Notes on the Design of Bioequivalence Study: Cabotegravir

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. 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 products containing cabotegravir.

Pharmacokinetics of cabotegravir

Cabotegravir is rapidly absorbed following oral administration, with median Tmax at 3 hours post dose for the tablet formulation. Cabotegravir may be administered with or without food. Food increases the extent of absorption of cabotegravir. Bioavailability of cabotegravir is independent of meal content: high fat meals increased cabotegravir $AUC_{0\text{-}inf}$ by 14% and increased C_{max} by 14% relative to fasting conditions. Cabotegravir has a mean terminal half-life of 41 h.

Cabotegravir IM injection exhibits absorption-limited (flip-flop) kinetics resulting from slow absorption from the gluteal muscle into the systemic circulation resulting in sustained plasma concentrations. Following a single intramuscular dose, plasma cabotegravir concentrations are detectable on the first day and gradually rise to reach maximum plasma concentration with a median Tmax of 7 days. Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection. Plasma cabotegravir exposure increases in proportion or slightly less than in proportion to dose following single doses ranging from 100 to 800 mg. Cabotegravir mean apparent terminal phase half-life is absorption-rate limited and is estimated to be 5.6 to 11.5 weeks after a single dose IM injection. The significantly longer apparent half-life compared to oral reflects elimination from the injection site into the systemic circulation.

Guidance for the design of bioequivalence studies

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

Design: A single-dose crossover design is recommended for the oral tablet. A single-dose, parallel design is recommended for the intramuscular prolonged-release suspension for injection.

Dose: As the EoI only includes the strength 30 mg as tablet and 600 mg / 3 ml intramuscular prolonged-release suspension for injection, the bioequivalence study should be conducted with these strengths. For the cabotegravir IM injection, intramuscular injection placement should be considered carefully to avoid subcutaneous depot deposition.

Fasted/fed: For the tablet product, the bioequivalence study should be conducted in the fasting state as cabotegravir tablets can be taken irrespective of meals. This is design element is not applicable for the intramuscular injection product.

Subjects: Healthy adult subjects should be recruited. It is not necessary to include patients in the bioequivalence study. In the case of a parallel design, stratified randomization should be employed to ensure balanced groups with respect to weight and sex and these covariates should be included in the statistical model.

For Cabotegravir IM injection, prior to injection, an optional oral lead-in dosing followed by a washout period may be considered to assess tolerability as described in the comparator labeling.

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 the parent compound.

Sample size: Cabotegravir C_{max} seems to be moderately variable (intra-subject CV of 22% approx.) when administered orally. After intramuscular administration the expected inter-subject CV is around 55-65%. These data may facilitate the calculation of a sufficient sample size for a parallel bioequivalence study.

Washout: Taking into account the elimination half-life of cabotegravir of 41 hours in healthy volunteers, a washout period of 2 -3 weeks is considered sufficient to prevent carry over in the bioequivalence study for the oral product. A washout is not applicable for the intramuscular prolonged-release suspension for injection as a parallel design is recommended.

Blood sampling: The blood sampling in the bioequivalence study for the oral tablet should be intensive for the first hours after administration to properly characterize the C_{max} of cabotegravir. It is not necessary to take blood samples beyond 72 hours for the characterization of cabotegravir pharmacokinetics. For example, samples can be taken pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72 hours after dosing.

The blood sampling in the bioequivalence study for the intramuscular injection should be taken frequently around the 7th day and for at least 42 weeks. **However, a reduced sampling period of 12 weeks may be employed if the test product has the same qualitative excipient composition (Q1) and similar quantitative composition (Q2) as the comparator product, although extrapolated AUC exceeds 20%.** For example, for a sampling period of 42 weeks, samples can be taken pre-dose and at 4, 8, 16, 24, 48, 96, 120, 144, 168, 192 hours, 2, 3, 4, 6, 8, 12, 20, 28, 36, and 42 weeks after administration. **For a sampling period of 12 weeks, samples can be taken pre-dose and at 4, 8, 16, 24, 48, 96, 120, 144, 168, 192 hours, 2, 3, 4, 6, 8 and 12 weeks after administration.**

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure cabotegravir in human plasma using LC-MS/MS analytical methodology (10 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). See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations.

Statistical considerations: The data for cabotegravir should meet the following bioequivalence standards in a single-dose cross-over or parallel design study:

For the oral tablet:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72\ h}$ 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%.

For the intramuscular prolonged-release suspension for injection:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}t}$ 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%.
- The 90% confidence interval of the relative mean $AUC_{0\text{-}inf}$ of the test to comparator product should be within 80.00 – 125.00% for a study conducted for 42 weeks. For studies conducted for 12 weeks, the 90% confidence interval of the relative mean $AUC_{0\text{-}inf}$ of the test to comparator product should be submitted as supportive information.
- The 90% confidence intervals of partial AUCs (e.g., $AUC_{0\text{-}8\ weeks}$ and $AUC_{8\ weeks\text{-}t}$ for the 42 weeks sampling period or $AUC_{0\text{-}6\ weeks}$ and $AUC_{6\ weeks\text{-}t}$ for the 12 weeks sampling period) should also be submitted as supportive information.