

Notes on the Design of Bioequivalence Study: Abacavir / Lamivudine

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-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 and lamivudine.

Pharmacokinetics of abacavir and lamivudine

Maximum abacavir concentrations are observed in plasma within 0.5 to 3.0 hours of dosing in the fasted state (median T_{max} of 1 - 1.5 hour). The 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.

Maximum lamivudine concentrations are observed in plasma within 0.5 to 3.0 hours of dosing in the fasted state (median T_{max} of 1 - 1.5 hour). The half-life of lamivudine is 5-7 hours. Co-administration of lamivudine with food results in a delay of T_{max} and a lower C_{max} (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorption is not influenced. Therefore, lamivudine can be taken with or without food.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of abacavir and lamivudine 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 lamivudine/abacavir 300/600 mg tablet (preferably scored) and 60/120mg tablet (scored and dispersible), the bioequivalence study should be conducted with the 300/600 mg tablet if both strengths are developed and the conditions for an additional strength biowaiver are fulfilled. Otherwise, a bioequivalence study is required for each proposed product (i.e. 5 units of the 60/120 mg dispersible test tablet vs. 1 unit of the 300/600 mg comparator tablet). As abacavir and lamivudine are BCS Class III APIs, a BCS-based biowaiver for a proposed 300/600mg product may be possible if the requirements for such a biowaiver are met.

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 30 - 50 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 abacavir and lamivudine 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 drugs are considered to best reflect the biopharmaceutical quality of the product. Therefore, bioequivalence should be based on the determination of the parent compounds.

Sample size: Abacavir C_{max} and lamivudine C_{max} seems to be moderately variable (15 - 25% approx.). These data may facilitate the calculation of a sufficient sample size for a cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of lamivudine in healthy volunteers of 5- 7 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 and lamivudine. It is not necessary to take blood samples beyond 12 hours for the characterization of abacavir pharmacokinetics and 24 hours for lamivudine. 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, 2.16, 2.33, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00 and 24.00 hours.

Analytical considerations: Information currently available indicates that it is possible to measure abacavir and lamivudine 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 and lamivudine 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: A BCS-based biowaiver for abacavir and lamivudine 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).