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Early Clinical Evaluation of a Novel 5-Lipoxygenase Activating Protein (FLAP) Inhibitor (GSK2190915A). Pharmacokinetics, Bioavailability and Dose Form Selection: Influence of Age, Food, Drug Interactions and Regional Absorption (LPA112071, LPA112362, LPA114604)

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Introduction and Methods: The 5-lipoxygenase-activating protein inhibitor, GSK2190915, attenuates production of leukotrienes. Reported here are three studies conducted in consenting healthy volunteers that investigated the oral bioavailability, regional gastrointestinal absorption and sources of pharmacokinetic variability for various GSK2190915 formulations, as well as its influence on rosuvastatin, a substrate of the organic anion transporters P1B1 and P1B3 (OATP1B1/1B3), which are inhibited *in vitro* by GSK2190915 (IC50s: 0.59/2.8 µM). Study LPA112071 compared the bioavailability of single doses (100 mg) of two tablet formulations of GSK2190915 (milled and micronised) in fasted and fed states (10 subject crossover design), as well as the influence of smoking (n=5) and age (n=10) on repeat doses of GSK2190915 solution (12 days, 200 mg/day) in older (>65 years) subjects. LPA112362 studied the potential for interaction between GSK2190915 (milled formulation) and rosuvastatin: 28 subjects received rosuvastatin (10 mg/day) for 7 days, then either GSK2190915 30 mg/day or GSK2190915 100 mg/day (in combination with rosuvastatin) for a further 7 days. Study LPA114604 investigated regional gastrointestinal absorption of GSK2190915 (milled formulation) using the Enterion™ capsule system (proximal and distal small bowel activations) in 10 female subjects, who received four single oral doses of GSK2190915A 100 mg on four occasions (with a minimum of 7 days washout).

Results: The milled formulation was more bioavailable than the micronised formulation. Geometric mean [95% CI] fasted GSK2190915 Cmax of the milled tablet was 491 [332, 728] ng/mL and the value for AUC0–24 was 5790 [3890, 8610] ng.h/mL. In the fed state, the geometric mean [CI] Cmax value for the milled tablet was 562 [414, 764] ng/mL and the AUC0–24 value was 6750 [5390, 8450] ng.h/mL. Accumulation was observed following repeat dosing of GSK2190915 200 mg solution, with values of Cmax and AUC0–24 1.8-fold higher on Day 12 than on Day 1. There was no apparent influence of smoking or age on the pharmacokinetics of GSK2190915. There was no clinically significant increase in rosuvastatin Cmax and AUC0-tau when co-administered with GSK2190915 (30 or 100 mg at steady-state). Absorption of GSK2190915 decreased with distance traversed along the small bowel: systemic exposure to GSK2190915 was greater (1.3-fold) when delivered to the proximal small bowel (vs. GSK2190915 100 mg reference tablet), whereas it was approximately halved following delivery to the distal small bowel. Geometric mean [CI] absolute oral bioavailability (F(0–t)) following administration of GSK2190915 100 mg tablet was 19.91% [12.40, 32.00]. Intravenous administration of 100 µg [^{14}C]GSK2190915 resulted in geometric mean [CI] total clearance of 2670 [2009, 3548] mL/h, volume of distribution at steady-state of 47384 [36867, 60897] mL and terminal elimination t½ of 19.30 [15.00, 24.90] h. GSK2190915 was well tolerated in all studies.

Conclusion: Absolute oral bioavailability of GSK2190915 was relatively low; nevertheless, its low clearance and long t½ make it suitable for once-daily administration. There was no clinically relevant interaction with food. Smoking status did not influence the pharmacokinetics of GSK2190915. There was no clinically relevant change in rosuvastatin pharmacokinetics when co-administered with GSK2190915 at steady-state.