Notes on the Design of Bioequivalence Study: Sofosbuvir

Notes on the design of bioequivalence studies with products invited for submission 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 sofosbuvir.

Pharmacokinetics of sofosbuvir

Following oral administration, sofosbuvir is absorbed quickly and the peak plasma concentration was observed ~0.5–2 hour(s) post-dose, irrespective dose level. Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardized high fat meal slows the rate of absorption of sofosbuvir. Further, with food, the extent of absorption of sofosbuvir is increased approximately 1.8-fold, with little effect on peak concentration. For this reason, administration is recommended with food in the Summary of Product Characteristics approved by the European Medicines Agency (EMA), although it can be taken irrespective of meals according to the Product Labelling approved by the US Food and Drug Administration (US FDA). The median terminal half-life of sofosbuvir is 0.4 hours.

Guidance for the design of bioequivalence studies

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

Dose: As sofosbuvir is marketed only as a 400 mg tablet, the applied strength (i.e. 400 mg strength) should be employed in the bioequivalence study.

Fasting/fed: It is preferred that the bioequivalence study be conducted in the fed state with a high-fat high-calorie meal as sofosbuvir exhibits a greater absorption in the presence of a high-fat meal. However, as the approved labeling for the posology for Sovaldi, the PQTm comparator product, differs between the EMA and the US FDA, a bioequivalence study conducted under fasted conditions will also be acceptable if the comparator product is obtained from a market where the approved labeling indicates that it may be taken without regard to food.

Subjects: Healthy adult subjects should be utilized. It is not necessary to include patients in the bioequivalence study.
**Analytical considerations**: The measurement of sofosbuvir is feasible (LLOQ = 0.5 ng/ml) and it 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 sofosbuvir.

**Sample size**: Sofosbuvir $C_{\text{max}}$ in the fed state seems to be highly variable (54%), whereas $AUC_{0-\text{t}}$ seems to have low variability (10%), based on the information available to the PQTm. These data will facilitate the calculation of a sufficient sample size for the bioequivalence study.

**Washout**: Taking into account the elimination half-life of sofosbuvir in fed state of 1.5 h (range: 0.3–9 h), a washout period of seven days is considered sufficient to prevent carry over.

**Blood sampling**: The blood sampling should be intensive the first four hours after administration to properly characterize the $C_{\text{max}}$ of sofosbuvir. It is not necessary to take blood samples beyond 8–12 hours for the characterization of sofosbuvir 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 sofosbuvir.

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

- The 90% confidence interval of the relative mean $AUC_{0-\text{t}}$ 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 to the PQTm suggests that the comparator product might be a highly variable drug product for $C_{\text{max}}$, but not for $AUC_{0-\text{t}}$. Widening of the acceptance range for $C_{\text{max}}$ might be acceptable if the applicant conducts a replicate cross-over study to estimate variability of the comparator product more accurately and the high variability of $C_{\text{max}}$ is demonstrated. For more information on replicate study designs and scaled average bioequivalence refer to Section 7.9.3 of Annex 7, TRS 992.