UNVEILING THE POTENTIAL OF C_{MAX} f_2 FACTOR APPLIED TO PILOT BIOAVAILABILITY/BIOEQUIVALENCE STUDIES

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Introduction

When companies are uncertain of the potential of a new formulation to be bioequivalent to a Reference product, it is common practice to carry out downsized pilot studies as a gatekeeping *in vivo* strategy to decide whether to move forward or not with a full-size pivotal study. In these trials, 12 to 30 subjects are usually enrolled, although, in principle, a sample size is not formally calculated. Analysis and interpretation of results from pilot studies usually rely on the application of the average bioequivalence approach. However, due to the small study size, these studies are inarguably more sensitive to variability.

Objectives

To address and mitigate the uncertainty on the conclusions of pilot studies and on the potential of Test formulations, the f_2 factor was proposed as an alternative approach to the average bioequivalence methodology to assess the potential bioequivalence concerning the maximum observed concentration (C_{max}) [1,2].

The f_2 factor has demonstrated a good relationship between avoiding type I and type II errors [1,2] based on simulated concentration-time profiles. To validate the f_2 factor method in a more diverse and realistic setting, a retrospective analysis was performed with real world pharmacokinetic data, from bioequivalence studies.

Methods

Pazopanib:

- Highly variable drug (intra-subject coefficient of variation ≃ 50%)

Formulations:

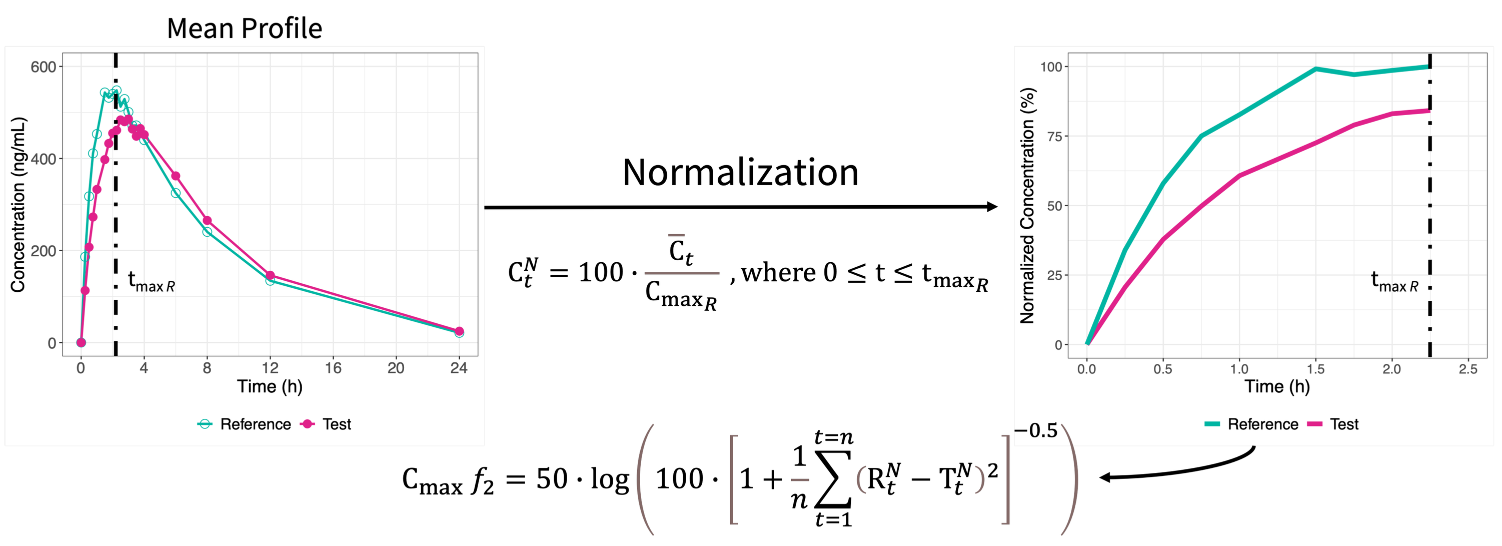
- Pazopanib 400 mg (Test product)
- Votrient® 400 mg (Reference product)

Table 1. Pilot and Pivotal Studies Information

	Pazopanib 400 mg	
	Pilot Study	Pivotal Study
Design	2×2×2	2×2×2
Enrolled	24	122
Completed	23	98

Analysis:

