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Risk of new onset diabetes mellitus in patients with asthma or COPD taking inhaled corticosteroids

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KEYWORDS
Budesonide;
Hyperglycaemia;
Side-effects

Summary
Background: A recent case-controlled study reported an increased risk of diabetes mellitus in patients treated with inhaled corticosteroids for asthma or COPD, versus age-matched controls.
Objective: The purpose of the current study was to evaluate whether there was an increased risk of new onset diabetes mellitus or hyperglycaemia among patients with asthma or COPD treated with inhaled corticosteroids.
Methods: A retrospective analysis evaluated all double-blind, placebo-controlled, trials in patients ≥4 years of age involving budesonide or budesonide/formoterol in asthma (26 trials; budesonide: $n = 9067$; placebo: $n = 5926$), and in COPD (8 trials; budesonide: $n = 4616$; non-ICS: $n = 3643$). A secondary dataset evaluated all double-blind, controlled trials in asthma involving the use of inhaled corticosteroids (60 trials; budesonide: $n = 33{,}496$; fluticasone: $n = 2773$).
Results: In the primary asthma dataset, the occurrence of diabetes mellitus/hyperglycaemia adverse events (AEs) was 0.13% for budesonide and 0.13% for placebo (HR 0.98 [95% CI: 0.38–2.50], $p = 0.96$) and serious adverse events (SAEs) was 0% for budesonide and 0.05% for placebo. In the secondary dataset, the occurrence of diabetes/hyperglycaemia as AE and SAE was 0.19% and 0.03%, respectively. In the COPD dataset, the occurrence of diabetes mellitus/hyperglycaemia AEs was 1.3% for budesonide and 1.2% for non-ICS (HR 0.99 [95% CI: 0.67–1.46], $p = 0.96$) and SAEs was 0.1% for budesonide and 0.03% for non-ICS.

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Conclusion and clinical relevance: Treatment with inhaled corticosteroids in patients with asthma or COPD was not associated with increased risk of new onset diabetes mellitus or hyperglycaemia.
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Introduction

Inhaled corticosteroids (ICS) are the mainstay of treatment for patients with asthma[1,2] and are an important part of the management of patients with chronic obstructive pulmonary disease (COPD), particularly those who have recurrent exacerbations.[3] While oral glucocorticosteroids may contribute in a dose-dependent manner to hyperglycaemia/impaired glucose tolerance and diabetes mellitus in vulnerable patients, the systemic concentrations achieved during ICS treatment for asthma or COPD are thought to be too low to affect plasma glucose in most patients. However, a large nested case-controlled study, involving patients treated with ICS for asthma or COPD, reported a 34% increase in the incidence of diabetes mellitus over 5.5 years of follow-up versus age-matched controls who were not treated with ICS.[4] By contrast, two other studies of ICS in elderly patients failed to demonstrate any increased risk of diabetes related to ICS exposure.[5,6] In a prospective cohort study of US veterans over 1 year, ICS exposure was associated with a dose-dependent increase in serum glucose concentrations in patients with established diabetes mellitus, but not in patients without diabetes.[7] Similarly, in a small, prospective, crossover study in patients with established type 2 diabetes mellitus, glycosylated haemoglobin levels rose significantly after 6 weeks of treatment with inhaled fluticasone.[8] Together, these observations suggest that ICS may exacerbate diabetes in asthma or COPD, by increasing blood glucose levels in patients with established diabetes mellitus. Their impact on incidence of diabetes mellitus, however, remains uncertain.

The ICS budesonide first became available in the early 1980s and is also available as a fixed-dose combination with the long-acting β_2-agonist formoterol for the treatment of asthma and COPD. The extensive clinical trial programme conducted for budesonide provides a considerable pool of patient data from which to examine the impact of ICS therapy on a variety of patient outcomes, including the risk for diabetes mellitus. The present pooled analysis was undertaken to determine whether ICS increases the risk of new onset diabetes mellitus or hyperglycaemia among patients with asthma or COPD treated with budesonide compared with those who did not receive budesonide in the randomised controlled trials.

Methods

Datasets

This study analysed data from all trials which used inhaled budesonide, and were randomized, double blinded, involved patients $\geq$4 years of age, who had either asthma or COPD, had a follow-up of more than 3 months (asthma) or >6 months (COPD) and were fully completed by December 2010.

Trials involving either placebo or active control therapies were included. This comprised 26 double-blind, placebo-controlled trials of budesonide or budesonide/formoterol in patients with asthma (included in the primary asthma dataset) (online repository Table), 34 double-blind active controlled trials of budesonide or budesonide/formoterol in patients with asthma (combined to give a total of 60 asthma trials in the secondary asthma dataset), and 8 double-blind trials of budesonide-containing products in patients with COPD, of which 7 were placebo-controlled (included in the COPD dataset) (online repository Table). Three trials with a duration of >1 year were censored at 365 days to allow cross-comparisons with other trials that were included in the analysis. Overall, the mean follow-up duration was 210 days in the 60 asthma trials and 268 days in the 8 COPD trials. The number of steroid naïve patients ranged from approximately 50% in the COPD trials, to between 0 and 100% in the asthma trials. Diabetes mellitus was not an exclusion criterion for any of these trials. The prevalence of diabetes was <1% in all of the asthma trials and between 5 and 10% in the COPD trials.

Outcome variables

Diabetes mellitus cases were identified as any adverse event (AE) or serious adverse event (SAE) coded to the MedDRA dictionary (version 13) as the term 'Diabetes mellitus (including subtypes)'; 'Diabetic ketoacidosis'; 'Diabetic hyperglycaemic coma' or 'Diabetic hyperosmolar coma'. Hyperglycaemia cases were identified as any AE (serious or non-serious) coded to the MedDRA dictionary (version 13) as the terms 'Hyperglycaemic conditions NEC', 'Blood glucose increased', 'Carbohydrate tolerance decreased', Glucose tolerance decreased, 'Glucose tolerance test abnormal' or 'Glycosylated haemoglobin increased'. Thus, diabetes AEs were defined as any new onset diabetes mellitus or worsening of existing diabetes. Patients with existing diabetes mellitus were not excluded, as the AEs were examined post randomization to either ICS or non-ICS treatment.

