European Respiratory Society
Annual Congress 2013

Abstract Number: 3244

Publication Number: P4133

Abstract Group: 5.1. Airway Pharmacology and Treatment

Keyword 1: Asthma - management **Keyword 2:** Bronchodilators **Keyword 3:** Lung function testing

Title: Phase III trial of tiotropium as add-on therapy to low-dose inhaled corticosteroids for patients with symptomatic mild persistent asthma: Design and planned analyses

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Body: Background: Tiotropium, a once-daily long-acting anticholinergic bronchodilator, improved lung function and reduced severe exacerbations in patients with severe symptomatic asthma despite using ICS/LABA (Kerstjens et al. NEJM 2012;367:1198-207). A Phase III, randomised, double-blind, parallel-group trial (NCT01316380) was designed to analyse tiotropium efficacy and safety versus placebo in patients with mild persistent asthma on low-dose ICS. Methods: Patients aged 18-75 years, with symptomatic asthma despite low-dose ICS (ACQ ≥1.5 at screening/randomisation), diagnosed ≥3 months prior to enrolment and before age 40, non-smokers or ex-smokers (≥1 year with <10 pack-years), were included. All received stable low-dose ICS for ≥4 weeks and had pre-bronchodilator FEV_1 ≥60% and ≤90% of predicted and positive reversibility testing. Patients received 2.5 µg or 5 µg tiotropium or placebo once daily via the Respimat® Soft Mist™ Inhaler for 12 weeks in addition to daily low-dose ICS. Rescue medication (salbutamol/albuterol) was allowed throughout. The primary end point, FEV_1 $peak_{(0\text{-}3h)}$ response (change from baseline) after 12 weeks, will be analysed using a restricted maximum likelihood-based mixed effects model with repeated measures. Secondary end points include trough FEV_1 response, FVC $peak_{(0\text{-}3h)}$ response, FEV_1 ($AUC_{0\text{-}3h}$), FVC ($AUC_{0\text{-}3h}$), ACQ score after 12 weeks, time to first exacerbation and rescue medication use. Conclusion: This trial provides information on the bronchodilator efficacy and safety of different doses of tiotropium versus placebo as add-on to low-dose ICS in patients with symptomatic mild persistent asthma.