Notes on the Design of Bioequivalence Study: Simeprevir

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 simeprevir.

Pharmacokinetics of simeprevir

Following oral administration, simeprevir is absorbed slowly and the peak plasma concentration is observed at about 4–6 hour post-dose. Relative to fasting conditions, the administration of a single dose of simeprevir with a high-fat, high calorie meal or a normal calorie (standard) meal slows the rate of absorption of simeprevir by approximately 1 and 1.5 hours, respectively. In addition, the extent of absorption (AUC) of simeprevir increases approximately 61% and 69%, respectively. For this reason administration is recommended with food in the product labeling approved by the EMA and the FDA. Plasma exposure (AUC) of simeprevir in HCV-infected subjects was about two to three-fold higher compared to that observed in HCV-uninfected subjects. The terminal elimination half-life of simeprevir is about 10 to 13 hours in HCV-uninfected subjects.

Guidance for the design of bioequivalence studies

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

**Dose:** As simeprevir is marketed only as a 150 mg capsule, this strength (i.e. 150 mg strength) should be employed in the bioequivalence study.

**Fasting/fed:** The bioequivalence study should be conducted in the fed state using a standard meal as simeprevir exhibits a greater absorption in the presence of food and yet the variability associated with administration of a normal meal may be less than that observed following administration with a high fat, high calorie meal. It is recommended that a standard meal with the following characteristics be employed: 500–600 Kcal from approximately 15–25 g fat, 60-70 g carbohydrate, and 15–25 g protein.

**Subjects:** Healthy adult subjects should be utilized. It is not necessary to include patients in the bioequivalence study.
**Analytical considerations**: The measurement of simeprevir in plasma is feasible (LLOQ = 2 ng/ml) and the use of the parent drug is considered to be more discriminative to differences in the biopharmaceutical performance of the drug products. Therefore, bioequivalence should be based on the determination of simeprevir.

**Sample size**: Simeprevir AUC₀−ₜ and Cₘₐₓ in the fed state seems to have a high inter-subject variability (73% and 87% (multiple dose), respectively). No information is available on the intra-subject variability at this time. Given the limited information available, a pilot study or the use of a two-stage sequential design bioequivalence study could be considered in order to deal with the lack of information available for sample size calculations. See Section 7.6.1 of Annex 7, TRS 992 for more information on this type of study design.

**Washout**: Taking into account the elimination half-life of simeprevir in fed state of 10−13 hours and the high variability in pharmacokinetics, a washout period of at least seven days is considered sufficient to prevent carry over.

**Blood sampling**: The blood sampling should be more intensive 3−7 hours after administration to properly characterize the Cₘₐₓ of simeprevir. Considering the elimination half-life, it is advised to take blood samples up to 72 hours after administration for the characterization of simeprevir pharmacokinetics.

**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 simeprevir.

**Statistical considerations**: The data for simeprevir should meet the following bioequivalence standards in a single-dose, crossover design study:

- The 90% confidence interval of the relative mean AUC₀−ₜ 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 the PQTm suggests that the comparator product might be a highly variable drug product for AUC and Cₘₐₓ in the fed state. Therefore, if the applicant suspects that the variability of Cₘₐₓ is high (CV>30%), the applicant may prefer to employ a replicate design study for at least the comparator product in order to scale the acceptance range of Cₘₐₓ. For more information on replicate study designs and average scaled bioequivalence, refer to Section 7.9.3 of Annex 7, TRS 992.

Biowaiver: According to the FDA and EMA, simeprevir is a BCS Class IV drug. Therefore, simeprevir is not eligible for a BCS-based biowaiver.