Group Sequential Method for PK Bioequivalence Crossover Studies[1]

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Abstract

Bioequivalence of two drug products is usually assessed using a single-stage cross-over study and analyzing the pharmacokinetic parameters AUCt, AUCinf, and Cmax of the products. A two-stage, group-sequential cross-over study design, measuring these same parameters, has been proposed instead. Our simulation shows that the power for the two-stage design is generally lower than the power for the regular one-stage design; this discrepancy increases with increasing within-patient coefficient of variation (CV).

Key Words: PK Bioequivalence test, interim analysis, geometric mean ratio (GMR), within-subject coefficient of variation (CV)

Introduction

Bioequivalence of two drug products, in particular a branded innovator ("Reference") and proposed generic ("Test"), is usually assessed using a single-stage cross-over pharmacokinetic (PK) study. The test T and reference R products are administered to the subjects on separate occasions, with random assignment to the possible sequences. Outcomes include the blood concentration parameters AUCt, AUCinf, and Cmax of the products.

A two-stage, group-sequential cross-over study design, measuring these same parameters, has been proposed instead. In this paper, we focus on the two-way crossover study TR/RT and compare the powers of the proposed two-stage design with the usual, single-stage design.

Assumptions

We assume that the log-transformed PK endpoints (i.e., ln(AUCt), ln(AUCinf), and ln(Cmax)) are normally distributed. Let μT and μR be the population means of the log-endpoints for the test and the reference products, respectively. The performance of the approaches considered depends on μT - μR, which is the log of the geometric mean ratio (GMR) of test versus reference. The within-subject standard deviation (σ) for the log-transformed endpoint is related to the within-subject coefficient of variation (CV) for the untransformed endpoint by the formula

$$\sigma = \sqrt{\ln\left(1 + CV^2\right)}$$

[1] This paper reflects the views of the authors and should not be construed to represent FDA's views or policies.

Study designs

A. Single-stage Study Design

For a given PK parameter, the regulatory standard to conclude bioequivalence in most cases is that the (single-stage) 90% confidence interval (CI) for the geometric mean ratio should be between the bioequivalence limits of [80%, 125%]. This is equivalent to the two one-sided tests procedure at α=0.05, with the sample size determined by the power desired.

B. Two-stage, group-sequential study design

Under the proposed design, an interim analysis is performed when half of the subjects finish (stage I). The trial could continue until the remaining subjects finish if necessary.

The following decision criteria for bioequivalence are applied using a type I error of α=0.025 at each stage.

Stop the trial and **reject** bioequivalence at **stage I**: If the point estimate of the ratio falls outside of the range 80% to 125%.
Stop the trial and conclude **bioequivalence** at **stage I**: If the 95% CI falls within the range of 80%-125%.

Continue the trial through the **stage II** (remaining half of subjects finish): Assessment of bioequivalence is inconclusive if 95% CI extends beyond the range 80% to 125% but point estimate lies within the range at stage I.

Conclude **bioequivalence** at final analysis stage, including all patients, if 95% CI falls within the range of 80%-125%.

Simulation

Simulation data sets were generated for: (1) values of the geometric mean ratio between the bioequivalence limits of [0.80, 1.25] (so that the two products should be considered bioequivalent) and (2) the within-patient coefficient of variation (CV%) equal to 10, 20 and 30 for the PK parameter. Sample sizes used (N=24 or 48) are typical of bioequivalence trials

The equivalence test was carried out using the analysis decision criteria described above.

We assumed that half of the total patients completed the trial in stage I and the remaining half in stage II (if the trial did not stop at stage I). The number of patients enrolled was the same at each sequence and period per each stage.

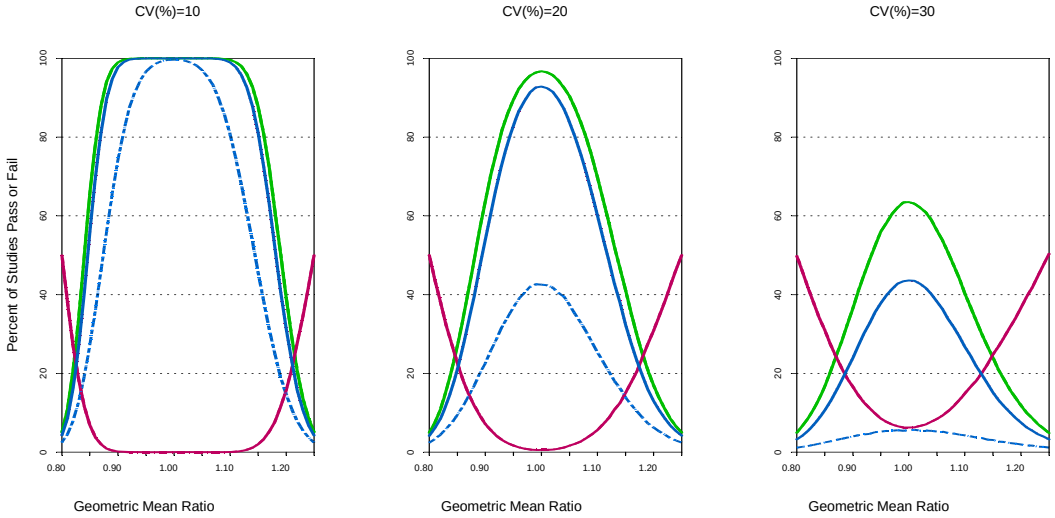
A single-stage equivalence test (all patients) using 90% confidence interval (type I error 0.05 per two-sided tests) was performed to compare with the two-stage equivalence test.

