Notes on the Design of Bioequivalence Study:
Abacavir

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (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-first Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

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

Pharmacokinetics of abacavir

Maximum abacavir concentrations are observed in serum within 0.5 to 3.0 hours of dosing in the fasted state (median T_{max} of 1 - 1.5 hour). The elimination half-life of abacavir is 1.5 hours. Food delayed absorption and decreased C_{max} of abacavir but did not affect overall plasma concentrations (AUC). Therefore, abacavir can be taken with or without food.

Guidance for the design of bioequivalence studies

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

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

Dose: As the EoI includes abacavir 300 and 600 mg tablets, as well as 60 mg scored and dispersible tablets, the bioequivalence study should be conducted preferably with the 600 mg strength if all strengths are developed and the requirements for the additional strength biowaiver are fulfilled. If only the 60 mg scored and dispersible tablet is developed, the bioequivalence study should be conducted with this strength. The 300mg tablet could be waived based on a Biopharmaceutics Classification System (BCS) biowaiver, if the corresponding requirements for BCS class III drugs are fulfilled, since abacavir is considered to be a BCS class III drug.

When conducting bioequivalence studies, it is essential to administer the test and the comparator product according to their corresponding instructions for use. In those cases where the test and the comparator product are different dosage forms with different methods of administration (e.g. a tablet that should be taken with a glass of water vs. a dispersible tablet to be dispersed in 10 mL of water) the bioequivalence study should be conducted employing the intended method of administration of each product. It is considered incorrect to standardise the volume of liquid in all these cases (e.g. administering a glass of water after the intake of a dispersible tablet or rinsing the container where a dispersible tablet has been suspended with the remaining liquid of a glass of water) because this standardisation does not occur in real life conditions.

Fasted/fed: As the comparator abacavir product can be taken with or without food, a fasted state study is recommended.

Subjects: Healthy adult subjects should be recruited. It is not necessary to include patients in the bioequivalence study.

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 abacavir.

Sample size: Information currently available to PQT/MED indicates that abacavir C_{max} intra-subject variability is 15 - 25%. 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 abacavir in healthy volunteers of 1.5 hours, a washout period of seven days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive for the first four hours after administration to properly characterize the C_{max} of abacavir. It is not necessary to take blood samples beyond 12 hours for the characterization of abacavir pharmacokinetics. For example, samples can be taken pre-dose and at 0.16, 0.33, 0.50, 0.67, 0.83, 1.00, 1.16, 1.33, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00 and 12.00 hours after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure abacavir in human plasma using LC-MS/MS analytical methodology. 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 abacavir 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 reference product should be within 80.00–125.00%.

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

Biowaiver: A BCS-based biowaiver for abacavir 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).