Statistical analysis

The risk of diabetes mellitus/hyperglycaemia as an AE or SAE was compared between patients assigned to budesonide or non-ICS treatments. Kaplan–Meier curves were generated to visually compare the time to the first reported cases of diabetes mellitus/hyperglycaemia AEs

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between treatment groups. Cox proportional hazards regression modelling, both adjusted and not adjusted by study, was used to estimate the relative risk of ICS on time to the occurrence of diabetes mellitus/hyperglycaemia AEs. Hazard ratios (HRs) and the associated 95% confidence intervals (CIs) were calculated from these models. In addition, a pooled relative risk (RR) was calculated using a Mantel–Haenszel approach stratified by study, adjusted for treatment exposure, and expressed as the pooled Mantel–Haenszel RR and 95% CIs. In the primary asthma dataset, a single trial, START,[9] contributed the majority of patients (n = 7221). As a sensitivity analysis, the overall RR was calculated for the START trial alone and for all trials in this dataset excluding START.

We also determined a possible dose response by evaluating high versus low dose budesonide. For the dose–response analysis in asthma, only trials that contained a low-dose treatment arm as well as a high-dose treatment arm were selected (14 trials), and for the budesonide vs fluticasone comparison only trials involving both ICS were selected (5 trials). We defined low dose as budesonide of $\leq$320 μg/day delivered via Turbuhaler or pressurised metered-dose inhaler (pMDI) or budesonide of $\leq$500 μg/day delivered as a nebulizing suspension. High dose was defined as budesonide $\geq$640 μg/day via Turbuhaler or pMDI or $\geq$1000 μg/day as a nebulizing suspension. From the STAY trial,[10] only adolescent and adult patients from the budesonide/formoterol 160/9 μg/day and the 640 μg/day treatment arms, respectively were included in the dose–response analysis since in this study the children 4–11 years of age received only half of these doses. The comparisons of high-dose vs. low dose budesonide, and of budesonide and fluticasone, were performed using a Mantel–Haenszel approach stratified by study and adjusted for treatment exposure on a subset of trials from the secondary asthma dataset. For the dose–response analysis, only trials that contained a low-dose treatment arm as well as a high-dose treatment arm were analysed.

In the COPD dataset, a dose–response analysis was conducted on the 3 studies which included two different doses of a budesonide/formoterol (640/18 μg and a 320/18 μg) using the Mantel–Haenszel approach stratified by study and adjusted for treatment exposure.

In both the secondary asthma and COPD datasets, risk factor analyses using linear-tailed restricted cubic splines in a Cox regression were used to model and adjust for potential non-linearities for age, body mass index (BMI) and baseline forced expiratory volume in 1 s (FEV_1) expressed as a percentage of predicted normal. Finally, as four studies in the COPD dataset included the measurement of laboratory safety data, an additional dataset was compiled consisting of all patients for whom a baseline and end-of-treatment blood glucose evaluation was available. These data were analysed to determine the mean change from baseline to end-of-treatment glucose levels for ICS- and non-ICS-treated patients.

As this was a retrospective review of results from a number of clinical trials, no approval was requested from Research Ethics Committees from those institutions where the data was collected.

Table 1 Incidence of new onset diabetes mellitus/hyperglycaemia AEs and SAEs among patients with asthma randomised to budesonide or non-ICS in the placebo-controlled studies (primary asthma dataset and COPD dataset).

Subgroup	Number on ICS	Number on non-ICS	Exposure on ICS in TTY	Exposure on non- ICS in TTY	Number (%; rate per TTY) of patients reporting diabetes AEs		Number (%; rate per TTY) of patients reporting diabetes SAEs	
					ICS	Non-ICS	ICS	Non-ICS
Asthma trials								
All trials excluding START	5437	2335	1.53	0.63	7 (0.13%, 4.6)	4 (0.17%; 6.3)	0	0
START alone	3630	3591	3.28	3.19	5 (0.14%; 1.5)	4 (0.11%; 1.3)	0	3 (0.08%; 0.9)
All asthma trials	9067	5926	4.80	3.82	12 (0.13%; 2.5)	8 (0.13%; 2.1)	0	3 (0.05%; 0.8)
COPD trials								
Budesonide trials	776	774	0.71	0.70	8 (1.0%, 11.3)	3 (0.39%, 4.3)	1 (0.13%, 1.4)	0
Budesonide/ formoterol trials	3840	2879	2.70	1.96	55 (1.4%, 20.4)	41 (1.4%, 20.9)	4 (0.10%, 1.5)	1 (0.03%, 0.5)
All trials	4616	3643	3.41	2.66	63 (1.3%, 18.5)	44 (1.2%, 16.5)	5 (0.11%, 1.5)	1 (0.03%, 0.4)

TTY: 1000 treatment years.

