P228 EFFICACY AND SAFETY OF FLUTICASONE PROPIONATE/FORMOTEROL IN PAEDIATRIC PATIENTS WITH ASTHMA

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10.1136/thoraxjnl-2014-206260.356

Background Fluticasone propionate (FP) and formoterol (FORM) have been combined in a single inhaler (FP/FORM;***flutiform***®) for the treatment of adolescents and adults with asthma. This study assessed the efficacy and safety of FP/FORM in paediatric asthma patients.

Methods A total of 512 patients aged 5 to <12yrs were randomised 1:1:1 to 12 weeks of treatment with either FP/FORM (100/10 µg BID), FP (100 µg BID) or fluticasone propionate/salmeterol (FP/SAL) (100/50 µg BID) in a double-blind, parallel group, multicentre study. The objectives were to demonstrate superiority of FP/FORM to FP and non-inferiority to FP/SAL. The primary endpoint was the change from predose FEV1 at baseline to 2-hour postdose FEV1 over the 12 weeks. The two key secondary endpoints were FEV1 AUC0–4h at Week 12 and change from pre-dose FEV1 over the 12 weeks.

Results FP/FORM was superior to FP for change from predose FEV1 at baseline to 2-hour postdose FEV1 (treatment difference = 0.07 L; 95% CI: 0.03, 0.11; p < 0.001) and FEV1 AUC0–4h at Week 12 (treatment difference = 0.09 L; 95% CI: 0.04, 0.13; p < 0.001). FP/FORM was non-inferior to FP/SAL for change from predose FEV1 at baseline to 2-hour postdose FEV1 (treatment difference = -0.00 L; 95% CI: -0.04, 0.04; p < 0.001), AUC0–4h at Week 12 (treatment difference = 0.01 L; 95% CI: -0.03, 0.06; p < 0.001) and change from predose FEV1 (treatment difference = -0.02 L; 95% CI: -0.06, 0.02; p < 0.001). The safety and tolerability profiles of all treatments were similar.

Conclusion In children 5 to <12yrs with asthma, FP/FORM was superior to FP, and non-inferior to FP/SAL for improvements in lung function, with a similar tolerability profile to both FP and FP/SAL.

P229 ONCE-DAILY TIOTROPIUM RESPIMAT® AS ADD-ON TO AT LEAST MEDIUM- TO HIGH-DOSE ICS, WITH OR WITHOUT LABA, IMPROVES LUNG FUNCTION IN PATIENTS WITH SYMPTOMATIC ASTHMA, INDEPENDENT OF ALLERGIC STATUS

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10.1136/thoraxjnl-2014-206260.357

Background A substantial number of patients have symptomatic asthma despite treatment according to guidelines. Several studies have confirmed that tiotropium Respimat®, a once-daily long-acting anticholinergic bronchodilator, improves lung function in symptomatic patients receiving at least medium-dose inhaled corticosteroids (ICS) + long-acting β_2-agonist (LABA) (Kerstjens *et al*. NEJM 2012;367:1198–207; Bateman *et al*. JACI 2011;128:315–22). Here we examine whether the atopic and/or allergic status of patients in these trials influenced their response to tiotropium Respimat®.

Method Two 48-week trials of tiotropium Respimat® 5 µg (PrimoTinA-asthma®: NCT00776984, NCT00772538) in patients (n = 912) on high-dose ICS + LABA; two 24-week trials of tiotropium Respimat® 5 µg and 2.5 µg (MezzoTinA-asthma®: NCT01172808, NCT01172821) in patients (n = 2100) on moderate-dose ICS. Pre-planned analyses (pooled populations) were performed in two subgroups defined at baseline as total serum immunoglobulin E (IgE) ≤ or >430 µg/L or blood eosinophils ≤ or >0.6×10^9/L or clinical judgement of allergic status ('No' or 'Yes'). All tiotropium doses were delivered via the Respimat® SoftMist™ inhaler.

Results Tiotropium Respimat® 5 µg or 2.5 µg improved peak and trough forced expiratory volume in 1 second versus placebo (Table) independent of IgE, eosinophil count and clinical judgement.

Abstract P229 Table 1

Adjusted mean difference for tiotropium Respimat® from placebo (mL)		IgE ≤/ >430 µg/L	Interaction p value[a]	Eosinophils ≤/>0.6×10^9/L	Interaction p value[a]	Clinical judgement 'No' or 'Yes'	Interaction p value[a]
	n[b]	336/377		654/175		335/516	
	Peak FEV_1 (0–3h)	148/102	0.742	115/58	0.7021	76/130	0.2114
PrimoTinA-asthma®	Trough						
Tiotropium Respimat® 5 µg	FEV_1	127/89	0.6209	103/52	0.7542	94/91	0.4099
	n[b]	356/610		769/201		349/624	
	Peak FEV_1 (0–3h)	168/193	0.9677	170/240	0.2375	180/189	0.6233
MezzoTinA-asthma®	Trough						
Tiotropium Respimat® 5 µg	FEV_1	139/152	0.8437	137/182	0.5148	138/153	0.6727
	n[b]	364/614		779/203		349/635	
	Peak FEV_1 (0–3h)	197/237	0.9677	236/176	0.2375	243/213	0.6233
MezzoTinA-asthma® Tiotropium Respimat® 2.5 µg	Trough FEV_1	167/188	0.8437	185/158	0.5148	209/164	0.6727

[a]For treatment×subgroup interaction; [b]Values for active and placebo groups combined
FEV_1, forced expiratory volume in 1 second

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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10.1136/thoraxjnl-2014-206260.358

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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10.1136/thoraxjnl-2014-206260.359

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