Conclusion Once-daily tiotropium Respimat® as add-on to ICS or ICS + LABA in patients with moderate to severe symptomatic asthma reduces airflow obstruction, apparently independent of their atopic and/or allergic status.

P230 ONCE-DAILY TIOTROPIUM RESPIMAT® IMPROVES LUNG FUNCTION IN PATIENTS WITH SEVERE SYMPTOMATIC ASTHMA INDEPENDENT OF LEUKOTRIENE MODIFIER USE

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Background Once-daily tiotropium Respimat®, a long-acting anticholinergic bronchodilator, has been shown in a Phase III programme to improve lung function and reduce severe exacerbation risk in patients with severe asthma who remain symptomatic despite using inhaled corticosteroids (ICS) + long-acting β_2-agonist (LABA). Use of pre-trial leukotriene receptor antagonists (LTRAs) was not restricted; we analysed whether pre-screening LTRA use affected tiotropium Respimat® efficacy.
Methods In two Phase III, replicate, randomised, double-blind, placebo-controlled, parallel-group trials (PrimoTinA-asthma®: NCT00772538, NCT00776984), symptomatic patients received high-dose ICS + LABA and once-daily tiotropium 5 µg or placebo (both delivered via the Respimat® SoftMist™ inhaler). LTRAs were permitted during run-in and treatment. Co-primary end points were peak and trough forced expiratory volume in 1 second (FEV_1) responses (difference from baseline) at 24 weeks. Subgroups were defined by pre-screening LTRA use: 'Yes'/'No'.
Results Of 912 randomised patients, 205 reported pre-screening LTRA use, 200 reported LTRA use during the treatment period and 187 had efficacy data at Week 24. Baseline characteristics were comparable between groups. Mean body mass index in LTRA 'Yes'/'No' groups was 27.8 kg/m^2 and 28.3 kg/m^2, respectively. Mean% predicted FEV_1 at baseline was 56% in both groups. Lung function responses improved independent of LTRA use: peak FEV_1 was 99 ± 50 mL (p = 0.049) in the LTRA 'Yes' group and 113 ± 28 mL (p < 0.001) in the LTRA 'No' group (peak FEV_1 improvements independent of concomitant LTRA use [interaction p value=0.6742]). Trough FEV_1 (difference from placebo) was 90 ± 46 mL (p = 0.052) in the LTRA 'Yes' group and 93 ± 25 mL (p < 0.001) in the LTRA 'No' group (trough FEV_1 improvements independent of concomitant LTRA use [interaction p value = 0.5218]).
Conclusion Once-daily tiotropium Respimat® added to ICS + LABA improves lung function in patients with severe symptomatic asthma, independent of initial LTRA use.

P231 ONCE-DAILY TIOTROPIUM RESPIMAT®: SAFETY AND TOLERABILITY RESULTS FROM FIVE PHASE III TRIALS IN ADULTS WITH SYMPTOMATIC ASTHMA

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Background Tiotropium Respimat®, a once-daily long-acting anticholinergic agent, is effective as add-on to inhaled corticosteroids (ICS) ± a long-acting β2-agonist (LABA) in adults with symptomatic asthma. Safety and tolerability are key issues in the development of new therapies or established therapies in new disease areas. We present key safety data from five Phase III, randomised, double-blind, parallel-group trials that evaluated the efficacy and safety of once-daily tiotropium Respimat® versus placebo in adults with symptomatic asthma. Methods: Two 48-week trials of tiotropium Respimat® 5 µg (PrimoTinA-asthma®: NCT00776984, NCT00772538) in patients on high-dose ICS (≥800 µg budesonide or equivalent) + LABA; two 24-week trials of tiotropium Respimat® 5 µg and 2.5 µg (MezzoTinA-asthma®: NCT01172808, NCT01172821) in patients on moderate-dose ICS (400–800 µg budesonide or equivalent); one 12-week trial of tiotropium Respimat® 5 µg and 2.5 µg (GraziaTinA-asthma®: NCT01316380) in patients on low-dose ICS (200–400 µg budesonide or equivalent). All tiotropium doses were delivered via the Respimat® SoftMist™ inhaler. Results:

Abstract P231 Table 1

%	Tiotropium Respimat® 5 µg QD (n = 456)	Placebo Respimat® QD (n = 456)	Tiotropium Respimat® 5 µg QD (n = 517)/ 2.5 µg QD (n = 519)	Salmeterol 50 µg BID (n = 541)	Placebo[a] (n = 523)	Tiotropium Respimat® 5 µg QD (n = 155)/ 2.5 µg QD (n = 154)	Placebo Respimat® QD (n = 155)
Any AE	73.5	80.3	57.3/58.2	54.3	59.1	32.3/31.2	29.0
Drug-related AE	5.7	4.6	7.4/6.9	5.2	5.4	1.3/1.3	1.3
Serious AE	8.1	8.8	2.1/2.3	2.0	2.7	0.6/0	0.6
Asthma	39.9	50.9	21.5/15.8	19.4	22.0	11.0/15.6	12.9
Bronchitis	5.5	4.4	2.1/1.7	1.7	1.0	1.9/0	0.6
Decreased peak expiratory flow rate	20.4	26.8	11.4/9.4	8.7	15.1	3.9/5.8	3.9
Headache	6.4	7.2	1.5/3.5	1.1	2.7	1.9/0.6	0
Nasopharyngitis	11.2	12.3	7.9/9.4	7.6	9.2	0.6/1.3	3.2
Upper respiratory tract infection	4.6	3.5	3.7/5.2	7.6	7.8	4.5/1.3	4.5

[a]Placebo Respimat® QD + placebo hydrofluoroalkane metered-dose inhaler BID BID, twice-daily; QD, once-daily

3476 patients were treated. Incidence of any adverse events (AEs), serious AEs and investigator-defined drug-related AEs was similar across treatment groups within each trial. AEs reported by ≥5% of patients were similar across all treatment groups within each trial (Table). The number of cardiovascular AEs was small in all five studies and comparable between tiotropium Respimat® and placebo. No deaths occurred in any trial. Conclusion: Once-daily tiotropium Respimat® is well tolerated and comparable with placebo in adult patients with symptomatic asthma receiving at least low- to high-dose ICS.

