Notes on the Design of Bioequivalence Study: Acoziborole

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 dosage forms containing acoziborole.

Pharmacokinetics of acoziborole

After oral administration to patients, acoziborole is slowly absorbed with a median peak blood concentration observed 48 hours after dosing. The tablets should be taken without food. The mean concentration remains at a plateau for 96 hours post dose. The mean terminal half-life of acoziborole was 296 hours (12.3 days) in patients.

Although acoziborole is a low solubility drug, the comparator product does not consist of a special formulation/technology. Its solubility is not notably dependent on the pH.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of acoziborole, the following guidance with regard to the study design should be taken into account:

Design: A single-dose, parallel design is recommended.

Dose: As the EoI includes 320 mg tablets only, this strength should be tested.

Fasted/fed: As the comparator product should be taken without food, a fasted state study is recommended.

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. Therefore, bioequivalence should be based on the determination of acoziborole.

Sample size: Information currently available to the PQT/MED indicates that the inter-subject variability for acoziborole is around 8-10% for AUC and Cmax. These data will facilitate the calculation of sufficient sample size

for the parallel bioequivalence study. Take into account that a minimum of 12 evaluable subjects is necessary per treatment group, although in theory 80% power can be achieved with 6 subjects per group.

Washout: N/A.

Blood sampling: As acoziborole exhibits a median peak blood concentration at 36 h after dosing of the 320 mg dose and sampling is not necessary after 72 h for immediate release products, samples should cover the whole range up to 72 h, e.g., pre-dose and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 36.0, 48.0, 60.0 and 72.0 hours post dose.

Analytical method: Information currently available to the PQT/MED indicates that it is possible to measure acoziborole in human plasma using LC-MS/MS analytical methodology (LLOQ of 25 ng/ml). 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). 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 on bioanalytical recommendations.

Statistical considerations: The data for acoziborole should meet the following bioequivalence standards in a single dose parallel design study:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72\ h}$ of the test to reference product should be within 80-125%.
- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80-125%.