Notes on the design of bioequivalence study: Raltegravir

In healthy volunteers administered single oral doses of raltegravir in the fasted state, raltegravir is rapidly absorbed with a tmax of approximately 3 hours post-dose. Raltegravir AUC and Cmax increase dose proportionally over the dose range 100 mg to 1,600 mg. Raltegravir may be administered with or without food. Food appears to increase pharmacokinetic variability relative to fasting.

The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter α-phase half-life (~1 hour) accounting for much of the AUC.

Guidance for the design of bioequivalence studies:

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

**Design:** A cross-over design is recommended.

**Dose:** As the EoI includes 400 mg tablets for adults, and 5 and 50 mg dispersible tablets (scored), the 400 mg strength is recommended for the bioequivalence study. A dose of 1 x 400 mg, 8 x 50 mg or 80 x 5 mg should be tested, if the waiver for the 5 mg dispersible tablet is not possible based on the 50 mg dispersible tablet. In the case of the 5 or 50 mg dispersible tablet the test product should be administered with the method of administration and volume of water intended in the dosing instructions of the product and compared with the reference tablet that should be taken with 240 ml of water.

**Fasting/fed:** The bioequivalence study should be conducted in the fasting state.

**Subjects:** Healthy volunteers
Sample size: Raltegravir pharmacokinetic parameters, Cmax and AUC₀₋₄₈, in the fasting state seem to possess high variability (>30%), although information available is limited and confounding factors might have inflated the intra-subject variability estimation. A pilot study is recommended for a proper estimation of intra-subject variability until more data becomes available to PQT-m. The pilot study data will facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: At least seven (7) days.

Blood sampling: Predose, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 h after drug administration. The pilot study data will also facilitate the selection of the sampling time points.

Analytical considerations: Information currently available indicates that it is possible to measure raltegravir in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the Cₘₐₓ in most profiles of each formulation (test or comparator).

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. The data for the parent compound should be used to assess bioequivalence.

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

- The 90% confidence interval of the relative mean AUC₀₋₄₈ of the test to reference product should be within 80-125%
- The 90% confidence interval of the relative mean Cₘₐₓ of the test to reference product should be within 80-125%

Information currently available to PQTm suggests that the comparator product is a highly variable drug product for both AUC₀₋₄₈ and Cmax in the fasting state. Widening of the acceptance range for AUC₀₋₄₈ is not acceptable, but the applicant may design a replicate cross-over study to estimate variability more accurately and to widen the acceptance range for Cmax. For more information on replicate study designs and average scaled bioequivalence, refer to Section 7.9.3 of Annex 7, TRS 992.