Notes on the design of bioequivalence study: Primaquine

Pharmacokinetics of primaquine
Peak plasma concentrations occur about 1 to 3 hours after a dose is taken and then rapidly diminish with a reported elimination half-life of 7 hours (3.7 to 9.6 hours).
Taking primaquine after a meal may reduce abdominal pain or cramps associated with ingestion of the drug.

Guidance for the design of bioequivalence studies:
Taking into account the pharmacokinetic properties of primaquine, the following guidance with regard to the study design should be taken into account:

Design: A cross-over design bioequivalence study is recommended. It is noted that a BCS-based biowaiver may be possible if sufficient data can be collected to confirm primaquine as BCS Class I or III.

Dose: As the EoI includes primaquine 3.75, 7.5 and 15 mg tablets, the 15 mg strength should be tested.

Fasting/fed: The bioequivalence study should be conducted in the fasted state as although it is generally taken after meals, this seems to be related to tolerability and not pharmacokinetics.

Subjects: Healthy adult subjects should be included in the bioequivalence study. It is not necessary to include patients.

Sample size: Limited information is available on primaquine variability. A pilot study is recommended to confirm the intra-subject variability and to explore the optimal sampling times.

Washout: Taking into account the elimination half-life of primaquine of 7 h, a wash out period of 1 week is recommended.
**Blood sampling:** The blood sampling should be intensive in the first 3 hours. It is not necessary to take samples after 24 hours. For example, blood samples might be taken at pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 h after drug administration.

**Analytical considerations:** Information currently available indicates that it is possible to measure primaquine 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\(\text{max}\) in most profiles of each formulation (test or comparator).

**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 primaquine.

**Statistical considerations:** The data for primaquine should meet the following bioequivalence standards in a cross-over design study:

- The 90% confidence interval of the relative mean AUC\(_{0-t}\) of the test to reference product should be within 80-125%

- The 90% confidence interval of the relative mean C\(\text{max}\) of the test to reference product should be within 80-125%.