Conclusions The increase in time to first severe exacerbation and first episode of asthma worsening found with the addition of tiotropium was not limited to specific subgroups of patients, including some characteristics that are usually found in patients with chronic obstructive pulmonary disease, such as former smoking, non-allergic status or minimal reversibility. Tiotropium seems effective across a broad spectrum of patients with severe persistent asthma who remain symptomatic and experience exacerbations despite the combination use of moderate- to high-dose inhaled corticosteroids plus long-acting beta agonists.

P164 USE OF BETA-AGONISTS PRIOR TO HOSPITAL ATTENDANCE FOR SEVERE EXACERBATIONS OF ASTHMA: INSIGHTS FROM A RANDOMISED CONTROLLED TRIAL USING ELECTRONIC MONITORING OF INHALER USE

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Introduction Observational studies have reported that the overuse of inhaled beta-agonists during severe asthma is a common feature associated with a fatal outcome. However, patterns of actual use of beta-agonists prior to hospital attendance for severe exacerbations are poorly understood.
Objectives We have recently reported that in 303 adult asthma patients randomised to receive either combination budesonide/formoterol metered dose inhaler (MDI) as part of a single maintenance and reliever therapy regimen ('SMART') or as fixed-dose maintenance treatment with salbutamol MDI for relief ('Standard'), overuse of beta-agonists without subsequent medical review occurred commonly in both groups. We now report on the use of beta-agonists by patients who attended hospital with a severe exacerbation of asthma. Our hypothesis was that extremely high beta-agonist doses would be used by patients in both groups and that inhaled corticosteroid (ICS) non-adherence may occur in the Standard group during severe asthma.
Methods Data on MDI use, as measured by electronic monitoring, were extracted for each patient for the 14 24-hour periods before the attendance time at hospital for a severe exacerbation.
Results Electronic data were available for 7/7 and 9/11 hospital attendances in the SMART and Standard groups respectively. The median (range) daily number of actuations 14 days before hospital attendance was 4 (2 to 12) budesonide/formoterol in SMART and 4 (0 to 26) salbutamol and 2 (0 to 8) budesonide/formoterol in Standard. This increased to 11 (6 to 39) budesonide/formoterol in SMART and 25 (3 to 86) salbutamol and 4 (0 to 39) budesonide/formoterol in Standard, in the 24-hours before attendance. The median (range) maximum daily number of actuations was 14 (9 to 63) budesonide/formoterol in SMART and 46 (6 to 95) salbutamol in Standard. Repeated days of no ICS use occurred in 3/9 patients in the Standard group, despite concomitant salbutamol overuse.
Conclusions Very high doses of beta-agonists are commonly self-administered by patients for prolonged periods prior to hospital presentation with severe asthma. The opportunity exists for clinical review and appropriate medical intervention during this period, which may reduce the risk of a life-threatening attack.

P165 THE RELIABILITY AND PERFORMANCE OF ELECTRONIC MONITORS OF INHALER USE IN A REAL WORLD ASTHMA CLINICAL TRIAL

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Introduction Electronic monitoring is one method to measure the use of inhaled therapy in asthma patients in clinical trials, though the reliability of these devices has been variable. Implementation of trial quality control processes and reporting on the performance of electronic monitors during patient use may help to better understand their utility and limitations. The Smartinhaler Tracker is an electronic monitor for metered dose inhalers (MDIs) that records the date, time and number of actuations to the nearest second.
Objectives In a recently completed 24-week real-world randomised controlled trial of 303 asthma patients at risk of severe exacerbations, Smartinhaler Tracker electronic monitors were used to measure actual use of budesonide/formoterol and salbutamol MDI therapy with two treatment regimens. Our aim is to report on the performance of these monitors, based on the implementation of extensive pre-trial and within-trial validation protocols for their use.
Methods Pre-study use checks involved two actuations of the MDI, with a further two actuations performed at least two hours later. Within-study monitor checks, performed prior to dispensing at follow-up clinic visits, included a computerised check of monitor clock function, actuation accuracy and battery life. Within-study data checks, performed after use of MDIs by participants during the trial, involved computerised checks of monitor clock function prior to data upload.
Results 2678/2728 (98.2%) monitors passed pre-study use checks; 46/50 monitors failed pre-study checks either because they did not record actuations that were performed, or erroneously recorded extra actuations. 76/2642 (2.9%) monitors dispensed to participants failed within-study monitor checks; 33/76 monitors failed because the battery was not fully charged. 51/2642 (1.9%) monitors failed data upload checks, mostly as a result of fluid immersion during participant use. 93/2642 (3.5%) monitors were lost or thrown away by participants. Complete data was available from 2498/2642 (94.5%) of dispensed monitors and 2498/2549 (98.0%) of returned monitors.
Conclusions The Smartinhaler Tracker is a reliable monitor for measuring MDI use in a real-world asthma clinical trial. Implementation of extensive monitor and data-checking protocols reduces data loss. The use of validated and reliable electronic monitors is the optimal method to assess patterns of inhaled medication use.

