Notes on the Design of Bioequivalence Study: Baricitinib

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team – Medicines (PQT/MED) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines of submission of documentation for WHO prequalification. In particular, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-seventh Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.* Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited immediate release products containing baricitinib.

Pharmacokinetics of Baricitinib

Following oral administration of baricitinib, a dose-proportional increase in systemic exposure was observed over the therapeutic dose range. Following oral administration, baricitinib is rapidly absorbed with a median t_{max} of approximately 1 hour (range 0.5 - 3.0 h) and an absolute bioavailability of approximately 79 %. Food intake led to a decreased exposure by up to 14%, a decrease in C_{max} by up to 18 %, and delayed t_{max} by 0.5 hours. Baricitinib is to be taken once daily with or without food and may be taken at any time of the day. In a clinical pharmacology study, approximately 75 % of the administered dose was eliminated in the urine, while about 20 % of the dose was eliminated in the faeces. The elimination half-life in healthy volunteers is around 8 h, although the elimination half-life in patients with rheumatoid arthritis and atopic dermatitis was 12.5 h and 12.9 h, respectively.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of baricitinib, the following guidance with regard to the study design should be taken into account:

Study design: A single-dose cross-over design is recommended.

Dose: As the EoI includes 2 mg tablets, a study with this strength should be conducted.

Fasted/fed: The bioequivalence study should be conducted in the fasting state as baricitinib can be taken irrespective of meals.

Subjects: Healthy adult subjects should be recruited. It is not necessary to include patients in the bioequivalence study. Prospective study participants should be tested and confirmed negative for latent tuberculosis before enrolling in a bioequivalence study, should have normal liver function tests, blood counts, and lipid profiles at baseline prior to study drug administration, and subjects at an increased risk for thrombosis should be excluded.

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Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. Therefore, bioequivalence should be based on the determination of baricitinib.

Sample size: Information currently available to PQT/MED indicates that baricitinib pharmacokinetic parameters, C_{max} and AUC_{0-t}, in the fasted state possess low to moderate variability (13–20%). These data may facilitate the calculation of a sufficient sample size for a single-dose cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of baricitinib of 12 h, a washout period of 7 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive for the first 3 hours after administration to properly characterize the C_{max} of baricitinib. It is not necessary to take blood samples beyond 48 hours for the characterization of baricitinib pharmacokinetics. For example, samples can be taken pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 24.00, 36.00 and 48.00 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that the measurement of baricitinib is feasible (LLOQ of 0.2 ng/ml). The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the C_{max} in most profiles of each formulation (test or comparator).

Statistical considerations: The data for baricitinib should meet the following bioequivalence standards in a single-dose crossover design study:

- The 90% confidence interval of the relative mean AUC_{0-t} of the test to comparator product should be within 80.00 – 125.00%

- The 90% confidence interval of the relative mean C_{max} of the test to comparator product should be within 80.00 – 125.00%.

Biowaiver: Baricitinib appears to be a BCS Class III API, although this would need to be confirmed by classification data in an application. Therefore, a BCS-based biowaiver for baricitinib is considered a possible alternative to a bioequivalence study, provided the requirements for granting a BCS-based biowaiver are met as outlined in the ICH Guideline "Biopharmaceutics Classification System-Based Biowaivers" M9 (2019) and the PQT/MED guidance "PQT/MED- specific Annotations for the ICH M9 Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications" (2021).