_{Ak} + \epsilon_{Bk})]/N}{2N}
\]

Note that the subject effect \( S_j \) and \( S_k \) are also cancelled out because of the crossover feature within the ABC cohort and within the ABD cohort, and therefore the standard error for the BLUE of D–C comparison is

\[
\sqrt{\text{Var}(T_D - T_C)} = \sqrt{\frac{\text{Var}\left( \sum_{j=N+1}^{2N} [Y_{Dj} - (Y_{Aj} + Y_{Bj})/2] / N \right)}{2N} + \text{Var}\left( \sum_{k=1}^{N} [Y_{Ck} - (Y_{Ak} + Y_{Bk})/2] / N \right)} / \sqrt{2N} = \sqrt{\frac{N(\sigma^2 + 2\sigma^2 / 4) / N^2 + N(\sigma^2 + 2\sigma^2 / 4) / N^2}{2N}}
\]

To achieve the same precision or power, the ratio of \( N \) to \( N_x \) is therefore 3 to 2. According to the intrasubject CV (19.52%) and point estimate (0.95) obtained from the pilot studies, \( N_x = 26 \) subjects are needed to achieve 90% power to demonstrate BE based on the dutasteride AUC for the D–C comparison, assuming the true ratio is 0.95. Therefore, \( N = 39 \) subjects are needed for each cohort, with a total number of 78 subjects in our 3-period partial-block design to achieve the same power for the D-to-C comparison based on AUC. Thus, the proposed 3-period partial crossover
Table III.

Results of Bioequivalence Study Simulations

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Comparison</th>
<th>Number (%) of Studies Inequivalent for AUC</th>
<th>Number (%) of Studies Inequivalent for Cmax</th>
<th>Number (%) of Studies Declared Inequivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B vs A</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>D vs C</td>
<td>2 (0.4%)</td>
<td>2 (0.4%)</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>2</td>
<td>B vs A</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>D vs C</td>
<td>23 (4.6%)</td>
<td>33 (6.6%)</td>
<td>39 (7.8%)</td>
</tr>
<tr>
<td>3</td>
<td>B vs A</td>
<td>15 (3%)</td>
<td>6 (1.2%)</td>
<td>17 (3.4%)</td>
</tr>
<tr>
<td></td>
<td>D vs C</td>
<td>158 (31.6%)</td>
<td>128 (25.6%)</td>
<td>190 (38%)</td>
</tr>
<tr>
<td>4</td>
<td>B vs A</td>
<td>495 (99%)</td>
<td>478 (95.6%)</td>
<td>497 (99.4%)</td>
</tr>
<tr>
<td></td>
<td>D vs C</td>
<td>493 (98.6%)</td>
<td>476 (95.2%)</td>
<td>494 (98.8%)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve.

Scenario definitions:
1. Treatment B (Dutasteride FDC under fed conditions) and Treatment D (Dutasteride FDC under fasted conditions) bioequivalent to reference treatments A and C (AVODART under fed and fasted conditions, respectively).
2. Bioavailability of both treatments B and D 5% lower than reference treatments (Treatments A and C).
3. Bioavailability of both treatments B and D 10% lower than reference treatments (Treatments A and C).
4. Bioavailability of both treatments B and D 20% lower than reference treatments (Treatments A and C).

The power calculation above is based on pharmacokinetic information from pilot studies. To justify the use of this partial-block design to regulatory authorities, specifically the D-to-C parallel comparison, population pharmacokinetic simulations were performed to assess the design’s operating characteristics. The population pharmacokinetic model used for dutasteride has been published previously and has been shown to be predictive under both single-dose and steady-state conditions. Only the dutasteride component of the combination formulation was investigated in these simulations, since both the sample size and the design are being driven by the unique pharmacokinetic characteristics of this drug.

The following 4 scenarios were investigated via this simulation study:

1. Treatment B (dutasteride FDC under fed conditions) and Treatment D (dutasteride FDC under fasted conditions) are bioequivalent to reference treatments A and C (AVODART under fed and fasted conditions, respectively).
2. On average, bioavailability of both treatments B and D is 5% lower than reference treatments (Treatments A and C).
3. On average, bioavailability of both treatments B and D is 10% lower than reference treatments (Treatments A and C).
4. On average, bioavailability of both treatments B and D is 20% lower than reference treatments (Treatments A and C).