P166 EFFECTS OF LOW-VS HIGH-DOSE FLUTICASONE/FORMOTEROL COMBINATION THERAPY ON AMP CHALLENGE IN ASTHMATIC PATIENTS

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Background The ICS fluticasone propionate (FP) and the LABA formoterol fumarate (FORM) have now been combined in a single aerosol inhaler (FP/FORM; ***flutiform***). The effect of low- (2 puffs 50/5 g bid) vs high-dose (2 puffs 250/10 g bid) FP/FORM on airway responsiveness to AMP was compared in an

incomplete block, placebo-controlled, 2-way crossover study. *Post hoc* data analysis from patients who received both FP/FORM doses is presented.

Methods 62 patients (33M, 29F; =18yrs; reversible FEV_1 =60% pred.) discontinued maintenance ICS medication for 2 - 3wks; those showing a provocative dose of AMP producing a 20% decline in FEV_1 (AMP PD_{20} FEV_1) of <60 mg were randomised to receive 2 of 3 treatments (FP/FORM high-, low-dose or placebo) during 2 periods of 28 ± 3 days each, separated by 2 - 3wks. AMP challenges were performed pre-dose and repeated 12h after last dose at the end of each treatment period. The difference in changes in AMP PD_{20} FEV_1 (day 1 vs day 28) between treatments were compared by an ANCOVA.

Results 15 patients were randomised to receive both high- and low-dose FP/FORM. The change in AMP PD_{20} FEV_1 was greater with FP/FORM high- compared with low-dose (LS means: high dose = 11 mg; 95% CI 4.3, 27.9; low dose = 4.6 mg, 95% CI 1.8, 11.8), with a statistically significant 2.4 fold difference in AMP PD_{20} FEV_1 (1.2 doubling doses) between doses (LS mean: 2.4; 95% CI 1.3, 4.5; p = 0.012). FP/FORM was well-tolerated; only few (mild or moderate) AEs occurred.

Conclusions A significant dose-response was found between low- and high-dose FP/FORM with the higher dose demonstrating a greater reduction in airway responsiveness to AMP.

P167 EFFICACY AND SAFETY OF OMALIZUMAB IN REAL–WORLD CLINICAL PRACTICE IN INDIAN PATIENTS WITH ALLERGIC (IGE-MEDIATED) ASTHMA: ANALYSIS BY BASELINE SEVERITY OF ASTHMA

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Omalizumab (OMA) is a humanised anti-immunoglobulin E (IgE) monoclonal antibody, indicated as add-on therapy for moderate-to-severe persistent allergic (IgE–mediated) asthma. Here, we report the interim results of a 52-week observational study of OMA in patients in India, stratified by baseline severity of asthma.

In this open-label, non-comparative, non-interventional study, patients (age =12 years) with moderate-to-severe persistent allergic asthma, inadequately controlled despite ICS + LABA (GINA step 4) treatment, were recruited. All patients were receiving OMA at baseline. Outcomes were assessed every 4 weeks, and included exacerbations, days missed at college or work, hospitalizations, and mean change (D) in FEV_1, ACQ5 score, ACT score and oral corticosteroid (OCS) dose versus baseline. Adverse events were also recorded. Asthma severity was assessed at baseline, in accordance with GINA guidelines, and classified as either moderate (group 1) or severe (group 2). Data were analysed using chi-squared and paired t-tests. All parameters were compared between baseline and Week 28 post-OMA treatment.

