Highlighting Utility of Stable Isotope Approach to Support Dissolution Specifications for a Commercial Tablet Product with Tafenoquine, a long half-life compound.

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Objective: Support dissolution specification for a commercial tablet product by characterizing the relative bioavailability of tablets exhibiting different dissolution profiles utilizing stable isotope label (SIL) approach.

Methods: A single center, 2 arm, randomized open label, parallel group study was conducted in healthy volunteers (NCT02751294). Each subject received one of the two 300mg tafenoquine (TQ) tablet formulations that differed in their in vitro dissolution profiles. Systemic TQ pharmacokinetic (PK) samples were collected over a period of 8 weeks. Each subject was also administered 30mg of stable isotope labelled (SIL) tafenoquine (TQ SIL) solution with the TQ tablet. The PK parameters AUC and Cmax were compared for the two TQ tablets with differing dissolution profiles, after correcting for the corresponding PK parameter of TQ SIL.

Results: A total of 14 subjects, 7 in each arm, completed the study. There was high correlation between the TQ and TQ SIL PK parameters. This greatly reduced the variability in the statistical test comparing the two formulations. Based on the ANCOVA analysis of PK parameters displayed in Figure 1, there were no clinically relevant differences in systemic TQ exposure between the two formulations.

Discussion: TQ has a long half-life of 11-35 days thus potentiating a parallel group bioavailability or bioequivalence (BA/BE) study to compare formulations. The SIL approach dramatically reduced the required sample size (from 32 to 6 evaluable subjects per treatment arm), due to the high correlation between SIL and non SIL compound. The study data will underpin the dissolution specification for the proposed TQ commercial tablet drug product.

Conclusion: The SIL approach has potential to significantly conserve resources (sample size, time and cost) in BA/BE settings and the Quality by design QbD paradigm in clinical drug development.