Notes on the design of bioequivalence study: Bedaquiline

Notes on the design of bioequivalence studies with products invited to be submitted to the WHO Prequalification Team – Medicines (PQTm) 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.


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

Pharmacokinetics of Bedaquiline

Bedaquiline is absorbed slowly after oral administration with a median tmax of 4 to 6 hours. At clinically relevant doses, the absorption of bedaquiline appears to be linear following administration of an oral solution containing solubility enhancers. In several studies a second peak was observed in the plasma concentration-time profile either due to bile salts aiding solubility and thereby absorption, or due to enterohepatic recycling.

The intake of a normal breakfast (not a high-fat, high-calorie breakfast) increases bedaquiline absorption (2.6-fold increase in \(C_{\text{max}}\) and 1.9-fold increase in \(AUC\) in one study, and 3.8-fold for \(C_{\text{max}}\) and 2.4-fold for \(AUC\) in another study with the same type of breakfast). The food effect from an oral solution was less pronounced (\(AUC\) increased only 27%) probably because the oral solution contained solubility enhancers or because of the intake of a different type of breakfast. The effect of high-fat meal has not been investigated. Bedaquiline is intended to be taken with food.

Bedaquiline is reported to exhibit a long-terminal half-life of approximately 5.5 months in patients, but approximately 30 hours in healthy volunteers after a 400 mg single-dose. The effective half-life is much shorter based on the accumulation ratio at 14 days (effective half-life of 24 h) and also the time to steady state (effective half-life of ca. 2 days).

No inter-conversion of bedaquiline into either the RR or the SS enantiomer was observed \textit{in vivo}.

The inter-individual variability is reported to be low to moderate. In DS-TB infected patients, CV of \(C_{\text{min}}\), \(C_{\text{max}}\), and \(AUC_{24h}\) ranged from 30% to 49%.

Guidance for the design of bioequivalence studies:

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

**Design:** A parallel design is recommended based on the long half-life of bedaquiline in patients, but a cross-over design seems to be feasible based on the reported half-life of approximately 30 hours in healthy volunteers.

**Dose:** As the EoI includes only the 100 mg strength of Bedaquiline tablet, this strength should be tested versus the comparator at a dose of 1 x 100 mg, assuming the bioanalytical methodology is sufficient (see below).
**Fasting/fed:** The bioequivalence study should be conducted in the fed state with a normal breakfast (500 – 600 Kcal), not a high-fat, high-calorie meal.

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

**Sample size:** Information currently available in the reference product public assessment report indicates that the inter-subject variability for bedaquiline is around 30% to 49%, but these values seem to refer to steady state conditions and the bioequivalence study is conducted after a single dose. In any case, these data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

**Washout:** Taking into account the long elimination half-life of the bedaquiline in patients, a parallel design is recommended and the wash out is not applicable. However, in healthy volunteers the half-life is reported to be approximately 30 hours, therefore, a cross-over design with a wash out period of 2 weeks could be feasible. It is recommended to investigate this possibility in a pilot study.

**Blood sampling:** The blood sampling should be intensive between 4 and 6 hours after administration. It is not necessary to take samples after 72 hours. For example, blood samples might be taken at pre-dose, 1.00, 2.00, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 h after drug administration.

**Analytical considerations:** Information currently available indicates that it is possible to measure bedaquiline 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\(_{\text{max}}\) 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 of bedaquiline.

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

- The 90% confidence interval of the relative mean AUC\(_{0-72h}\) of the test to reference product should be within 80-125%.

- The 90% confidence interval of the relative mean C\(_{\text{max}}\) of the test to reference product should be within 80-125%.

Information currently available in the reference product public assessment report indicates that the comparator product is not a highly variable drug product.