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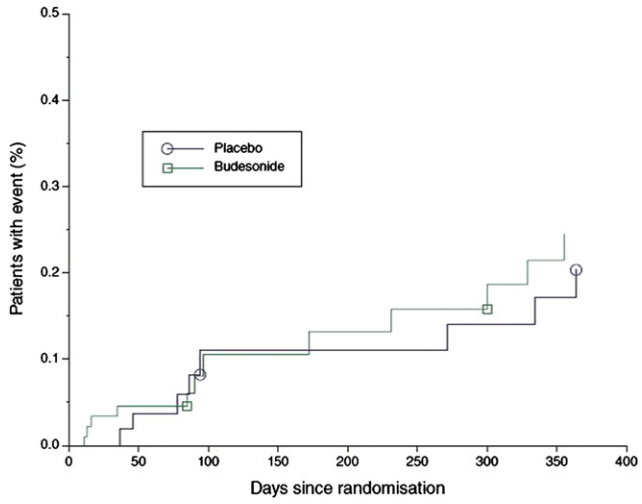


Figure 1 Kaplan–Meier survival curve describing the incidence of diabetes mellitus/hyperglycaemia AE in patients in the placebo-controlled asthma trials (budesonide vs. non-ICS: HR 0.98; 95% CI: 0.38–2.50; $p = 0.96$).

Results

The risk of new onset diabetes mellitus in patients with asthma

The primary asthma dataset comprised 14,993 patients with 8624 patient-years of exposure, while the secondary asthma dataset included 33,496 patients exposed to budesonide and 2773 patients exposed to fluticasone. In the asthma dataset, the mean age was 34.4 years, mean BMI was 24.9 kg/m^2 and mean baseline FEV_1 was 82% predicted normal.

In the primary asthma dataset, the incidence of diabetes mellitus/hyperglycaemia AEs was 0.13% ($n = 12$; rate 2.5 per 1000 treatment years [TTY]) among patients randomised to budesonide and 0.13% ($n = 8$; 2.1 per TTY) among those randomised to non-ICS (Table 1); diabetes mellitus/hyperglycaemia as an SAE were reported by 0% of patients with asthma ($n = 0$) randomised to budesonide and 0.08% ($n = 3$; 0.8 per TTY) of those randomised to non-ICS. In addition, the time to first diabetes mellitus/hyperglycaemia AE was not significantly different between budesonide- and non-ICS-treated asthma patients (HR 0.98; 95% CI: 0.38–2.50; $p = 0.96$) (Fig. 1). The overall Mantel–Haenzel RR for the reporting of diabetes mellitus/hyperglycaemia as an AE was not statistically significantly different between asthma patients randomised to budesonide and those randomised to non-ICS (Mantel–Haenzel RR 1.02; 95% CI: 0.42–2.53; $p = 0.96$). No statistically significant differences emerged when the results were analysed separately for the START study (Mantel–Haenzel RR 1.22; 95% CI: 0.33–4.53; $p = 0.77$) or for all trials except START (RR 0.87; 95% CI: 0.25–3.04; $p = 0.82$). In the secondary asthma dataset, diabetes mellitus/hyperglycaemia was reported as an AE by 0.19% ($n = 65$; 3.0 per TTY) and as an SAE by 0.03% ($n = 6$; 0.3 per TTY) of patients randomised to budesonide. There was no statistically significant difference in the exposure adjusted RR, stratified by trial, for high-dose versus low-dose budesonide (RR 2.56; 95% CI: 0.49–13.4), or for budesonide versus fluticasone (RR 0.44; 95% CI: 0.12–1.62) in the active treatment-controlled asthma trials.

The risk of new onset diabetes mellitus in patients with COPD

The COPD dataset included 8259 patients with 6070 patient-years of exposure. In this dataset the mean age

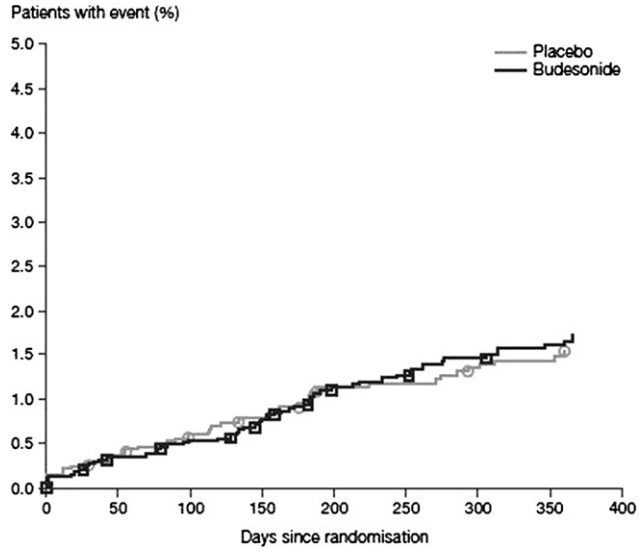


Figure 2 Kaplan–Meier survival curve describing the incidence of diabetes mellitus/hyperglycaemia AE in patients in the COPD trials (budesonide vs. non-ICS: HR 0.99; 95% CI: 0.67–1.46; $p = 0.96$).

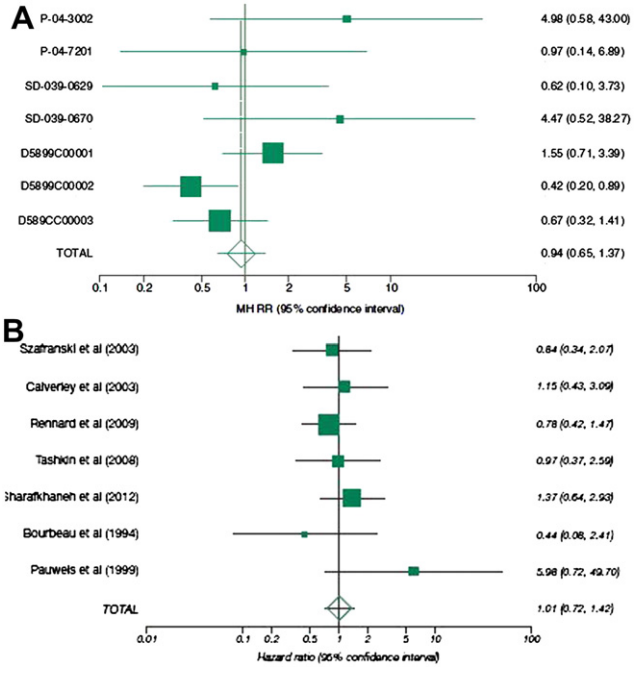


Figure 3 Forest plot of the risk ratio for reporting diabetes mellitus/hyperglycaemia as an AE in the COPD trials. The size of the boxes reflects the number of patients included in the trial.

