Notes on the design of bioequivalence study: Sofosbuvir/Velpatasvir

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (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-seventh report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations,* Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

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

Pharmacokinetics of Sofosbuvir and Velpatasvir

Following oral administration of sofosbuvir/velpatasvir, sofosbuvir was absorbed quickly and the peak median plasma concentration was observed 1 hour post-dose. Velpatasvir median peak concentrations were observed at 3 hours post-dose.

Relative to fasting conditions, the administration of a single dose of sofosbuvir/velpatasvir with a moderate fat (~600 kcal, 30% fat) or high fat (~800 kcal, 50% fat) meal resulted in a 34% and 21% increase in velpatasvir $AUC_{0\text{-}inf}$, respectively, and a 31% and 5% increase in velpatasvir C_{max}, respectively. The moderate or high fat meal increased sofosbuvir $AUC_{0\text{-}inf}$ by 60% and 78%, respectively, but did not substantially affect the sofosbuvir C_{max}. The response rates in Phase 3 studies were similar in HCV-infected patients who received sofosbuvir/velpatasvir with food or without food. Sofosbuvir/velpatasvir can be administered without regard to food.

The median terminal half-lives of sofosbuvir and velpatasvir following administration of sofosbuvir/velpatasvir were 0.5 and 15 hours, respectively.

Velpatasvir AUC increases in a nearly dose proportional manner over the dose range of 25 mg to 150 mg. Sofosbuvir is near dose-proportional over the dose range of 200 mg to 1,200 mg.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of sofosbuvir and velpatasvir 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 only the fixed combination of Sofosbuvir/Velpatasvir tablet 400mg/100mg, this dose should be tested.

Fasted/fed: The bioequivalence study should be conducted in the fasted state since the comparator product can be taken without regard to food.

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

Parent or metabolite data for assessment of bioequivalence: The parent drugs are 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 velpatasvir.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for velpatasvir is >30% (44%, up to 77%). These data may facilitate the calculation of a sufficient sample size for the bioequivalence study. A pilot study is recommended to estimate the intra-subject variability with better precision.

Washout: Taking into account the elimination half-life of velpatasvir in the fasted state of 15 h, a washout period of 7 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive for the first four hours after administration to properly characterize the C_{max} of sofosbuvir and velpatasvir. Blood samples for the characterization of velpatasvir pharmacokinetics should be taken for 72 h post-dose in order to determine AUC_{0-t}. For example, blood samples might be taken at pre-dose, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00, and 72.00 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure sofosbuvir and velpatasvir 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). As per ICH M10, the bioanalytical method of sofosbuvir should be validated in the presence of velpatasvir and vice versa.

Statistical considerations: The data for sofosbuvir and velpatasvir 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} for sofosbuvir and velpatasvir of the test to reference product should be within 80.00–125.00%

- The 90% confidence interval of the relative mean C_{max} for sofosbuvir and velpatasvir of the test to reference 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} / AUC_{0-72h} 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} / AUC_{0-72h}. For more information on replicate study designs and widening the limits of average bioequivalence, refer to Section 7.9.3 of Annex 8, TRS 1052 and PQT/MED guidance document “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED”.