P232 TREATMENT OF ALLERGIC RHINITIS WITH THEOPHYLLINE : A DOUBLE-BLIND, RANDOMISED, CROSSOVER STUDY

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Background Allergic rhinitis and Asthma are considered as 'one airway disease'. Theophylline has been used as a bronchodilator in asthma for decades but more recently its anti-inflammatory properties have been identified. We hypothesise that treatment with low dose theophylline in patients with persistent allergic rhinitis is likely to improve the total nasal symptom scores and there by demonstrate a clinically meaningful difference.
Methods This was a single centre double- blind, randomised, placebo-controlled cross-over study of the effects of theophylline (one capsule of Theophylline 200 mgs as Uniphyllin continus twice a day for 4 weeks) in 21 patients with persistent allergic rhinitis in Norwich, U. K. Reference: NCT0113278. Primary outcome was Total Nasal Symptom Score (TNSS) after each intervention period. Secondary endpoint measures were differences in the domiciliary average total nasal symptom score, differences in nasal peak inspiratory flow (PNIF), differences in domiciliary nasal peak inspiratory flow and difference in Sino-Nasal Outcome Test (SNOT)-22.
Results Primary Endpoint

There was no significant (p = 0.276) difference in Total Nasal Symptoms scores during Theophylline treatment period and placebo period, mean (SD) (Table). The intention-to-treat analysis results were in keeping with the per protocol analysis.

Secondary End points

PNIF in the Theophylline period was 112.38(±43.49) compared to the placebo period 122.86(±53.77), p = 0.171 (Table). There was no change in SNOT-22 (p = 0.867) between treatment periods but there was a non-significant improvement with Theophylline (39.00 ± 19.78) compared to placebo (38.00 ± 19.63) treatment period. There was a non-significant improvement in the domiciliary total nasal symptom scores (TNSS) between Theophylline (3.53 ± 2.35) and placebo (2.81 ± 2.46). Nasal scrape samples were stained with HDAC2 antibodies and the signals were very week.

Abstract P232 Table 1 Changes after intervention between treatments: Per Protocol Results

Outcome Variable	Placebo Mean (SD)	Theophylline Mean (SD)	p Value	95% CI
TNSS	4.90 (3.08)	4.14 (2.33)	0.276	-0.76 (-2.13,0.61)
PNIF	122.86 (53.77)	112.38 (43.49)	0.171	-10.48 (-25.49,4.54)
SNOT-22	38.00 (19.63)	39.00 (19.78)	0.867	0.63 (-6.67,7.92)

Conclusion This is the first study evaluating Theophylline in persistent rhinitis. Low-dose Theophylline had no significant effects on Total nasal Symptom scores; Rhinosinusitis symptoms and nasal patency assessed using peak nasal inspiratory flow. There was a non-significant improvement in the total nasal symptom scores and sino-nasal outcome test and domiciliary nasal scores.

P233 LONG-TERM IMPACT OF INHALED CORTICOSTEROIDS ON BONE MINERAL DENSITY AND FRACTURE RISK IN PATIENTS WITH ASTHMA: SYSTEMATIC REVIEW AND META-ANALYSIS

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Background A recent meta-analysis of 16 randomised controlled trials (RCTs) and 7 observational studies demonstrated a modest but statistically significant increase in fracture risk with inhaled corticosteroid (ICS) use in chronic obstructive pulmonary disease. However, it is not clear whether ICS use has similar skeletal adverse effects in patients with asthma. We aimed to evaluate the association between ICS and fractures and changes in bone mineral density when used for >12 months in asthma.
Methods We initially searched MEDLINE and EMBASE in July 2013, and performed an updated PubMed search in June 2014. We used a combination of search terms involving drug name and adverse effects of interest, and we also hand-searched reference lists of existing systematic reviews and trial reports. We selected RCTs and controlled observational studies of any ICS vs non-ICS control treatment for asthma (at least 52 weeks duration). Meta-analysis of odds ratios was conducted using RevMan 5.3 with the primary outcome measure being fracture events. We also analysed mean differences in bone mineral density (gram per cm squared) using inverse variance method. Heterogeneity was assessed using the I2 statistic.
Results We selected nine RCTs and 11 observational studies for the meta-analysis. There was no significant association between ICS and fractures in children in one RCT, or in a pooled analysis of two observational studies, (OR 1.02, 95% CI 0.94–1.10). No significant fracture risk in adults was reported in 4 observational studies (pooled OR 1.09, 95% CI 0.45–2.62). Meta-analysis of bone mineral density at the lumbar spine did not show significant reductions with ICS use in children (three RCTs and three observational studies), or in adults (three RCTs and four observational studies). Similarly, meta-analysis of bone mineral density at the neck of femur in adults did not demonstrate significant reductions compared to control (three RCTs and four observational studies).
Conclusion In our systematic review of 20 studies, use of ICS for >12 months in patients with asthma was not associated with statistically significant adverse effects on bone mineral density or fractures.

P234 IMPACT OF INHALED CORTICOSTEROIDS ON GROWTH IN CHILDREN WITH ASTHMA: SYSTEMATIC REVIEW AND META-ANALYSIS

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