The following graphs summarize the results of simulated bioequivalence tests:

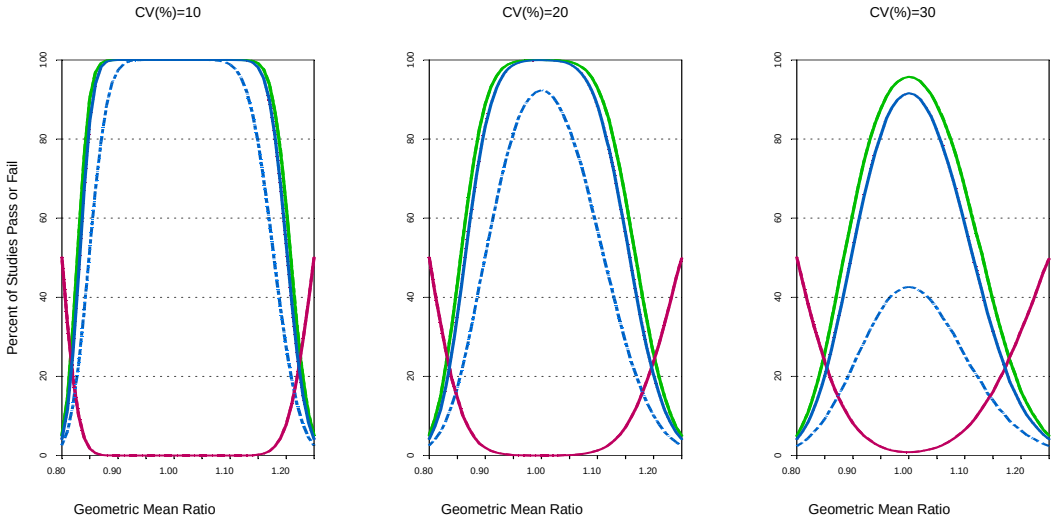
Pass bioequivalence (BE) in single-stage (Green)
Fail BE in stage I (Red)
Pass BE in stage I (Blue dash)
Pass BE in stage I and II (Blue)

On the x-axis are the values of the geometric mean ratio (GMR), ranging from 0.8 to 1.25; on the y-axis is the percent of studies passed (or, failed in red) (0 – 100 %).

N=24



N=48



Discussion

When the true ratio μT/μR is equal to 0.80 and/or 1.25, the proposed two-stage procedure appears to have similar properties for each value of CV(%). The trial has around 50% chance to be stopped at stage I due to the point estimate falling outside of [0.80, 1.25]. The overall probability of passing the bioequivalence test is around 0.05.

For CV(%) equal to 10 or 20, the proposed two-stage procedure appears to have good properties when the true ratio of μT/μR is between 0.85 and 1.20. The chance to pass the equivalence test and stop the trial at stage I is near 15 to 100 percent for the 10 CV(%) case and 6 to 43 percent for the 20 CV(%) case when N=24; and near 27 to 100 percent for 10 CV(%) case and 10 to 92 percent for 20 CV(%) case when N=48. Even if the trial has to go to stage II, the overall chance of passing the equivalence test is lower than that in single-stage study. The overall reduction is near 0 to 10 percent for the 10 CV(%) case and 4 to 10 percent for the 20 CV(%) case when N=24; near 0 to 9 percent for 10 CV(%) case and 20 CV(%) case when N=48..

For CV(%) equal to 30, the proposed two-stage procedure has poor properties when the true ratio of μT/μR is between 0.85 and 1.20. There is a 2 to 6 percent when N=24 and 6 to 43 percent when N=48 of passing the equivalence test; 6 to 37 percent when N=24 and 1 to 32 percent when N=48 of stopping the trial as failure at stage I. Even if the trial goes to stage II, the overall chance of passing the equivalence test is lower than the single-stage study. The overall reduction is near 4 to 20 percent when N=24 and 3 to 9 percent when N=48.

Conclusion

Power for the two-stage sequential design is generally lower than the power for the usual single-stage design. The advantage of sequential design decreases when the CV increases.

Another important point is that the test product has to pass an equivalence test for all three PK parameters, AUCt, AUCinf, and Cmax. Even if the parameters AUCt and AUCinf pass at stage I, the trial may have to go to stage II if the parameter Cmax, which often has a larger CV, fails at stage I.

An investigator designing a bioequivalence study should carefully consider the power of the single-stage design that would be given up with a two-stage design.

References

E. Diletti, D. Hauschke and V. W. Steinijans (1991), “Sample size determination for bioequivalence assessment by means of confidence intervals”, *International Journal of Clinical Pharmacology, Therapy and Toxicology*, Vol. 29 No. 1 (1-8).

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