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Title: Small impact of mild and moderate renal impairment on the pharmacokinetics of inhaled NVA237

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Body: Introduction NVA237 (glycopyrronium bromide) is a long-acting muscarinic antagonist for the treatment of COPD. It is primarily eliminated by the kidneys. Since renal function decreases in elderly and the target population of NVA237 includes elderly patients it is important to investigate the effect of renal impairment (RI) on NVA237 pharmacokinetics. Methods Subjects: 8 with mild RI, 8 with moderate RI, 8 with severe RI, 6 with end-stage renal disease requiring dialysis (ESRD) and 18 demographically matching healthy volunteers (HV). Renal function was assessed by the estimated glomerular filtration rate (eGFR). Doses: Single 100 µg dose of NVA237 delivered via the Breezhaler® device. ESRD subjects received a single dose on two occasions, between two dialysis sessions and at start of a 4-hr dialysis. Results A moderate increase in NVA237 total systemic exposure (AUClast) of up to 1.4-fold (on average) was seen in subjects with mild and moderate RI as compared to HVs. An increase of up to 2.2-fold was observed in subjects with severe RI and ESRD. Renal clearance (CLr) of NVA237 was strongly correlated with the degree of RI. In subjects with severe RI, CLr was reduced by about 80% compared with HVs. NVA237 was partially cleared during hemodialysis with an extraction ratio of 24.3%. NVA237 was well tolerated by HVs and RI subjects. Conclusion RI had an impact on NVA237 total systemic exposure which was moderate in subjects with mild and moderate RI (eGFR $\geq$ 30 mL/min/1.73m^2). The limited effect of severe RI on systemic exposure to NVA237 and the correlation analysis of total systemic clearance versus eGFR suggests that non-renal clearance mechanisms play a role in the elimination of NVA237.