- Average bioequivalence for C_{max} (standard method), performed with Phoenix® WinNonlin® 8.2 (Certara USA Inc., Princeton, NJ).
- Similarity f_2 factor (alternative method) [1,2], using the R package 'f2PilotBE' [3].



$$C_t^N = 100 \cdot \frac{\overline{C}_t}{C_{max_R}}, \text{where } 0 \le t \le t_{max_R}$$

$$C_{max}\, f_2 = 50 \cdot \log\left(100 \cdot \left[1 + \frac{1}{n}\sum_{t=1}^{t=n}(R_t^N - T_t^N)^2\right]^{-0.5}\right)$$

Figure 1. Application of the f_2 factor methodology for C_{max}

Conclusions

The f_2 factor has shown to be capable of predicting bioequivalence between two pazopanib formulations using data from a pilot study, as opposed to the methodology of the average bioequivalence, despite the limited sample size of only 23 subjects included in the study, considered to be underpowered facing the high intrasubject variability known for the drug. The methodology is intended to be applied to data from other bioequivalence trials covering different BCS class drugs. Nevertheless, the f_2 factor has been exhibiting potential to reduce the uncertainty associated with pilot studies and to be helpful in terms of the decision to go forward with pivotal bioequivalence studies.

References

[1] Henriques, S.C.; Albuquerque, J.; Paixão, P.; Almeida, L.; Silva, N.E. (2023). Alternative Analysis Approaches for the Assessment of Pilot Bioavailability/Bioequivalence Studies. *Pharmaceutics*. *15*(5), 1430. doi: 10.3390/pharmaceutics15051430.

[2] Henriques, S.C.; Paixão, P.; Almeida, L.; Silva, N.E. (2023). Predictive Potential of C_{max} Bioequivalence in Pilot Bioavailability/Bioequivalence Studies, through the Alternative f_2 Similarity Factor Method. *Pharmaceutics*. *15*(10), 2498. doi: 10.3390/pharmaceutics15102498.

[3] Henriques, S.C.; Silva, N.E. (2024). Package "F2PilotBE". F2 Factor Alternative Approach for Pilot Bioequivalence Studies. Available online: https://github.com/saracarolinahenriques/f2PilotBE.