Each scenario was run 500 times using Trial Simulator (version 2.2, Pharsight, Palo Alto, CA). The primary statistical comparisons of interest were

- Bioequivalence under fed conditions (B vs A) – AUC(0-72), Cmax
- Bioequivalence under fasted conditions (D vs C) – AUC(0-72), Cmax

The pharmacokinetic parameters were computed from simulated concentration vs time data from each simulated study. These parameters were then analyzed using a general linear model with terms for subject, treatment, and period. For the B vs A comparison, the test formulation was considered equivalent to the reference if the 90% confidence intervals of both AUC(0-72) and Cmax for the ratio of test to reference fall within 80%-125%. For the D vs C comparison, the 90% confidence intervals of AUC(0-72) and the point estimate of Cmax for the test-to-reference ratio had to fall between 80%-125% for the test dosage form to be declared equivalent to the reference treatment.
**BIOEQUIVALENCE STUDY FOR DUTASTERIDE**

### Table IV. Statistical Assessment of Dutasteride Serum PK Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison of Interest</th>
<th>Geometric LS Means</th>
<th>90% CI</th>
<th>CV%²¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-t)² (ng.hr/mL)</td>
<td>B : A</td>
<td>31.1</td>
<td>0.97</td>
<td>(0.92,1.03)</td>
</tr>
<tr>
<td></td>
<td>A : C</td>
<td>31.9</td>
<td>1.09</td>
<td>(1.01,1.18)</td>
</tr>
<tr>
<td></td>
<td>D : C</td>
<td>29.7</td>
<td>1.01</td>
<td>(0.91,1.12)</td>
</tr>
<tr>
<td></td>
<td>B : D</td>
<td>31.1</td>
<td>1.05</td>
<td>(0.97,1.13)</td>
</tr>
<tr>
<td>Cmax¹ (ng/mL)</td>
<td>B : A</td>
<td>1.97</td>
<td>1.00</td>
<td>(0.94,1.05)</td>
</tr>
<tr>
<td></td>
<td>A : C</td>
<td>1.98</td>
<td>1.01</td>
<td>(0.93,1.09)</td>
</tr>
<tr>
<td></td>
<td>D : C</td>
<td>1.95</td>
<td>0.99</td>
<td>(0.89,1.09)</td>
</tr>
<tr>
<td></td>
<td>B : D</td>
<td>1.97</td>
<td>1.01</td>
<td>(0.94,1.09)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; CV, coefficient of variation; LS mean, least square mean; PE, point estimate.
²Point estimate is the ratio of adjusted geometric means between regimens.
CV% represents a pooled estimate of inter-subject variability across regimens.

Note: Regimen A = Flomax 0.4 mg and AVODART 0.5 mg in a fed state (Reference), Regimen B = Dutasteride and Tamsulosin Hydrochloride combination capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fed state (Test), Regimen C = Flomax 0.4 mg and AVODART 0.5 mg in a fasted state (Reference), Regimen D = dutasteride and tamsulosin hydrochloride combination capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fasted state (Test).

### Table V. Statistical Assessment of Tamsulosin Serum PK Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison of Interest</th>
<th>Geometric LS Means</th>
<th>90% CI</th>
<th>CV%²¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-∞)¹ (ng.hr/mL)</td>
<td>B : A</td>
<td>178.6</td>
<td>1.04</td>
<td>(0.98,1.10)</td>
</tr>
<tr>
<td></td>
<td>A : C</td>
<td>171.9</td>
<td>0.93</td>
<td>(0.86,0.99)</td>
</tr>
<tr>
<td></td>
<td>D : C</td>
<td>186.6</td>
<td>1.01</td>
<td>(0.92,1.10)</td>
</tr>
<tr>
<td></td>
<td>B : D</td>
<td>186.6</td>
<td>0.99</td>
<td>(0.89,1.03)</td>
</tr>
<tr>
<td>AUC(0-t)¹ (ng.hr/mL)</td>
<td>B : A</td>
<td>170.5</td>
<td>1.03</td>
<td>(0.97,1.09)</td>
</tr>
<tr>
<td></td>
<td>A : C</td>
<td>165.8</td>
<td>0.91</td>
<td>(0.85,0.98)</td>
</tr>
<tr>
<td></td>
<td>D : C</td>
<td>181.4</td>
<td>1.00</td>
<td>(0.91,1.10)</td>
</tr>
<tr>
<td></td>
<td>B : D</td>
<td>170.5</td>
<td>0.94</td>
<td>(0.87,1.01)</td>
</tr>
<tr>
<td>Cmax¹ (ng/mL)</td>
<td>B : A</td>
<td>10.6</td>
<td>1.08</td>
<td>(1.00,1.15)</td>
</tr>
<tr>
<td></td>
<td>A : C</td>
<td>9.85</td>
<td>0.70</td>
<td>(0.64,0.77)</td>
</tr>
<tr>
<td></td>
<td>D : C</td>
<td>15.1</td>
<td>1.07</td>
<td>(0.95,1.21)</td>
</tr>
<tr>
<td></td>
<td>B : D</td>
<td>10.6</td>
<td>0.70</td>
<td>(0.64,0.77)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; LS mean, least square means; PE, point estimate.
¹Point estimate is the ratio of adjusted geometric means between regimens.
CV% represents a pooled estimate of inter-subject variability across regimens.

