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. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, 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 and 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 crossover 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 comparator product can be taken without regard to food. Due to the low solubility of velpatasvir, the comparator product employs a complex manufacturing process in order to enhance the dissolution and

absorption of velpatasvir. Due to the low solubility of this API and the complexity of the manufacturing process employed, there is an increased risk that the in vivo performance of such a product will be impacted differently by varying gastrointestinal (GI) conditions between the fasted and fed conditions. Therefore, for such drug products, bioavailability differences related to differences in formulation and/or manufacturing process may not be detected with a single BE study, i.e., results from a fasting BE study may not be extrapolated to predict fed BE study outcome or vice versa, thus both fasting and fed BE studies should be conducted, unless otherwise justified (e.g., by demonstrating the use of a formulation with the same or similar excipient composition and the same manufacturing process as in the comparator product).

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. Therefore, bioequivalence should be based on the determination of sofosbuvir and ledipasvir.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for velpatasvir in fasted state is >30% (up to 60%) and that of sofosbuvir may be similar. These data may facilitate the calculation of a sufficient sample size for the bioequivalence studies.

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 five 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). The bioanalytical method for each analyte should be validated in the presence of the other analyte (see Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information).

Statistical considerations: The data for sofosbuvir and velpatasvir should meet the following bioequivalence standards in each single-dose crossover 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} 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”.