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Development and verification of PBPK model for a topical cream formulation of Trifarotene to simulate local and systemic exposure and model application to simulate potential CYP-mediated drug-drug interactions

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PURPOSE

A growing number of regulatory submissions include Physiologically Based Pharmacokinetic (PBPK) models. The main purposes of PBPK models in regulatory submissions are to quantitatively and qualitatively predict drug-drug interactions (DDIs), to support initial dose selection in pediatric and first in human trials [1, 2,3]. Hence, PBPK modeling provides a practical solution for extrapolating PK behavior of a drug in a situation where PK profiles are difficult to obtain. Due to low systemic exposure and the necessary time to achieve steady state conditions, clinical metabolic DDI studies for topical products are typically difficult to conduct. In addition, the topical route often results in large inter-individual variability of PK parameters which may necessitate larger number of subjects to achieve study power.

OBJECTIVE(S)

A full body PBPK model for topical administration of a cream formulation containing Trifarotene (a NCE for acne treatment) for multiple dose strengths was developed. The model was verified using clinical data of local skin tissue concentrations as well as systemic concentrations for single and multiple doses. The verified model was then used to simulate potential CYP-mediated DDIs.

METHOD(S)

A PBPK model was built using the mechanistic dermal absorption (MechDermA) model [Fig. 1] of Simcyp V15R1 based on physicochemical parameters, formulation and metabolism information of Trifarotene. The predicted volume of distribution was verified with observed rat radioisotope tissue distribution study data. The simulated local skin concentrations were verified against clinical data obtained from tape stripping for stratum corneum (SC) and punch biopsy for viable epidermis while the simulated plasma concentrations at two dose strengths were compared to clinical data at day 1, 15 and 30 after once daily application. DDI with CYP2C9 and CYP3A4 inhibitor fluconazole as well as complete inhibition of CYP2C9 was simulated to estimate exposure of Trifarotene in those scenarios.

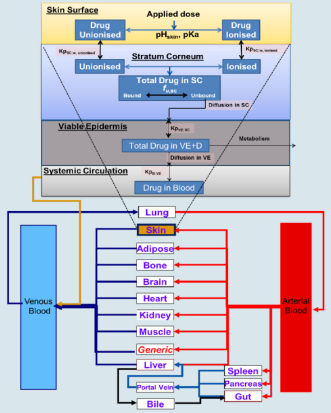

Figure 1. Mechanistic Dermal absorption model with full body PBPK distribution model; pHSkin is the pH of the skin at area of application; pKa is the ionization rate constant of drug; VE is viable epidermis; D is dermis; SC is stratum corneum; Kpx:y is the partition coefficient between x compartment and y compartment

RESULT(S)

Ninety-five percent of the clinical data points were within 5th and 95th percentile of simulated trials along with central tendencies indicating reasonably good model predictive performance [Fig 2]. The model predicted the local concentration in SC tissue reasonably well [Fig 3]. The average (geometric mean) increase in AUC and Cmax of Trifarotene (CD5789) in presence of fluconazole was 19% and 17% respectively with 95% confidence intervals of 17-20% and 15-18%, respectively. As fluconazole is not a strong inhibitor, a worst case scenario was simulated by completely inhibiting metabolism by the CYP2C9 pathway which resulted in an average (arithmetic mean) increase in the AUC and Cmax by 51% and 35%, respectively [Fig 4].

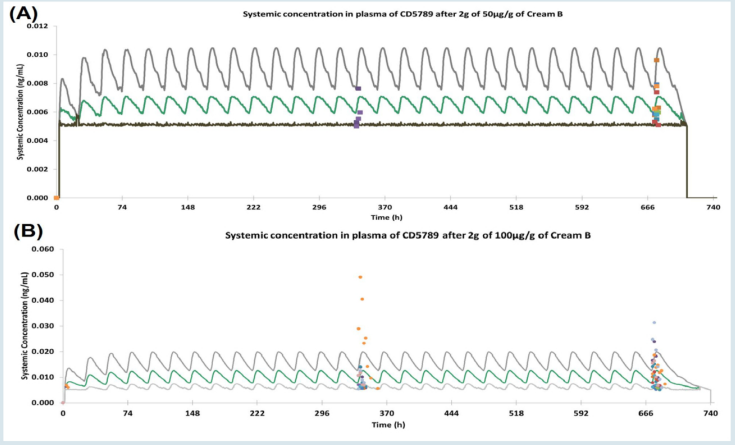

Figure 2. Simulated (Lines: Green – Mean, Dark Grey – 95th percentile, Light Grey – 5th percentile of 10 trials of 18 or 21 individuals for 50 µg/g and 100 µg/g doses, respectively) overlaid with clinically observed (markers) plasma drug concentration –time profiles after 29 once-daily applications of 2 g of (A) 50 µg/g and (B) 100 µg/g of Cream formulation

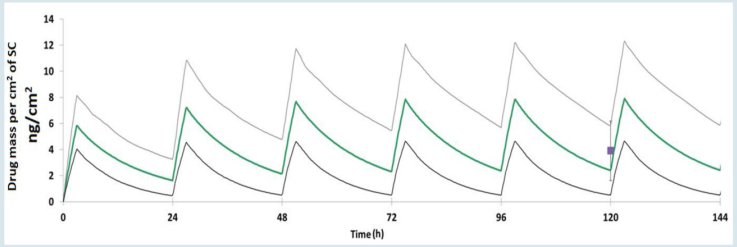

Figure 3. Simulated (Lines: Green – Mean, Grey – 95th percentile, Black – 5th percentile of 10 trials of 18 individuals) and clinically observed (markers) drug concentration in SC profiles (ng/cm²) after once-daily application of 2g of 50µg/g of Cream B for 6 days

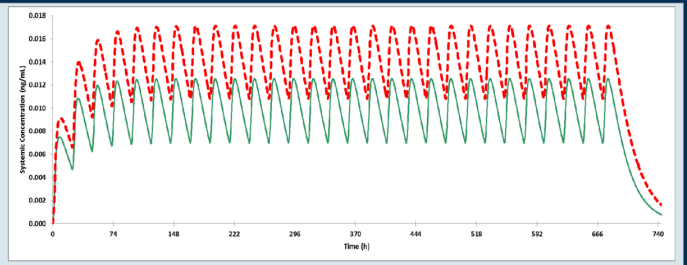

Figure 4. Mean plasma concentration time profiles of Trifarotine after application of 2 g of 100 µg/g of Cream QD for 29 days without any inhibition (green continuous line) and with complete inhibition of CYP2C9 pathway (red dotted line).

CONCLUSION(S)

A robust and predictive PBPK model for Trifarotene was developed and verified both at skin and systemic levels. The developed model indicated low to moderate effect of CYP2C9 inhibitors. Even complete inhibition of CYP2C9, resulted in low systemic concentrations leading to a good safety margin within the accepted range for such drugs. PBPK models can strongly benefit for topical drug product development and regulatory assessment.

REFERENCES

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