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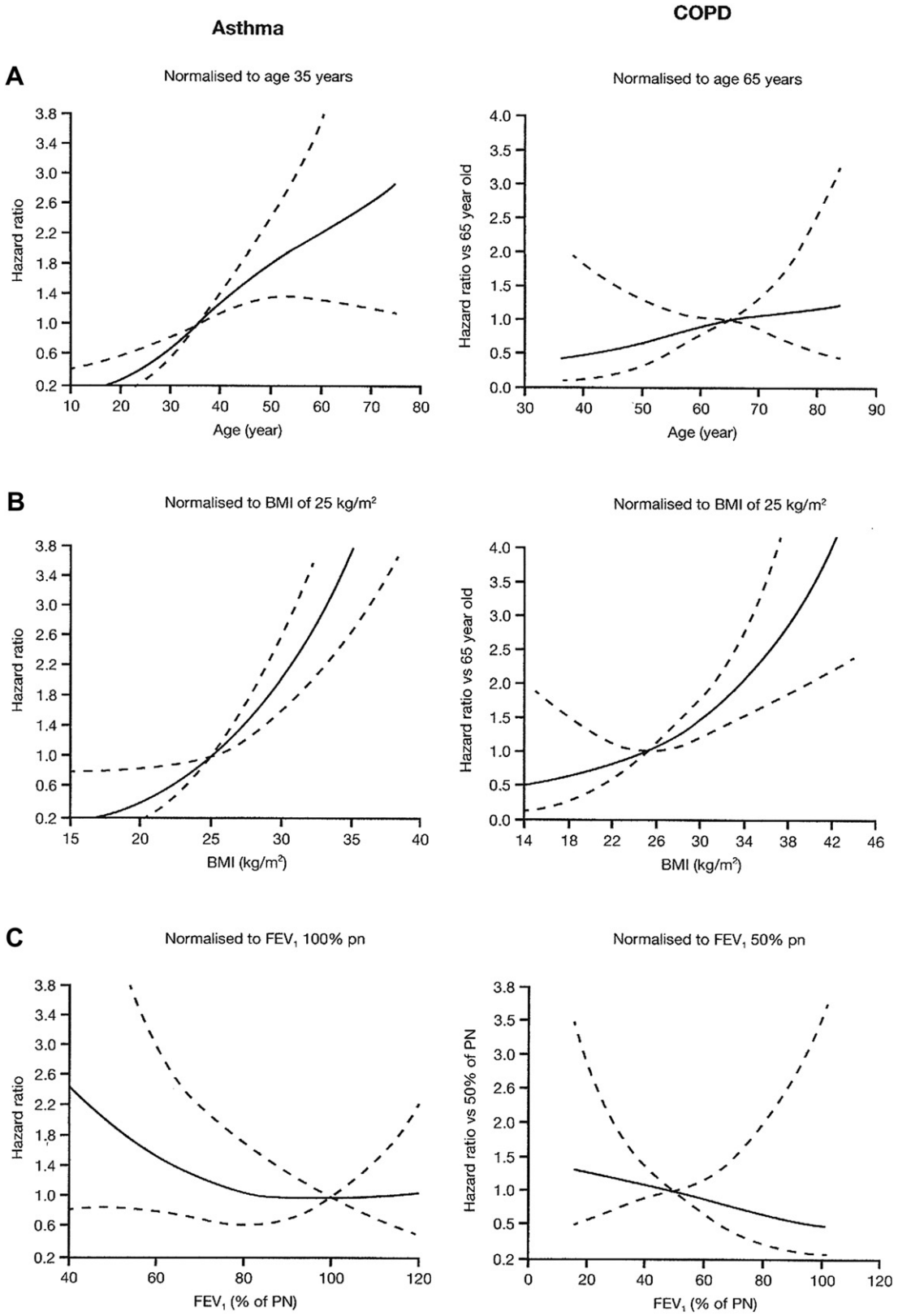


Figure 4 Univariate spline modelling of hazard ratio (HR) of diabetes mellitus/hyperglycaemia AEs by: (A) age (normalised to age 35 years for asthma, 65 years for COPD); (B) BMI (normalised to BMI of 25 kg/m^2 for asthma and COPD); and (C) disease severity (baseline FEV_1; normalised to FEV_1 100% of predicted normal for asthma, FEV_1 50% of predicted normal for COPD) among asthma and COPD patients exposed to budesonide. The solid line gives the HR over the predictor range and the dashed lines indicate the corresponding 95% CIs.

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was 61.8 years, mean BMI was 25.9 kg/m^2 and mean baseline FEV_1 was 49% of predicted normal. The incidence of diabetes mellitus/hyperglycaemia AEs was 1.3% ($n = 63$; rate 18.5 per TTY) among patients randomised to budesonide and 1.2% ($n = 44$; 16.5 per TTY) among those randomised to non-ICS therapy; diabetes mellitus/hyperglycaemia as an SAE was reported by 0.1% of COPD patients ($n = 5$; 1.5 per TTY) randomised to budesonide and 0.03% ($n = 1$; 0.4 per TTY) of those randomised to non-ICS treatment (Table 1). The time to first diabetes mellitus/hyperglycaemia AE was not significantly different between budesonide- and non-ICS-treated patients (HR 0.99; 95% CI: 0.67–1.46; $p = 0.96$) (Fig. 2). The overall Mantel–Haenzel RR for the reporting of diabetes mellitus/hyperglycaemia as an AE was similar between those randomised to budesonide and those randomised to non-ICS treatment (Mantel–Haenzel RR 0.94; 95% CI: 0.65–1.37; $p = 0.74$) (Fig. 3).

