Notes on the Design of Bioequivalence Study: Daclatasvir/Sofosbuvir

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team – Medicines (PQT/MED) 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.

The current notes should be read and followed in line with the general guidelines of submission of documentation for WHO prequalification. In particular, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in *Fifty-first Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

Below, additional specific guidance is provided on the invited immediate release products containing sofosbuvir and daclatasvir.

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 of the 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.

Pharmacokinetics of daclatasvir

Daclatasvir administered as a tablet was readily absorbed following multiple oral doses with peak plasma concentrations occurring between 1 and 2 h. Daclatasvir C_{max}, AUC, and C_{min} increased in a near dose-proportional manner. In healthy subjects, administration of daclatasvir 60 mg tablet after a high-fat meal decreased daclatasvir C_{max} and AUC by 28% and 23%, respectively, compared with administration under fasting conditions. Administration of daclatasvir 60 mg tablet after a light meal resulted in no reduction in daclatasvir exposure. Following multiple-dose administration of daclatasvir in hepatitis C-infected patients, the terminal elimination half- life of daclatasvir ranged from 12 to 15 hours.

Guidance for the design of bioequivalence studies

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

Design: A single-dose cross-over design is recommended.

Dose: As the EoI includes sofosbuvir/daclatasvir 400/60 mg tablet and 400/30 mg tablet, the bioequivalence study should be conducted with the highest strength if the conditions for an additional strength biowaiver are fulfilled. Otherwise, bioequivalence should be shown for each strength vs. the reference product mono-components administered simultaneously.

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

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

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 compounds should be used to assess bioequivalence of sofosbuvir and daclatasvir.

Sample size: Sofosbuvir C_{max} in the fed state seems to be highly variable (54%), whereas AUC_{0-t} seems to have low variability (10%), based on the information available to PQT/MED. Daclatasvir C_{max} in the fasted state has a low to moderate intra-subject variability (17–20%).These data may facilitate the calculation of a sufficient sample size for the cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of daclatasvir in healthy volunteers (approximately 15 hours), a washout period of 7 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_{max} of sofosbuvir and daclatasvir. It is not necessary to measure sofosbuvir in blood samples beyond 8−12 hours. It is not necessary to take blood samples beyond 72 hours for the characterization of daclatasvir pharmacokinetics.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure sofosbuvir and daclatasvir 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).

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

- The 90% confidence interval of the relative mean AUC_{0-t} of the test to comparator product should be within 80.00 – 125.00%.

- The 90% confidence interval of the relative mean C_{max} of the test to comparator product should be within 80.00 – 125.00%.

Information currently available to PQT/MED indicates that the comparator product is a highly variable drug product. Therefore, if the Applicant suspects that the variability of C_{max} or AUC_{0-t} is high (CV>30%), the applicant may prefer to employ a full replicate design study in order to widen the acceptance range of C_{max}. and/or AUC_{0-t}. For more information on replicate study designs and widening the limits of average bioequivalence, refer to Section 7.9.3 of Annex 6, TRS 1003 and PQT/MED guidance document “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED”.