Results

Pharmacokinetic Data

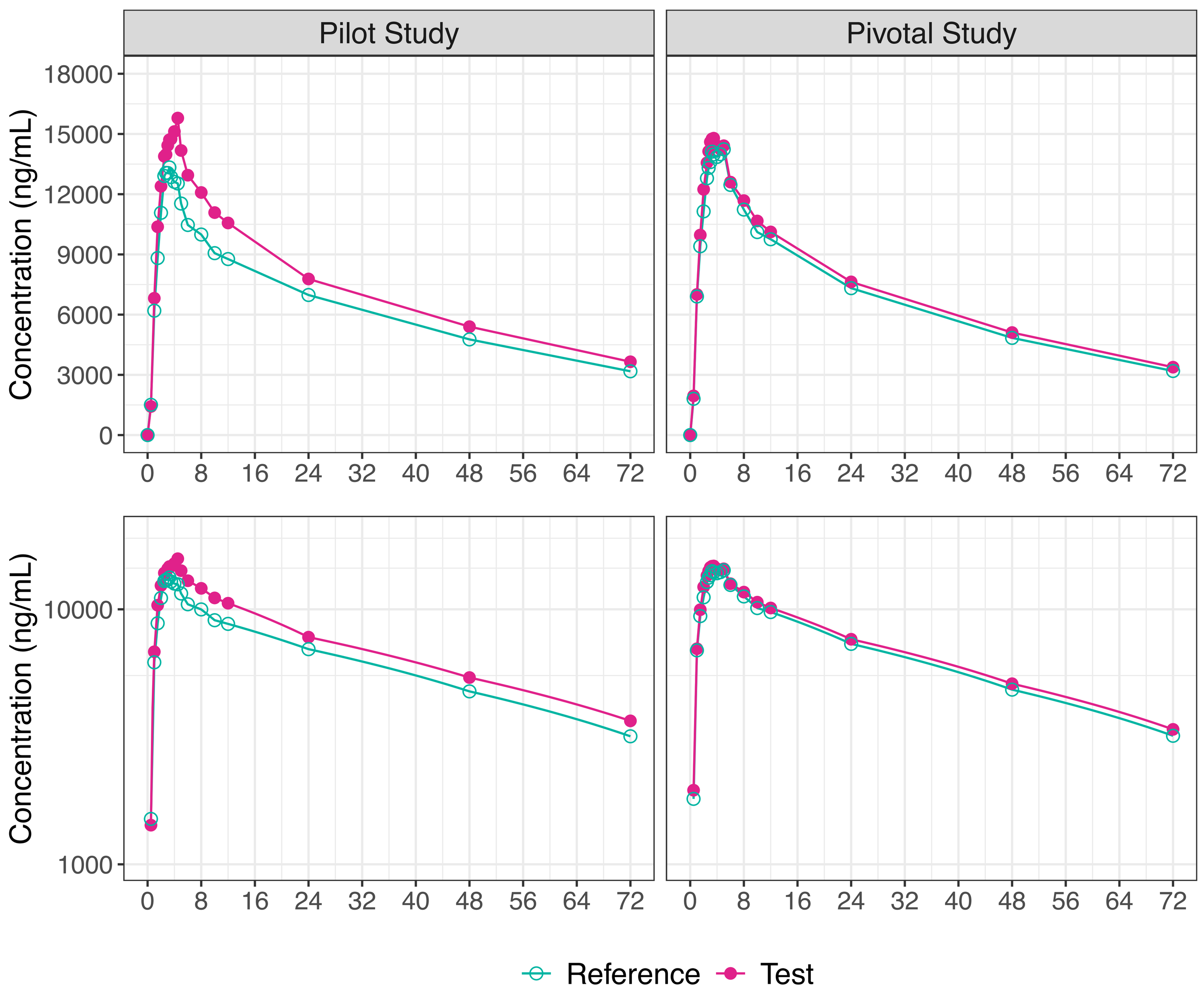


Figure 2. Plasma Concentration-Time Profiles Following Administration of Pazopanib 400 mg Test and Reference Formulation, in Pilot (n=23, Left) and Pivotal (n=98, Right) Studies, in Linear (Above) and Semi-Logarithmic (Below) Scales

