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Title: Effect of moderate hepatic impairment (MHI) on umeclidinium (UMEC) and vilanterol (VI) pharmacokinetics (PK)

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Body: Introduction: The long-acting muscarinic antagonist UMEC (GSK573719) alone and combined with the long-acting β_2 agonist VI is in development as a once-daily therapy inhaled maintenance bronchodilator treatment to relieve symptoms associated with COPD. Preclinical and clinical data suggest predominant elimination of both compounds is via the liver. Objectives: To evaluate the effect of MHI on plasma and urine PK, safety and tolerability of inhaled UMEC and UMEC/VI. Methods: Open-label, non-randomised study of 9 subjects with MHI (Child-Pugh score=7–9) and 9 healthy controls (HC). Subjects took a single dose of UMEC/VI 125/25mcg and, after 7–14 days' washout, repeat-dose UMEC 125mcg once daily for 7 days. Primary endpoints: single- and repeat-dose UMEC and VI plasma PK parameters. Secondary endpoints: UMEC urine PK; safety; tolerability. Results: All 18 enrolled subjects completed the study. See Table for plasma exposure data; UMEC urine PK data reflected similar trends. Plasma and urine UMEC accumulations were similar in MHI and HC subjects following UMEC 7-day dosing. UMEC and UMEC/VI were well tolerated.

Conclusions: Administration of UMEC 125mcg or UMEC/VI125/25mcg to subjects with MHI did not result in clinically significant increases in UMEC or VI exposures vs HC. No dose adjustment for UMEC or UMEC/VI is warranted in subjects with MHI. Funded by GSK (DB2114637, NCT01577680).