In the COPD and secondary asthma datasets, the risk for diabetes mellitus/hyperglycaemia increased with age, BMI and disease severity as measured by baseline FEV_1 (Fig. 4). Additionally, in 4 trials of the COPD dataset, there was no statistically significant change from baseline to end-of-treatment in non-fasted blood glucose levels for budesonide- versus non-ICS-treated patients. The mean [±SD] baseline blood glucose was 5.80 ± 1.72 mmol/L for budesonide-treated and 5.77 ± 1.89 mmol/L for non-ICS treated patients. The mean change from baseline to end-of treatment was +0.12 mmol/L for budesonide-treated and +0.13 mmol/L for non-ICS treated patients (difference −0.008 mmol/L; $p = 0.88$) (Fig. 5).

In the COPD dataset there was no evidence of a higher risk for diabetes mellitus/hyperglycaemia AEs for high-dose versus low-dose budesonide (RR 0.67; 95% CI: 0.37–1.22; $p = 0.20$).

Discussion

These analyses of all of the clinical trials of the ICS, budesonide, did not identify any increased risk of new onset diabetes mellitus or hyperglycaemia (reported as an AE or SAE) in patients with asthma or with COPD. They also did not identify a difference in these outcomes for high versus low dose ICS. Furthermore, in four large clinical trials in COPD in which glucose measurements were performed, ICS did not modify blood glucose concentrations. Together, these data do not support a link between ICS (in the doses employed in these studies) and new onset diabetes mellitus in asthma or COPD patients.

Systemic corticosteroids are associated with insulin resistance and hyperglycaemia. Therefore, it might be anticipated that inhaled corticosteroids, particularly at high doses, might also result in hyperglycaemia. Suissa et al.[4] have reported, in a large nested case-controlled study, that ICS exposure was associated with an increase in the risks of diabetes onset and diabetes progression. However, others have only been able to show an effect of ICS on blood sugar in patients already treated for diabetes[7] and Dendukuri et al.[6] did not find any association of diabetes (identified by its treatment with medications) with the dispensing of ICS. The main limitation of these other

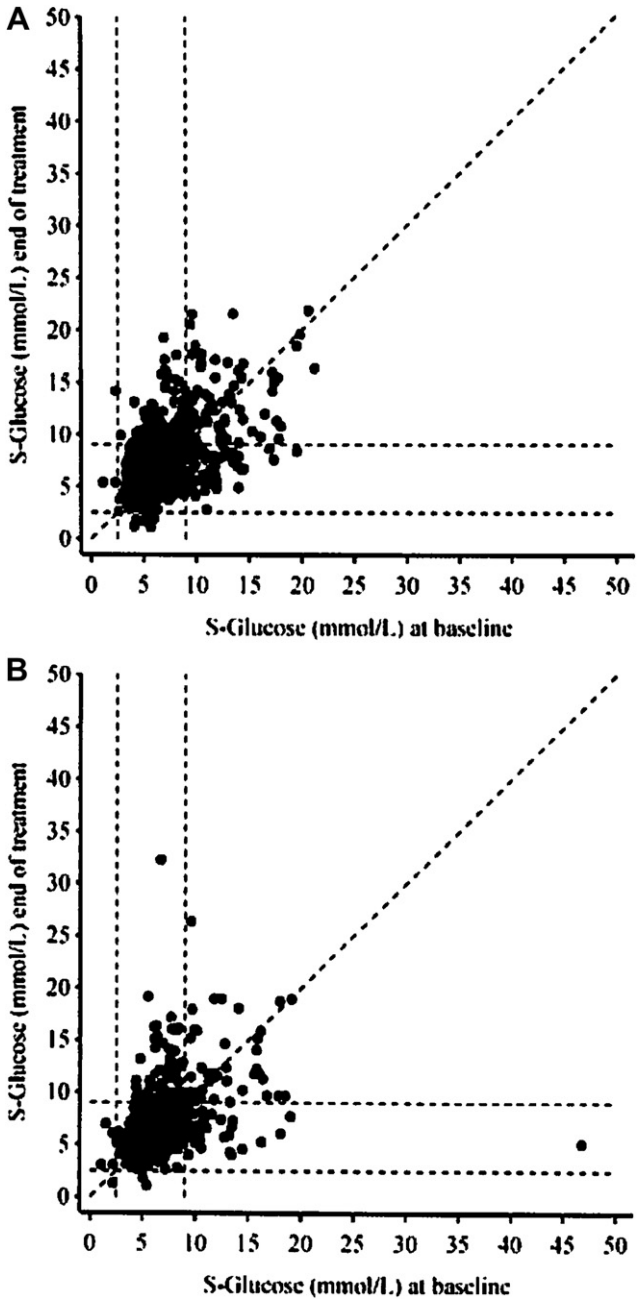


Figure 5 Individual blood glucose (mmol/L) at baseline and at end of treatment for: (A) ICS-treated ($n = 2929$), and (B) non-ICS-treated COPD patients ($n = 2060$).

studies was that they were observational in nature and could not account for measured and unmeasured factors that may have distorted the findings such as confounding by indication (i.e sicker patients with co-morbidities including diabetes may have been more likely to have received ICS) or reverse confounding (i.e as sicker patients are more likely to have co-morbidities including diabetes, ICS may have been avoided in such patients). The major strength of the present study was that it evaluated data from large randomized controlled trials and analysed based on intention-to-treat, which mitigated the risk of confounding.

