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Title: Safety, tolerability and pharmacokinetics (PK) of single and repeat nebulised doses of a novel phosphoinositide 3-kinase δ inhibitor (PI3Kδ), GSK2269557, administered to healthy male subjects in a phase I study

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Body: Introduction: GSK2269557 was investigated in a single centre, double blind, placebo controlled trial in healthy male subjects and smokers. Safety, tolerability and PK data were collected following single (25-6400 µg) and repeat dose (3200 µg b.i.d. for 7 days) in healthy and biomarker cohorts (400 and 6400 µg single doses) in smokers (ERS abstract ref 850263). Plasma PK and lung PK data (from bronchoalveolar lavage) were calculated. Lung PK are expressed as the concentrations in epithelial lining fluid (ELF) using [urea] as a marker of lavage dilution. Results: Adverse Events (AE's) were few and mostly of mild to moderate intensity. 5 withdrawals occurred with 1 deemed study drug related (an inability to tolerate administration of 6400 µg). After single dosing plasma C_{max} (T_{max} at approx 5 min) dropped rapidly (< 6 hours) followed by a slower elimination phase. The elimination $t_{1/2}$ was 19-42h. Dose proportionality was observed and plasma PK was unaffected by smoking status. Mean plasma C_{max} and $AUC_{(0-24h)}$ values were 0.06 to 4.3 ng/mL (50 to 6400 µg) and 0.38 to 34 ng.h/mL (200 to 6400 µg) respectively. Twice daily dosing for 7 days showed accumulation in plasma with peak and trough levels increased by 2.4-fold and 6-fold respectively. Derived mean ELF concentration at 3h was 598 ng/mL (lung:plasma ratio 440:1). Conclusions: GSK2269557 was well tolerated in healthy male subjects. There was a low incidence of AE's and plasma PK was well defined with ELF data confirming high levels of drug within the lung compared to plasma.