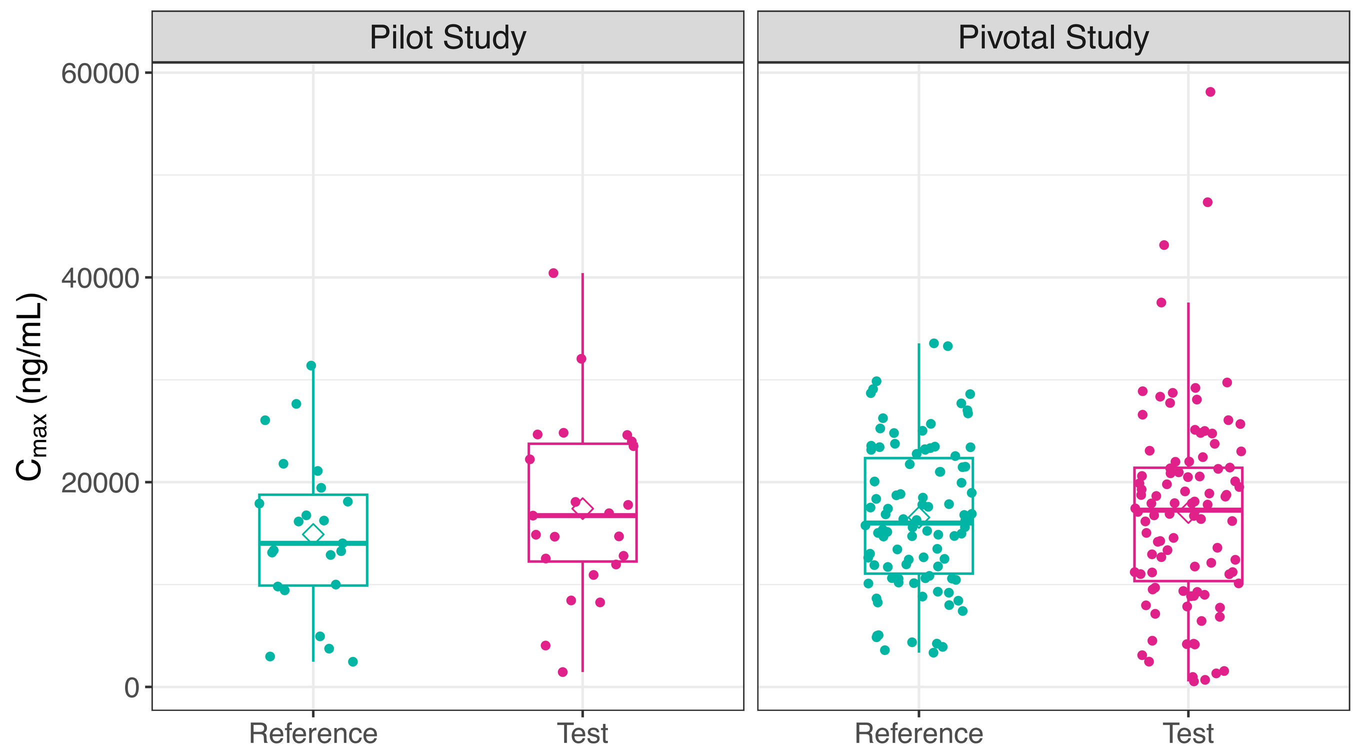


Figure 3. Box Plots of Distribution of C_{max} Following Administration of Pazopanib 400 mg Test and Reference Formulation, in Pilot (n=23, Left) and Pivotal (n=98, Right) Studies. Individual Values are Represented as Points, While Median and Mean Values are Represented as a Line and a Diamond Shape, Respectively

Average Bioequivalence Analysis

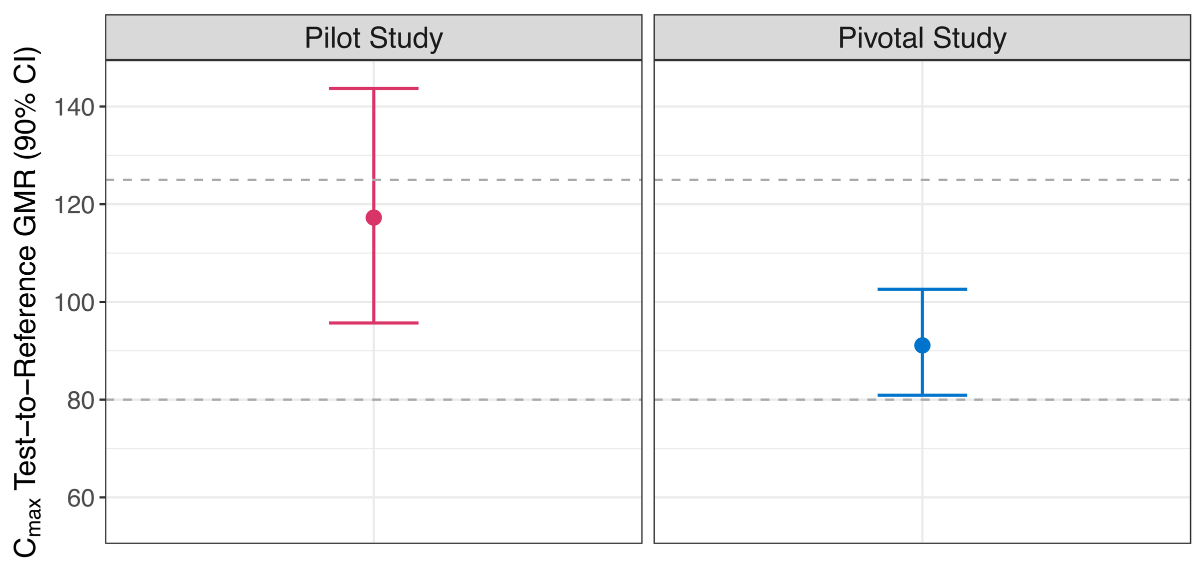


Figure 4. Test-to-Reference Geometric Least Square Means Ratio (GMR) and Corresponding 90% Confidence Interval (CI) Estimated for C_{max}, Following Administration of Pazopanib 400 mg, in Pilot (n=23, Left) and Pivotal (n=98, Right) Studies

Table 2. Average Bioequivalence Results for C_{max}

	Pazopanib 400 mg	
	Pilot Study	Pivotal Study
ISCV (%)	50.1	59.8
GMR [90% CI] (%)	117.26 [95.69 – 143.68]	91.11 [80.91 – 102.61]

Pilot study showed a suprabioavailability of the Test formulation for C_{max} metric, with the upper limit of the 90% confidence interval outside the acceptance bioequivalence range of [80.00-125.00]%, discouraging to go forward with a pivotal study. Pivotal study showed however bioequivalence between Test and Reference formulations.

