Notes on the Design of Bioequivalence Study: Velpatasvir

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-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 velpatasvir.

Pharmacokinetics of velpatasvir

Following oral administration of sofosbuvir/velpatasvir, 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 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-life of velpatasvir following administration of sofosbuvir/velpatasvir was 15 hours. Velpatasvir AUC increases in a nearly dose proportional manner over the dose range of 25 mg to 150 mg.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of 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 velpatasvir 100 mg tablet, the bioequivalence study should be conducted with this product vs. the fixed combination of sofosbuvir and velpatasvir as comparator product.

Fasted/fed: The bioequivalence study should be conducted in the fasted state as sofosbuvir/velpatasvir is recommended to be taken with or without food.

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 compound should be used to assess bioequivalence of 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 Cmax of 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 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).

Statistical considerations: The data for 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} 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 8, TRS 1052 and PQT/MED guidance document “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED”.