Objectives: Develop a plasma/dermis population pharmacokinetic (PK) model using Phase I data.

Methods: A two-compartment model (1st compartment dermis and 2nd compartment plasma) was developed using NONMEM based on healthy volunteer plasma concentration data from a Phase I study in which subjects received single or multiple daily topical administrations of 0.1%-1.0% (w/w) GSK1940029 gel. Application was to the thighs or back at varying body surface area [BSA] under occluded or non-occluded conditions. Data from an in vitro human abdominal-skin percutaneous absorption experiment was added to the dataset for subjects receiving 1% gel under non-occluded conditions for simultaneous analysis with the plasma data. The flux determined from the same in vitro experiment was used to back-calculate the amount of dose that could have been absorbed into the systemic circulation. The final plasma/dermal model was evaluated with visual predictive check.

Results: Based on PK results from non-compartmental analysis, the strength of the gel formulation did not affect systemic absorption/exposure at the gel strengths studied (0.1% to 1%), thus these different gel strengths were assumed to have the same flux. Flux under occluded conditions was assumed to be 5-fold higher than under non-occluded conditions (Hostynek 1997). Under these assumptions, BSA was a limiting factor for systemic absorption with PK exposure approximately proportional to BSA. Load of the gel formulation applied did not affect systemic absorption/exposure at the load studied (between real world use of 1mg gel/cm$^2$ and maximum artificial use of 10mg gel/cm$^2$). Pharmacokinetic parameters were precisely estimated (relative standard error RSE 7.2-49.8%). Inter-individual variability (IIV) estimates ranged 52.5-82.2% for CL, V, and skin tissue unbound $f_{uu}$. No IIV on R1 (flux) was needed. Residual error was determined for plasma (CV 71.8%).

Conclusions: A two-compartment plasma/dermis population PK model was developed. The model predicted a free dermis concentration 1.6-fold the human IC50, suggesting a different formulation with higher flux would be needed for efficacy when treating skin conditions.