Note: Regimen A = Flomax 0.4 mg and AVODART 0.5 mg in a fed state (Reference), Regimen B = Dutasteride and Tamsulosin Hydrochloride Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fed state (Test), Regimen C = Flomax 0.4 mg and AVODART 0.5 mg in the fasted state (Reference), Regimen D = Dutasteride and Tamsulosin Hydrochloride Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fasted state (Test).

**RESULTS**

Simulation Results

Table III depicts, for each scenario, the number (percentage) of simulated studies that were declared inequivalent for AUC and Cmax, as well as the number of studies that did not show BE. For Scenario 1, in which treatments B and A (crossover) and D and C (parallel) were assumed to be bioequivalent, the simulations suggest that the current design will virtually always return the correct result. For Scenario 2 (bioavailability of test formulations [B and D 5% lower than A and C]), there is 7.8% chance of finding Treatments D and C (the parallel comparison) inequivalent, but Treatments B and A (crossover) will always be found bioequivalent.

For Scenario 3, most of the time Treatments B and A will be found bioequivalent; however, there is a nearly 40% chance that Treatments C and D will not
be found bioequivalent if the ratio is truly 0.9. This is not a surprise and exactly matches statistical theory, since we powered the B vs A comparison assuming the ratio of Cmax is 0.90 and the D–C comparison assuming the ratio of AUC is 0.95. This risk of bioinequivalence can be considered a producer risk, as it indicates that there is a greater chance of finding nonequivalence if the formulations differ by as little as 10% on average. Moreover, it demonstrates that the study design is more than adequate to detect meaningful differences between test and reference formulations. Finally, the results for Scenario 4, bioavailability of test formulations (B and D 20% lower than A and C), show that the current design will detect this difference nearly 100% of the time and return the correct conclusion of lack of BE.

Study Results

Table IV summarizes the actual dutasteride results obtained from the BE study conducted using the partial-block crossover design. During Regimens A and B, subjects received the standard FDA “high-fat” breakfast (2 eggs fried in butter, 2 strips bacon, 4 oz. hash brown potatoes, 8 oz. whole milk, 2 slices of toast or biscuit with 2 tsp. butter). Subjects were randomized to 1 of the following sequences: ABC, ACB, BAC, BCA, CAB, CBA, ABD, BAD, BDA, DAB, or DBA. Blood sampling for PK assessments were taken at predose (time 0) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48, and 72 hours post-dosing.

Of the 101 male subjects randomized, 81 subjects completed all aspects of the study. The mean (range) age, weight, and body mass index were 29.5 (19-45) years, 79.38 (59.0-106.4) kg and 25.6 (19-30) kg/m², respectively. Seventy-seven percent of the subjects were white, and 23% were of African American/African heritage.

In the fasted state, both the dutasteride and tamsulosin components of the FDC were bioequivalent to the reference formulations (AVODART and Flomax) administered in the fasted state (Table V). The 90% confidence intervals for both the AUC and Cmax comparisons were entirely contained within the interval of 0.80-1.25. Similarly, in the fed state, both the dutasteride and tamsulosin components of the FDC were bioequivalent to the reference formulations administered in the fed state. Comparing each formulation in the fed or fasted condition (A:C and B:D), similar effects of food were seen with both components of the test and reference treatments. For dutasteride, both the FDC and AVODART showed no effect of food when compared under fasting conditions. Likewise for tamsulosin, both Flomax and the FDC showed no effect of food on AUC. However, the mean tamsulosin Cmax for both Flomax and FDC showed a 30% decrease under fed conditions, consistent with Flomax labeling.

There were no deaths or other severe adverse events reported during the study. There were 4 adverse event (AE) withdrawals, only 1 of which was considered to be related to the study drug. The most commonly reported AEs (>20%) were dizziness and headache. All AEs reported were either mild or moderate in severity.

These positive BE results are given added support by the simulation studies, which demonstrated that there is virtually no chance of the test product being declared bioequivalent under either fasting or fed conditions if the products differed from each other by 20%. As expected from the simulation results, with the point estimates near unity, BE was demonstrated for both the B vs A and D vs C comparisons.

