European Respiratory Society
Annual Congress 2012

Abstract Number: 7009

Publication Number: P2121

Abstract Group: 5.1. Airway Pharmacology and Treatment

Keyword 1: COPD - management **Keyword 2:** Pharmacology **Keyword 3:** Bronchodilators

Title: Umeclidinium (GSK573719) dose response and dosing interval in COPD

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Body: Introduction: Dose differentiation is important in selecting COPD treatments. Objective: Characterize umeclidinium (UMEC), a long-acting muscarinic antagonist, dose response in COPD patients. Methods: Randomized, double blind, placebo controlled, crossover study. Subjects were randomized to a sequence of 3 treatments for 7 days separated by a 10–14 day washout. Four once-daily (OD) UMEC doses (15.6, 31.25, 62.5, 125mcg) or 2 twice-daily (BID) doses (15.6, 31.25mcg) were administered via dry powder inhaler. Tiotropium (18mcg) was an active control. Primary endpoint was morning trough FEV_1 on Day 8; population model analysis was applied with ANCOVA. Serial FEV_1, pharmacokinetics and safety were examined. Post hoc analysis of the primary endpoint was performed without one investigative site due to poor study practices. Results: 163 subjects (mean age 59.5yrs, 52% female) were randomized. Emax dose response in trough FEV_1 was characterized with OD dose ordering of UMEC 125>62.5>31.25=15.6mcg. A high potency ED50 (37mcg, 95% CI: 18–57, OD regimen) was estimated. Post hoc results were similar. 125mcg OD had more consistent increases in FEV_1 from baseline across serial timepoints over 24h compared with other UMEC doses and tiotropium. No advantage of BID over OD dosing was observed. Drug absorption and elimination were rapid. AEs were highest with UMEC 125mcg OD (18%), placebo (8%), tiotropium (4%), other UMEC doses (5–12%). Two non-drug related, non-fatal SAEs (acute respiratory failure, 15.6mcg OD; myocardial infarction, 31.25mcg OD) were reported. Conclusions: Dose response for umeclidinium was in the order 125>62.5>31.25=15.6mcg; a once-daily dosing interval was confirmed. GlaxoSmithKline funded (AC4115321; NCT01372410).