The other major strength of the present study was the large sample size, which afforded robust statistical power

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to detect small, but clinically relevant, differences between ICS exposed and non-exposed patients with asthma or COPD. The large sample size also provided a unique opportunity to evaluate risk factors for diabetes mellitus in these respiratory populations. We found that the risk for diabetes mellitus/hyperglycaemia AEs in budesonide treated patients with asthma or COPD increased with increasing age, increasing BMI and increasing asthma or COPD severity, as measured by decreasing baseline FEV_1. The significant increases in risk observed in this part of the analysis for age and BMI have been well established. However, the increased risk for low baseline FEV_1 is novel. This study was not designed to determine the mechanisms or a cause and effect relationship behind this association. Future studies will be needed to explore this relationship in depth.

There were limitations to the present study. First, the baseline risk and number of cases of diabetes was low and the confidence intervals were wide enough to have missed a clinically important effect of ICS on the risk of diabetes. Second, we did not have biochemical validation of diabetes. Thus, case misclassification was possible, which would have diluted the results. Third, the follow-up was relatively short. As ICS are recommended as maintenance therapy, future studies will be needed to evaluate the long-term effects of ICS on these endpoints. Finally, the patients included in this pooled analysis were, for the most part, free of any significant co-morbidities. Thus, we could not determine the possible effect of ICS on diabetes in patients with multiple co-morbidities.

Notwithstanding these limitations, the present analyses suggest that, in contrast to regular oral corticosteroid use, 1 year of ICS treatment does not increase the risk of new onset diabetes or hyperglycemia.

Acknowledgements

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Conflict of interest statement

PO'B has been on Advisory Boards for AIM, Almirall, AstraZeneca, GSK, Merck, Nycomed, has received lecture fees from Chiesi, and his institution has received research funds from AIM, Amgen, AstraZeneca, Genentech, and ONO.

SR has received honoraria for lectures from AARC, Almirall, AstraZeneca, Incite, Forest, HSC Medical, Nycomed, PeerVoice, and Shaw Science, consultancy fees from Align2Action, AstraZeneca, Bellenson, Boerhinger Ingleheim, Clarus Acuity, Forest, Frankel Group, Gerson Lehman, Globe Life, GSK, Guidepoint, Health Advances, LeerinkSwan, McKinsey, Merck, Novartis, Nycomed, Osterman, Pearl, Penn Technology, Pennside, Pfizer, Sankyo. Shaw Science, Summer Street and ThinkEquity, fees for serving on monitoring or editorial boards from ABIM, APT, Pulmonary Reviews and Schering and grant support from NHLBI, Nebraska DHHS, University of Nebraska Medical Center, Pfizer, Boehringer Ingelheim, Nycomed, Otsuka and GSK.

HCG has been on advisory boards for AstraZeneca, BMS, Merck, Sanofi, GSK, Novo Nordisk, Sanofi, Lilly, and Roche and his institution has received research funds from GSK, Sanofi, and Lilly.

DDS has received honoraria for speaking engagements from AstraZeneca, GSK, Nycomed, and Pfizer, and has research funding from AstraZeneca, GSK and Merck.

FR, SP, BL, L-GC are employees of AstraZeneca.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2012.07.011.

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On Line Repository Table.

Trials included in the asthma and COPD datasets

Double-blind placebo-controlled asthma trials included in the dataset

Studycode	Duration	Age min	Age max	Number of patients			Total exposure (1000 treatment years)			Total daily delivered doses of budesonide* («g)	Comparison
				Total	ICS	Non-ICS	Total	ICS	Non-ICS		
Budesonide pMDI trials											
04-2180	3 months	18	72	86	57	29	0.02	0.01	0.01	320	BUD CFC vs PLA
04-2182	3 months	6	18	59	30	29	0.01	0.01	0.01	320	BUD CFC vs PLA
Budesonide Turbuhaler trials											
04-2184	12 months	19	62	37	19	18	0.03	0.02	0.02	320	BUD TBH vs PLA
04-2205	12 months	18	68	74	38	36	0.06	0.03	0.03	320	BUD TBH vs PLA
04-2291	3 months	12	70	324	245	79	0.07	0.05	0.02	1280	BUD TBH vs PLA
04-3020	3 months	18	70	472	380	92	0.09	0.08	0.01	160;320;640;1280	BUD TBH vs PLA
04-3021	3 months	19	70	273	184	89	0.06	0.04	0.02	160;320	BUD TBH vs PLA
04-3023	3 months	6	18	404	301	103	0.08	0.06	0.02	160;320;640	BUD TBH vs PLA
04-3049	3 months	16	66	260	172	88	0.06	0.04	0.02	160;640	BUD TBH vs PLA
04-3078	4 months	18	52	31	16	15	0.01	0.00	0.00	640	BUD TBH vs PLA vs Sodium cromoglicate (N=15, excluded)
04-3083	3 months	18	70	286	227	59	0.06	0.05	0.01	160	BUD TBH vs PLA
04-3084	3 months	7	16	162	122	40	0.04	0.03	0.01	80;160	BUD TBH vs PLA
SD-004-0009	4 months	18	70	309	205	104	0.09	0.07	0.03	160;320	BUD TBH vs PLA
SD-004-0111**	12 months of 36 months	4	66	7221	3630	3591	6.47	3.28	3.19	320 (children 160)	BUD TBH vs PLA on top of regular asthma treatment
SD-004-0278	3 months	18	70	177	90	87	0.04	0.02	0.02	320	BUD TBH vs PLA
SD-004-0279	3 months	18	70	184	93	91	0.03	0.02	0.01	160	BUD TBH vs PLA
SD-004-0280	3 months	6	17	274	183	91	0.05	0.04	0.02	160;320	BUD TBH vs PLA
SD-004-0620	3 months	18	80	621	497	124	0.12	0.10	0.02	160;640	BUD TBH vs PLA
SD-004-0726	3 months	6	17	516	410	106	0.11	0.09	0.02	160;640	BUD TBH vs PLA

On Line Repository Table.

