**Title:** Safety, pharmacodynamics (PD) and pharmacokinetics (PK) of darotropium (DARO) and vilanterol (VI) in healthy subjects: Two phase 1 studies

**Body:** Introduction: DARO (GSK233705) is a long-acting muscarinic antagonist previously in development as a combination therapy with the long-acting β₂ agonist VI (GW642444) for COPD. Objectives: To evaluate safety, PD and PK of DARO and VI in healthy Caucasian (Study 509) and healthy Japanese (Study 146) subjects. Methods: Two single-centre, randomised, four-way crossover studies. Subjects (n=16 per study) received single doses of DARO 200mcg, VI 50mcg, DARO 200mcg/VI 50mcg and placebo via dry powder inhaler, separated by a 7-day minimum washout period. Primary endpoint was safety. Secondary endpoints: plasma PD and PK parameters. Results: All subjects completed the studies. DARO, VI and DARO/VI were well tolerated. No clinically significant changes in vital signs, haematology and biochemistry, or 12-lead and 24h Holter ECGs were observed. There were no serious AEs. There was no evidence of a difference in systemic exposure between DARO/VI vs DARO or VI alone (Table).

Conclusions: In healthy Caucasian and Japanese subjects, DARO/VI was well tolerated and not associated with any clinically relevant PD or PK changes compared with DARO or VI alone. Funded by GSK (DB1111509 [NCT00671216];DB1112146 [NCT00783003]).