Weight based dosage adjustments are not required for WCK 771, a novel broad-spectrum floroloquinolone

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Background & Objective

Background

WCK 771, a novel broad-spectrum fluoroquinolone with enhanced activity against MRSA and quinolone-resistant staphylococci, is being developed by Wockhardt as a parenteral anti- MRSA agent[1-3].

Objective

The aim of this analysis was to reconcile a 2-fold lower steady-state exposure in subjects from the United States in comparison to subjects in India given the same dose, and determine if any dose adjustments would be required for either population due to differences in body weight.

Methods

Modeling Population

Plasma concentration-time data were obtained 54 Indian patients in various Phase I clinical trials given either single dose (range of 600-1200 mg) or multiple dose (range 600-1200 mg BID or TID for 5 days), as well as 30 Caucasian subjects in a single US trial (600, 800, 1000 mg BID for 5 days). For individuals given multiple doses, trough samples as well as rich samples were available for all individuals for analysis.

Model Development

The data was modeled using Phoenix NLME (Nonlinear Mixed Effects v1.3) with the FOCE-ELS algorithm.

Results

Final Model

The WCK771 concentrations were analyzed using a 2-compartment IV-infusion model. The absorption of WCK771 after intravenous dosing was described using a zero-order infusion process where the duration of infusion (D1) was estimated. The systemic clearance CL, the distribution clearance Q, the volumes of distribution of the central compartment (Vc) and peripheral compartment (Vp) were also estimated.

Exposure Differences

A significant portion of the 2-fold differences in AUC and Cmax between the Indian and US studies for the same dose was explained by allometrically scaling CL and V by body weight. Hence, differences were attributed to the difference in the body weights of the subjects.

Results

Table 1: Pharmacokinetic Parameters from final population PK model

Parameter	Estimate	BSV (% CV)
Duration of infusion (h)	1	-
CL (L/h/70kg)	5.40	19.1%
Vc (L/70kg)	37.12	29.1%
Q (L/h/70kg)	0.63	42.3%
Vp (L/70kg)	7.15	55.3%
Residual Error (Proportional)	16.5%	

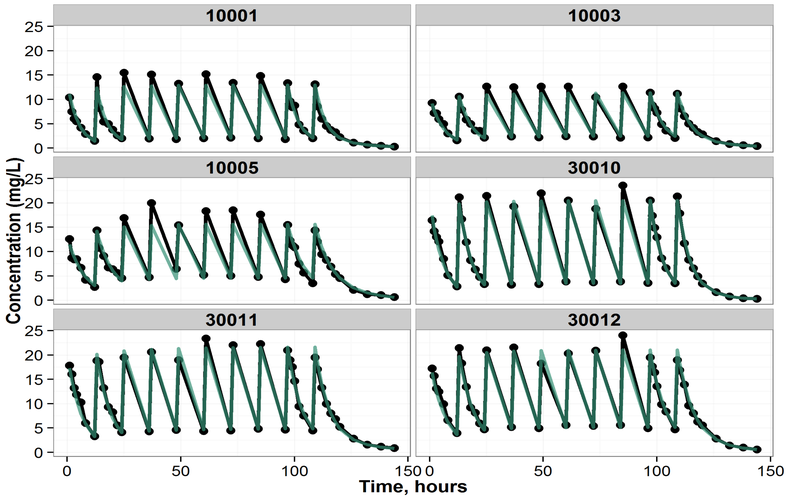

Figure 1:Representative individual PK profiles (black) and model predictions (green) for US subjects who received WCK 771 600 to 1000 mg BID

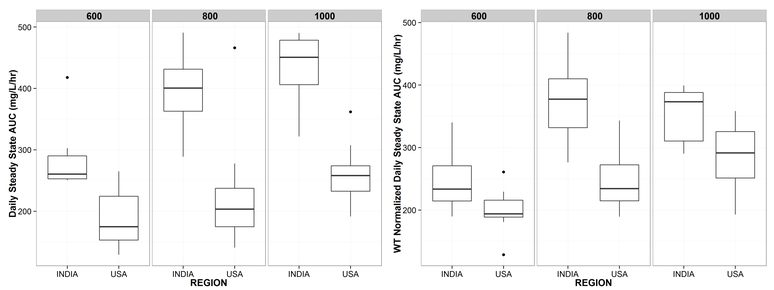

Figure 2: Range of exposures of WCK 771 between the US and India population at different doses of WCK 771 before (left) and after (right) accounting for weight

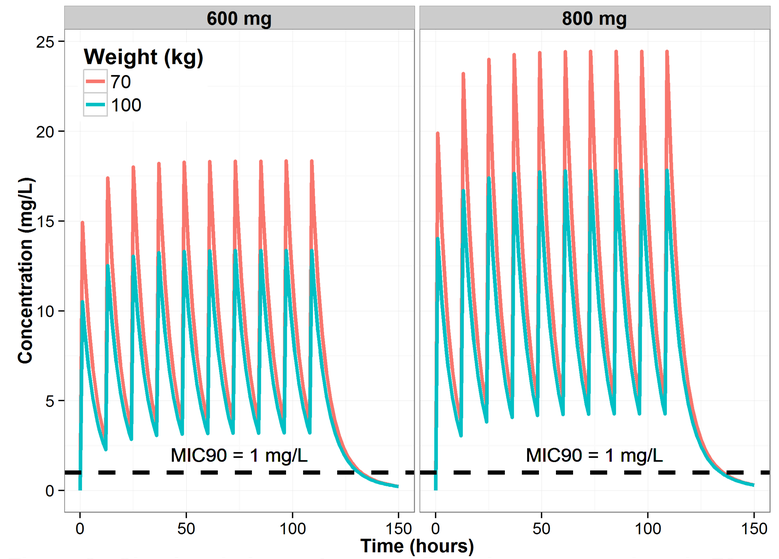

Figure 3: Simulated plasma Levonadifloxaxin concentrations in 70 and 100 kg subject above MIC at WCK 771 600 and 800 mg BID Doses.

Conclusions

Simulations showed that the typical steady-state concentrations of WCK771 after multiple-doses of 600 and 800 mg stay above the MIC of 1 mg/L for WCK771 for light and heavy patients. Therefore, no weight based dosage adjustments are required for WCK 771.

References

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