Trials included in the asthma and COPD datasets

Double-blind placebo-controlled asthma trials included in the dataset

Studycode	Duration	Age min	Age max	Number of patients			Total exposure (1000 treatment years)			Total daily delivered doses of budesonide* («g)	Comparison
				Total	ICS	Non-ICS	Total	ICS	Non-ICS		
Budesonide nebulizing suspension trials											
04-3069***	3 months	4	8	218	160	58	0.05	0.03	0.01	250,500;1000	BUD NEB vs PLA
04-3072	3 months	4	9	178	134	44	0.04	0.03	0.01	500;1000;2000	BUD NEB vs PLA
04-3100***	3 months	4	9	271	212	59	0.05	0.04	0.01	250,500;1000	BUD NEB vs PLA
Budesonide/formoterol pMDI trials											
SD-039-0716	3 months	6	89	511	257	254	0.10	0.05	0.04	320/18; 320	BUD/FORM HFA vs BUD HFA vs FORM TBH (18µg) vs PLA
SD-039-0717	3 months	8	87	596	348	248	0.11	0.07	0.04	640/18; 640; 640+18	BUD/FORM HFA vs [BUD HFA plus FORM TBH]vs BUD HFA vs FORM TBH (18µg) vs PLA
SD-039-0726	3 months	16	79	751	598	153	0.17	0.14	0.03	160/9; 320	BUD/FORM HFA vs BUD HFA vs PLA
Formoterol Turbuhaler trials											
SD-037-0345	12 months	12	76	698	459	239	0.60	0.39	0.21	160 plus 9; 160	BUD TBH vs [BUD TBH plus FORM TBH] vs PLA
Total				**14993**	**9067**	**5926**	**8.62**	**4.80**	**3.82**		

*Delivered doses of 80, 160, 320, 640 or 1280 µg correspond to metered doses of 100, 200, 400, 800 and 1600 µg of budesonide

** Only data from the first 12 months have been included in the analysis

*** Patients aged 3 years and younger have been removed from the dataset and have thus not been counted

Double-blind controlled asthma trials included in the dataset

Studycode	Duration	Age min	Age max	Number of patients			Total exposure (1000 treatment years)			Total daily delivered doses of budesonide («g)	Comparison
				Total	Budesonide	Comparator	Total	Budesonide	Comparator		
Budesonide pMDI trials											
04-2180	3 months	18	72	86	57	29	0.02	0.01	0.01	320	BUD CFC vs PLA
04-2182	3 months	6	18	59	30	29	0.01	0.01	0.01	320	BUD CFC vs PLA
Budesonide Turbuhaler trials											
04-2184	12 months	19	62	37	19	18	0.03	0.02	0.02	320	BUD TBH vs PLA
04-2205	12 months	18	68	74	38	36	0.06	0.03	0.03	320	BUD TBH vs PLA
04-2291	3 months	12	70	324	245	79	0.07	0.05	0.02	1280	BUD TBH vs PLA
04-2292	3 months	12	70	257	257	0	0.06	0.06	0	320	BUD TBH vs BUD TBH
04-3000	4 months	18	68	158	158	0	0.05	0.05	0	320 vs 640	BUD TBH vs BUD TBH
04-3020	3 months	18	70	472	380	92	0.09	0.08	0.01	160;320;640;1280	BUD TBH vs PLA
04-3021	3 months	19	70	273	184	89	0.06	0.04	0.02	160;320	BUD TBH vs PLA
04-3023	3 months	6	18	404	301	103	0.08	0.06	0.02	160;320;640	BUD TBH vs PLA
04-3049	3 months	16	66	260	172	88	0.06	0.04	0.02	160;640	BUD TBH vs PLA
04-3064	12 months	7	11	91	46	45	0.04	0.04	0.07	320	BUD TBH vs Sodium cromoglicate
04-3066	6 months (of 18 months)	5	10	178	117	64	0.06	0.06	0	dose titration	BUD TBH dose titration (open-label vs Sodium cromoglicate N=64)
04-3078	4 months	18	52	46	16	30	0.01	0.00	0.00	640	BUD TBH vs PLA (N=15) (vs Sodium cromoglicate N=15)
04-3083	3 months	18	70	286	227	59	0.06	0.05	0.01	160	BUD TBH vs PLA
04-3084	3 months	7	16	162	122	40	0.04	0.03	0.01	80;160	BUD TBH vs PLA
04-3085	3 months	5	13	206	206	0	0.05	0.05	0	160;320	BUD TBH vs BUD TBH
BN-00P-0070	3 months	18	70	197	96	101	0.04	0.02	0.02	640	BUD TBH vs FLUT
SD-004-0009	4 months	18	70	309	205	104	0.09	0.07	0.03	160;320	BUD TBH vs PLA