f_2 Factor Analysis

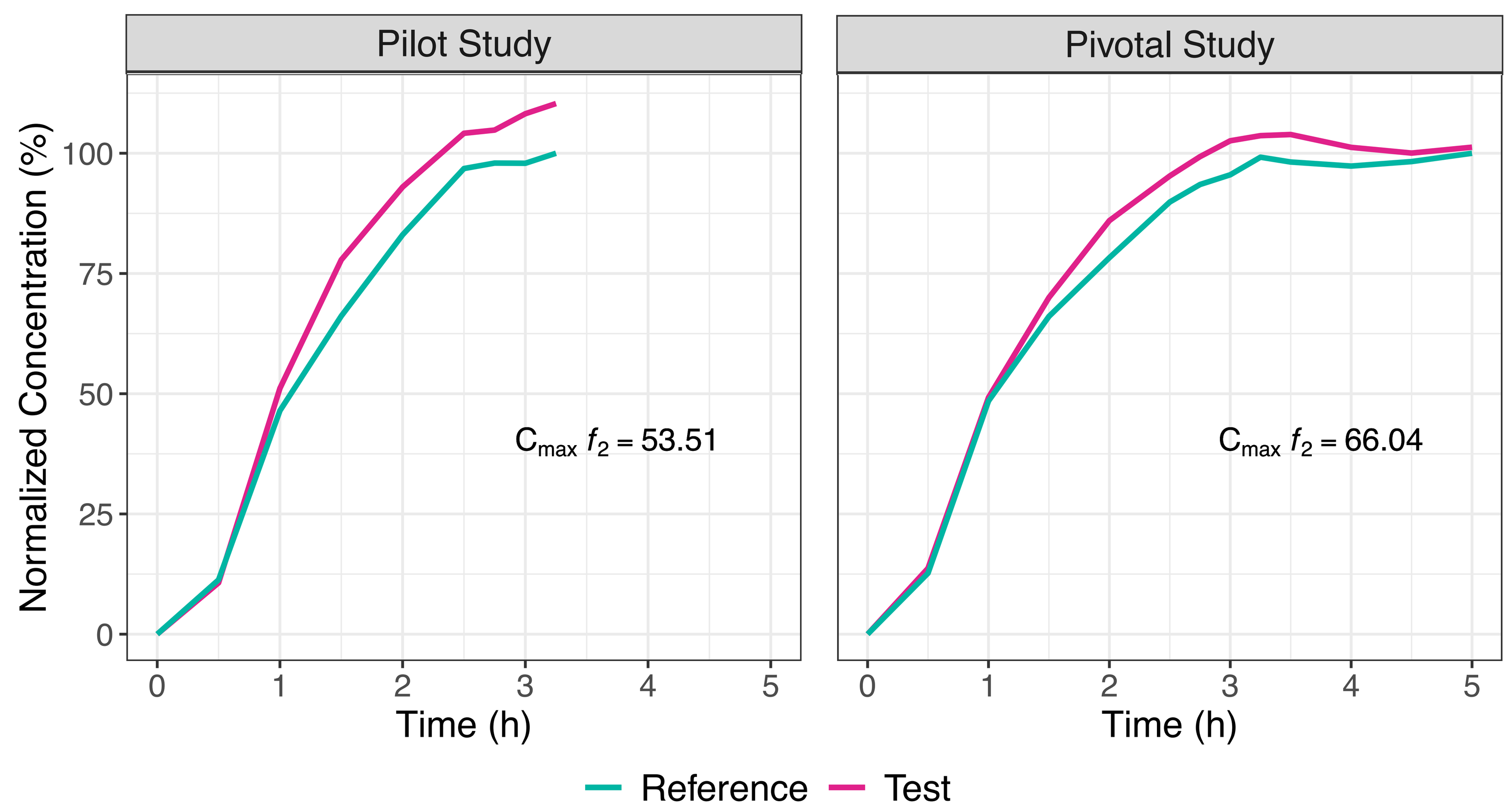


Figure 5. Normalized Test and Reference Mean Concentration-Time Curves, to the Reference C_{max}, Until the Reference t_{max}, for the Estimation of the Similarity f_2 factor, Following Administration of Pazopanib 400 mg, in Pilot (n=23, Left) and Pivotal (n=98, Right) Studies

The f_2 factor applied to pilot study data showed to be above 50, which according to conclusion from previous simulations, indicates a 90% probability that the Test product is truly bioequivalent to the Reference product in terms of C_{max} [1,2], and therefore encouraging to go forward with a pivotal study.

Presented at the 32nd Annual Meeting of the Population Approach Group in Europe (PAGE), June 26 – 28, 2024, Rome, Italy
www.page-meeting.org/?abstract=11251