Notes on the Design of Bioequivalence Study: Lenacapavir sodium

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 may be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines on submission of documentation for WHO prequalification. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, 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 tablet and the subcutaneous injection containing lenacapavir sodium.

Pharmacokinetics of lenacapavir

Following oral administration, maximum lenacapavir plasma concentrations are observed around 4h after dosing in the fasting state. AUC and C_{max} increases less than dose proportionally over the dose range of 50– 1800 mg. The elimination half-life of orally administered lenacapavir is about 10 – 12 days.

After administration of lenacapavir with food, no relevant food effect is observed, and therefore, lenacapavir may be administered with or without food.

Following subcutaneous injection, maximum lenacapavir plasma concentrations are observed around 85 days after dosing. AUC and C_{max} increases dose proportionally over the dose range of 309 - 927 mg. The elimination half-life of subcutaneous administered lenacapavir is about 8 – 12 weeks.

Guidance for the design of bioequivalence studies

Lenacapavir sodium is available as a solution for subcutaneous injection and an oral tablet.

Solution for subcutaneous injection

The lenacapavir 463.5 mg base/1.5 ml (eq 309 mg base/ml) subcutaneous injection is an aqueous solution for injection. The comparator product contains the API, macrogol and water for injection only, but it exhibits a slow re-dissolution from the site of subcutaneous administration with peak plasma concentrations occurring 84 days post-dose. The test product may qualify for a biowaiver of the in vivo bioequivalence study if it contains the same API and the same excipients and the same grade of excipients in the same molar concentrations as the comparator product.

Oral tablet

Taking into account the pharmacokinetic properties of lenacapavir, the following guidance with regard to the study design should be taken into account for the 300 mg tablet:

Design: A single-dose parallel study is recommended, considering the long elimination half-life.

Dose: As the 300 mg tablet and the 463.5 mg injectable are the only invited strengths, these strength should be employed.

Fasted/fed: In clinical practice, lenacapavir may be taken without regard to food. The comparator product employs a complex manufacturing process, *i.e.*, a solid dispersion process, in order to enhance the solubility of lenacapavir sodium being released from the product (see the EPAR of Sunlenca for more information). Due to the low solubility of this API and the complexity of the manufacturing process employed, there is an increased risk that the *in vivo* performance of such a product will be impacted differently by varying gastrointestinal conditions between fasted and fed conditions. Therefore, for such drug products, bioavailability differences related to differences in formulation and/or manufacturing process may not be detected with a single BE study, *i.e.*, results from a fasting BE study may not be extrapolated to predict fed BE study outcome or vice versa, thus both fasting and fed BE studies should be conducted, unless otherwise justified (e.g., by demonstrating the use of a formulation with the same or similar excipient composition and the same manufacturing process as in the comparator product).

On this scientific basis, for lenacapavir sodium products, two bioequivalence studies are required, *i.e.*, single-dose, parallel design bioequivalence studies should be conducted under both fasting and high-fat, high-calorie fed conditions.

In the case of the subcutaneous injectable, the study can be conducted irrespective of food, although the chosen conditions should be consistent for all subjects.

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 lenacapavir.

Sample size: Information currently available to PQT/MED indicates that the inter-subject variability for oral lenacapavir is around 60% for C_{max} and AUC, while inter-subject variability of injectable lenacapavir ranges from 28% to 58% (Hitchcock et al. Lenacapavir: A novel injectable HIV-1 capsid inhibitor. Int J Antimicrob Agents. 2024;63(1):107009. doi: 10.1016/j.ijantimicag.2023.107009). These data may facilitate the calculation of the sample size for the parallel bioequivalence studies.

Washout: A parallel study design is recommended, considering the elimination half-life of lenacapavir (10 – 12 days after oral administration and 8 – 12 weeks after subcutaneous injection). A washout is not applicable.

Blood sampling: The blood sampling should be intensive for the first 6 hours after oral administration to properly characterize the C_{max} of lenacapavir. It is not necessary to take blood samples beyond 72 hours for the oral formulation. For example, blood samples might be taken at pre-dose, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00, and 72.00 h after drug administration. In the case of the subcutaneous injection, samples should be taken to ensure that C_{max} is properly characterised and AUC_{0-t} covers more than 80% of AUC_{0-inf}. For example, blood samples might be taken at pre-dose, 0.5, 1, 2, 3, 7, 10, 14 days and 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 20, 32, 44 and 56 weeks after injection.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure lenacapavir in human plasma using LC-MS/MS analytical methodology with a LLOQ of 0.1 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). The bioanalytical method should be validated according to the WHO Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6.

Statistical considerations: The data for lenacapavir should meet the following bioequivalence standards in single-dose parallel design studies conducted under fasting and high-fat, high-calorie fed conditions for the oral formulation and for the injectable formulation irrespective of food intake:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72h}$ for the oral formulation and $AUC_{0\text{-}t}$ for the injectable formulation 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%.