Notes on the Design of Bioequivalence Study: Glecaprevir/Pibrentasvir

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 glecaprevir and pibrentasvir.

Pharmacokinetics of glecaprevir and pibrentasvir

Glecaprevir and pibrentasvir should be taken with food. Glecaprevir and pibrentasvir maximum concentrations are observed 5 h after administration. Glecaprevir half-life is 6 – 9 h and pibrentasvir half-life is 23 – 29 h.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of glecaprevir and pibrentasvir, 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 glecaprevir/pibrentasvir 100 mg /40 mg tablet, the bioequivalence study should be conducted with this product.

Fasted/fed: The bioequivalence study should be conducted in the fed state (moderate or high-fat high-calorie meal).

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 glecaprevir and pibrentasvir.

Sample size: Glecaprevir and pibrentasvir C_{max} and AUC seem to be highly variable (40 – 54%). However, limited data is available and a pilot study is recommended to estimate more accurately the intra-subject variability in fed state.

Washout: Taking into account the elimination half-life of pibrentasvir is 23 – 29 h, a washout period of 7 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive around 5 h after administration to properly characterize the C_{max} of glecaprevir and pibrentasvir. It is not necessary to measure glecaprevir in blood samples beyond 24 hours. It is not necessary to take blood samples beyond 72 hours for the characterization of pibrentasvir pharmacokinetics.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure glecaprevir and pibrentasvir 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 ICH Harmonised Guideline M10 for more information).

Statistical considerations: The data for glecaprevir and pibrentasvir 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”.