Use of PBPK Modeling to Identify Unexpected Ferroquine Pharmacokinetics in a Phase I Study and to Support a Phase IIb Study

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Objectives: To understand reasons for the unexpected ferroquine pharmacokinetics (PK) in a Phase I study in healthy volunteers (HVs), and predict ferroquine PK to support a Phase IIb study in patients with malaria.

Methods: A physiologically based pharmacokinetic (PBPK) model was established for HVs and patients with malaria. The model performance was evaluated using observed PK data. Ferroquine PK parameters such as bioavailability (F), fraction absorbed (Fa), fraction escaped through the gut (Fg) and clearance (CL) were predicted to understand the super proportional exposure-dose response occurred in the Phase I study.

Results: Both PBPK models for HVs and patients demonstrated good performance with simulated over observed exposure ratio of 0.80 – 1.54x for HVs, 0.84 – 1.32x for patients.

In the Phase I study, extended drug precipitation time (Tp) of ferroquine (15620s) was measured in vitro mimicking drug intake medium i.e. milk plus OZ439 re-suspended in 0.8% v/v polysorbate 80 in water & Ora-sweet. A complete absorption (Fa), dose dependent Fg (38.6-72.1%) and linear clearance were predicted over the dose range of 300-1200 mg. As a result, dose dependent oral bioavailability was predicted from 35.9 to 66.4%.

In the phase IIb study, ferroquine capsules are taken with water and OZ439 is administered with vitamin E-TPGS plus sucrose. The measured Tp in the intake medium was 1120s as a model input. From 400 to 1200 mg, the predicted Fa was from 96 to 85%, Fg increased from 57 to 74%, and the overall bioavailability was predicted to be from 50 to 57%. Thus, ferroquine exposure in patients at the highest dose i.e. 1200 mg is anticipated to be similar to that observed at 1200 mg in HVs.

Conclusions: This modeling result supports the phase IIb study for combination therapy of ferroquine and OZ439 in patients with similar ferroquine exposure predicted at the highest dose of 1200 mg as compared to the previous well tolerated study in HVs at 1200 mg.