Notes on the design of bioequivalence study:
Rifabutin

Pharmacokinetics of rifabutin

Rifabutin maximum plasma concentrations are reached approximately 2-4 hours after oral administration. The pharmacokinetics of rifabutin are linear after single administration of 300, 450, and 600 mg to healthy volunteers. With these doses, Cmax is in the range of 0.4-0.7 µg/ml.

The half-life of rifabutin is approximately 35-40 hours.

Rifabutin can be administered independently of meals.

Guidance for the design of bioequivalence studies:

Taking into account the pharmacokinetic properties of rifabutin, 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 only the 150 mg capsule, the 150 mg strength is recommended for the bioequivalence study. A dose of 1x150 mg should be tested.

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

Subjects: Healthy volunteers

Sample size: Rifabutin pharmacokinetic parameters, Cmax and AUC0-t, in the fasting state seem to possess high intra-subject variability (36% for AUC), based on Moyle et al. Br J Clin Pharmacol. 54(2): 178–182, but limited data is available, therefore, a pilot study is recommended to estimate the intra-subject variability of AUC and Cmax.

Washout: At least 14 days.
**Blood sampling:** Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48, and 72 h after drug administration.

**Analytical considerations:** Information currently available indicates that it is possible to measure rifabutin 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).

**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 rifabutin should meet the following bioequivalence standards in a single-dose 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_{max} of the test to reference product should be within 80-125%.

Information currently available suggests that the comparator product is a highly variable drug product for both AUC and probably also for C_{max} in the fasting state. The applicant may wish to design a replicate cross-over study to estimate variability more accurately and to widen the acceptance range for C_{max}. For more information on replicate study designs and average scaled bioequivalence, refer to Section 7.9.3 of Annex 7, TRS 992.