To date, 100 patients have completed 28 weeks of follow-up (36 patients in group 1 and 64 in group 2). Results are presented in the Table. The proportion of patients with =1 exacerbation, missing any day at work/college and requiring hospitalisation decreased appreciably in both groups. There was also significant improvement in lung function and asthma control, and a reduction in OCS need. Overall, 5 patients (5%) reported adverse events (AEs), of whom 2 (2%) reported serious AEs (SAEs). The most frequent non-serious AEs were gastrointestinal (GI) and nervous system disorders and were suspected to be related to omalizumab. GI, respiratory, thoracic and mediastinal SAEs were reported, but were not suspected to be related to omalizumab. All reported AEs and SAEs resolved with treatment. 28 weeks' treatment with omalizumab was associated with reductions in asthma exacerbations and OCS requirements, and improvements in lung function and asthma control, that were comparable between patients with moderate or severe asthma at baseline

Abstract P167 Table 1.

Parameter	Group 1 (n=36)		Group 2 (n=64)		Group 1 vs. 2	
	baseline	28 weeks	baseline	28 weeks	p-Value	
Patients with ≥1 exacerbation	9.5%	0.0%	9.3%	1.1%	0.530	
Patients missing any day at work/college	23.8%	0.0%	25.9%	7.4%	0.200	
Hospitalization rate	19.0%	0.0%	27.8%	0.0%	-	
	D vs. baseline	p-Value	D vs. baseline	p-Value	Mean difference	p-Value
FEV_1 (L)	+1.1	0.000	+1.0	0.000	0.1	0.244
ACQ5 score (composite)	-7.5	0.000	-7.3	0.000	-0.2	0.786
ACQ5 score (mean)	-1.5	0.000	-1.5	0.000	0.0	0.981
ACT score(mean)	+9.4	0.000	+10.2	0.000	-0.8	0.396
OCS dose (mg/day)	-11.3†	0.002	-18.8‡	0.000	7.5	0.099

†13 and ‡16 patients were receiving OCS at baseline in group 1 and 2, respectively.

P168 THE EFFECT OF FLUTICASONE PROPIONATE/FORMOTEROL FUMARATE COMBINATION THERAPY ON QUALITY OF LIFE SCORES IN ASTHMA PATIENTS

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Introduction The Asthma Quality of Life Questionnaire (AQLQ) is a validated questionnaire which measures the effect of asthma on patient's lives. AQLQ data from four phase III studies were pooled to assess how AQLQ scores are affected by treatment with fluticasone propionate (FP)/formoterol fumarate (FORM) in a single MDI (FP/FORM; ***flutiform***) compared with other combination treatments.

Method AQLQ data from a pooled analysis of two phase III open-label studies in patients with mild-moderate/severe asthma [pool 1; FP/FORM 50/5 or 125/5 (n = 206) vs. FP 50 + FORM 12 given together in separate inhalers and FP/salmeterol 50/25 or 125/25 (n = 206)], and a pooled analysis of two phase III double-blind studies in patients with moderate/severe asthma [pool 2; FP/FORM 250/10 (n = 294) vs. FP 250 + FORM 12 given together in separate inhalers and budesonide/FORM 200/6 (n = 295)] were analysed. AQLQ scores range from 1–7; a low score indicates the most severe impairment. Change in AQLQ from baseline to end of study was analysed using an ANCOVA. The proportion of subjects achieving a clinically relevant change of = 0.5 units was analysed using a logistic regression model.

Results In pool 1, both groups had a similar increase in overall AQLQ score from baseline to end of study (0.635 in the FP/FORM group and 0.771 in the combination group) and the percentage of patients with a clinically relevant change in overall AQLQ score was 56% and 59%, respectively. In pool 2, the mean increase in overall AQLQ score from baseline to end of study was 0.837 in the FP/

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P166 Effects of low-vs high-dose fluticasone/formoterol combination therapy on AMP challenge in asthmatic patients

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