European Respiratory Society
Annual Congress 2013

Abstract Number: 3950

Publication Number: P759

Abstract Group: 5.1. Airway Pharmacology and Treatment

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

Title: Pooled analyses of QTcF across six phase 2b studies with glycopyrrolate-formoterol fumarate (GFF) MDI (PT003), its components and active comparators

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Body: Rationale GFF MDI is comprised of glycopyrrolate (GP) and formoterol fumarate (FF). Individual Phase 2 trials showed no clinically significant change in QTcF in patients treated with GFF MDI, GP MDI, or FF MDI across a wide range of doses evaluated. Pooled analyses of QTcF data from 6 Phase 2b studies were done to further evaluate cardiovascular safety. Methods Patients that met criteria for the safety population from 6 studies were included in pooled analyses of QTcF on Day 1 and Day 7. Five studies were randomized, double-blind, chronic dosing (7-14 days), placebo-controlled, multicenter, crossover studies in patients with COPD; the sixth study was a parallel group design. Doses ranged from 0.6 to 36 μg BID for GP MDI, from 1.2/9.6 to 72/9.6 μg for GFF MDI, and from 7.2 to 9.6 μg for FF MDI. Results 946 patients were included in the pooled analyses. On Day 1, all GFF doses had a mean change in QTcF lower than 5 ms except for GFF MDI 1.2/9.6 μg where the mean increase post-dosing was 6.22 ms at 30 min and 6.49 ms at 1 h. On Day 7, all GFF doses had a change in QTcF lower than 5 ms except GFF MDI 1.2/9.6 μg where a change of 5.19 ms was observed 2 h post-dose. The 95% CIs for the changes from baseline did not reach 10 ms at any time on Day 1 or Day 7. Results were similar for GP MDI, FF MDI, placebo and the active comparators (Spiriva Handihaler 18 μg, Foradil Aerolizer 12 μg and Atrovent HFA 34 μg). Conclusion The effect of GFF MDI on QTcF has been well characterized. Pooled analyses of QTcF data from six studies demonstrate that GFF MDI 18/9.6 μg had no significant impact on QTcF supporting its selection and progression into Phase III.