Notes on the design of bioequivalence study: Delamanid

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 delamanid.

Pharmacokinetics of delamanid

In different studies, peak delamanid concentrations have been observed at ~ 4-8 h and around 4 hours in patients.

The oral bioavailability of delamanid improves when administered with a standard meal by about 2.7-fold compared to fasting conditions. After a 200 mg dose administered after a standard meal, the mean AUC_{∞}, AUC_t and C_{max} were 2.9-, 3.0- and 3.4-fold greater, respectively, compared to that observed under fasted conditions. Administration after a high fat meal produced a > 4-fold increase on AUC vs. the fasting state with a 400 mg dose.

Delamanid plasma exposure increases less than proportionally with increasing dose. Across studies, the available data suggests that delamanid is eliminated from plasma with a $t_{1/2}$ of 30 to 38 hours. Delamanid does not undergo chiral inter-conversion in vivo.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of delamanid 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 50 mg strength, this strength (1 x 50 mg) should be tested versus the comparator.

For studies involving a 50 mg immediate release tablet, the Test and Comparator products should be administered in the bioequivalence study with the same posology, e.g. administration with 240 ml of water. For a 50 mg dispersible tablet, the Test dispersible product should be administered as it will be labeled to be administered in the clinical setting, e.g. disperse in a small volume (for example 50 ml) of water and administer, followed by a rinse with a second small volume of water (for example 50 ml), while the Comparator should be administered with 240 mL water as per normal.

Fasted/fed: In clinical practice, delamanid is to be taken with food. The Comparator product employs a complex manufacturing process, *i.e.*, a solid dispersion process, in order to enhance the solubility of delamanid being released from the product (see the WHOPAR for TB388 for more information). Due to API characteristics 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, performance 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.

On this scientific basis, for delamanid products, two bioequivalence studies are required, *i.e.*, single-dose, crossover bioequivalence studies should be conducted under both fasting and high-fat, high-calorie fed conditions.

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 the bioequivalence of delamanid.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for delamanid is around 27 to 39%, with highest values in primarily outpatient conditions and, therefore, with more variable food intake. 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 delamanid in healthy volunteers (about 38 h), a washout period of 2 weeks is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive between 2 and 8 hours after administration. It is not necessary to take samples after 72 hours. For example, blood samples might be taken at pre-dose, 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 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 delamanid 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 delamanid should meet the following bioequivalence standards in single-dose cross-over design studies conducted under fasting and high-fat, high-calorie fed conditions:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72h}$ of the test to reference product should be within 80.00–125.00%

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