DISCUSSION

To support the product label for the combination dutasteride/tamsulosin hydrochloride product, a study was needed to establish BE of the FDC to the administration of separate capsules of commercially available dutasteride and tamsulosin formulations. Although there are food effect data on dutasteride and tamsulosin when administered individually, a study was also needed to evaluate the effect of food (high-fat meal state vs fasted state) on the absorption of dutasteride and tamsulosin when given in the FDC formulation.

Although dutasteride can be dosed in a fed or fasted state, tamsulosin is labeled to be dosed within 30 minutes after a meal owing to the significant increase of peak exposure without food. Therefore, the FDC will be dosed in the fed state, which requires that BE of the combination product compared to the individual components is demonstrated in the fed state. However, for Health Canada, BE of both components in both fed and fasted states is required for marketing approval.

To address these BE and food effect requests, one usually would need a 4-period crossover study or 2 crossover studies (one 2-period crossover study for demonstrating BE under fed conditions and one 2-period crossover study for demonstrating BE under fasting conditions). For a compound like dutasteride with an extremely long half-life, a 4-period trial might lead to a substantial number of dropouts because of the length of the study. Also, in such a design, each subject would be dosed in 2 sessions under fasting conditions, which exposes the subjects
to a greater risk of hypotension owing to the higher peak concentration of tamsulosin typically observed under fasting conditions. In the 3-period, partial-block crossover design described in this article, all regulatory requirements have been addressed. In addition, this goal was achieved with a minimal number of subjects. Finally, in the partial crossover design, each subject was exposed to drug under the fasted state in only 1 session, which exposed the volunteers to less risk of hypotension.

Partial-block (incomplete-block) designs were first proposed by Yates for use in agricultural studies and have been widely accepted in statistical experiment design. The name “partial-block design” refers to the situation in which the number of treatments is larger than the block size in the experiment. The guiding principle for block size is to have a homogeneous set of experimental units for more precise treatment comparisons. A partial-block design can be balanced so that each treatment is paired an equal number of times with every other treatment in the same blocks in the design, or it can be partially balanced, in which different treatment pairs occur in the same blocks an unequal number of times. A balanced partial-block design is needed when all the treatment comparisons are of equal importance and require the same precision. However, a balanced design cannot always be constructed for every experimental situation. Even when it can be constructed, it frequently requires excessive numbers of experiment units. The partially balanced partial-block design, in which some treatment comparisons need to be made with greater precision than others owing to an unequal number of times that treatment pairs occur in the same block, was first introduced by Bose and Nair. With limited resources, a partially balanced partial-block design can be an attractive alternative to the balanced design, which requires a larger sample size.

In BE trials, the typical design is to compare the test vs reference within the same subject, since the intrasubject variation is usually much smaller than intersubject variation. Therefore, the randomized, balanced crossover design, in which each subject is treated as a block and the number of period (sessions) in the trial is the block size, is usually used in BE trials. In the majority of BE trials, only 2 treatments are involved (test and reference) or, if there is more than 1 test and/or reference treatment, the comparisons are all equally weighted. Therefore, in the majority of the crossover BE trials, the number of periods is the same as the number of treatments in the trial, such that all the treatment comparisons will be direct, within-subject comparisons.

However, when not all the comparisons require the same precision, as in the present case, the partially balanced partial-block design can be a more appropriate option. Such designs deserve more use in the BE area, as the savings (both in patients and in cost) may be substantial. In the case presented in this article, the savings (compared to conducting 2 separate crossover studies) were estimated to be approximately 30 subjects and approximately $200,000.

In the derivation of the parallel (D–C) comparison, we estimate the difference indirectly through comparing D – (A+B)/2 and C – (A+B)/2 (see Estimation of Power for the Parallel [C vs D] Treatment Comparison, above). Under the assumption that (A+B)/2 is the same in both cohorts, our derivation of the D-to-C comparison is unbiased when compared to the direct parallel comparison of D–C. For the same population with a relatively large sample size, this is a tenable assumption. In the case in which (A+B)/2 is different in the 2 cohorts, the C and D comparison in a parallel manner may be inappropriate. Effective randomization should make this scenario unlikely.

In this article, a partially balanced partial-block design is proposed after carefully considering the objectives of the study. Statistical theory and clinical trial simulations show that such design can be both well powered for the objectives and at the same time minimize the consumer risk. A well-designed partial-block BE study can be as informative as a complete-block design but use less resources.

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REFERENCES


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