Double-blind controlled asthma trials included in the dataset

Studycode	Duration	Age min	Age max	Number of patients			Total exposure (1000 treatment years)			Total daily delivered doses of budesonide («g)	Comparison
				Total	Budesonide	Comparator	Total	Budesonide	Comparator		
SD-004-0024	4 months (of 17 months)	18	67	61	61	0	0.02	0.02	0	1280;2560	BUD TBH vs BUD_TBH
SD-004-0111	12 months of 36 months	4	66	7221	3630	3591	6.47	3.28	3.19	320 (children 160)	BUD TBH vs PLA on top of regular asthma treatment
SD-004-0210	3 months	18	74	589	589	0	0.13	0.13	0	160;960	BUD TBH vs BUD TBH
SD-004-0278	3 months	18	70	177	90	87	0.04	0.02	0.02	320	BUD TBH vs PLA
SD-004-0279	3 months	18	70	184	93	91	0.03	0.02	0.01	160	BUD TBH vs PLA
SD-004-0280	3 months	6	17	274	183	91	0.05	0.04	0.02	160;320	BUD TBH vs PLA
SD-004-0620	3 months	18	80	621	497	124	0.12	0.10	0.02	160;640	BUD TBH vs PLA
SD-004-0726	3 months	6	17	516	410	106	0.11	0.09	0.02	160;640	BUD TBH vs PLA
Budesonide nebulizing suspension trials											
04-3069	3 months	4	8	218	160	58	0.05	0.03	0.01	250,500;1000	BUD NEB vs PLA
04-3072	3 months	4	9	178	134	44	0.04	0.03	0.01	500;1000;2000	BUD NEB vs PLA
04-3100	3 months	4	9	271	212	59	0.05	0.04	0.01	250,500;1000	BUD NEB vs PLA
SD-004-0764	3 months	12	77	767	767	0	0.15	0.15	0	500;1000;2000; 4000;640	BUD NEB vs PBUD TBH
Budesonide/formoterol pMDI trials											
D5896C00001	3 months	12	79	618	618	0	0.13	0.13	0	160/9;320/9; 320/18; 320	BUD/FORM HFA vs BUD HFA
SD-039-0681	3 months	11	79	679	679	0	0.15	0.15	0	640/18 vs 640	BUD/FORM HFA vs BUD/FORM TBH vs BUD CFC
SD-039-0682	3 months	6	11	622	622	0	0.14	0.14	0	320/18 vs 320	BUD/FORM HFA vs BUD/FORM TBH vs BUD CFC
SD-039-0716	3 months	6	89	511	257	254	0.10	0.05	0.04	320/18; 320	BUD/FORM HFA vs BUD HFA vs FORM TBH (18μg) vs PLA
SD-039-0717	3 months	8	87	596	348	248	0.11	0.07	0.04	640/18; 640; 640+18	BUD/FORM HFA vs [BUD HFA plus FORM TBH]vs BUD HFA vs FORM TBH (18μg) vs PLA

Double-blind controlled asthma trials included in the dataset

Studycode	Duration	Age min	Age max	Number of patients			Total exposure (1000 treatment years)			Total daily delivered doses of budesonide («g)	Comparison
				Total	Budesonide	Comparator	Total	Budesonide	Comparator		
SD-039-0718	3 months	6	15	411	273	138	0.08	0.05	0.03	160/18;160	BUD/FORM HFA vs BUD HFA vs FORM TBH
SD-039-0725	3 months	6	15	521	521	0	0.12	0.12	0	160/18;160/9, 160	BUD/FORM HFA vs BUD HFA
SD-039-0726	3 months	16	79	751	598	153	0.17	0.14	0.03	160/9; 320	BUD/FORM HFA vs BUD HFA vs PLA
SD-039-0728	12 months	12	81	708	708	0	0.63	0.63	0	640/18; 1280/36;1280	BUD/FORM HFA vs BUD HFA
Budesonide/formoterol Turbuhaler trials											
D5890C00002	6 months	12	80	2304	1151	1153	1.09	0.55	0.54	640/18	BUD/FORM TBH vs FLUT/SALM
SD-039-0348	3 months	18	78	467	467	0	0.10	0.10	0	160/9 vs 320	BUD/FORM TBH vs BUD TBH
SD-039-0349	3 months	18	78	362	362	0	0.08	0.08	0	640/18 vs 640	BUD/FORM TBH vs BUD TBH
SD-039-0353	3 months	4	17	286	286	0	0.06	0.06	0	320/18 vs 320	BUD/FORM TBH vs BUD TBH
SD-039-0618	3 months	17	75	344	168	176	0.08	0.04	0.04	320/9	BUD/FORM TBH vs FLUT
SD-039-0665	3 months	18	80	616	616	0	0.13	0.13	0	160/9 vs 160	BUD/FORM TBH vs BUD TBH
SD-039-0666	3 months	18	78	523	523	0	0.11	0.11	0	320/9 vs 320	BUD/FORM TBH vs BUD TBH
SD-039-0667	6 months	11	79	696	696	0	0.33	0.33	0	160/9 (SMART) vs 320	BUD/FORM TBH vs BUD TBH
SD-039-0668	12 months	11	80	1890	1890	0	1.69	1.69	0	320/9 (SMART) vs 640	BUD/FORM TBH vs BUD TBH
SD-039-0673	12 months	4	79	2753	2753	0	2.48	2.48	0	160/9 (SMART) vs 160/9 vs 640	BUD/FORM TBH vs BUD TBH
SD-039-0686	7 months	12	85	658	434	224	0.34	0.22	0.12	640/18; ind dose	BUD/FORM TBH vs FLUT/SALM
SD-039-0688	3 months	4	11	630	630	0	0.14	0.14	0	320/18 vs 320	BUD/FORM TBH vs BUD TBH
SD-039-0689	6 months	12	79	456	456	0	0.20	0.20	0	1280/36;1280	BUD/FORM TBH vs BUD TBH
SD-039-0714	3 months	11	17	270	270	0	0.06	0.06	0	320/9 vs 320	
SD-039-0734	12 months	12	89	3382	3382	0	3.14	3.14	0	320/9 (SMART) vs 320/9	BUD/FORM TBH vs BUD/FORM TBH

Double-blind controlled asthma trials included in the dataset

Studycode	Duration	Age min	Age max	Number of patients			Total exposure (1000 treatment years)			Total daily delivered doses of budesonide («g)	Comparison
				Total	Budesonide	Comparator	Total	Budesonide	Comparator		
SD-039-0735	6 months	11	83	3321	2202	1119	1.50	0.99	0.51	320/9 (SMART) vs 640/18	BUD/FORM TBH vs BUD/FORM TBH vs FLUT/SALM
Formoterol Turbuhaler trials											
37-3018	12 months	17	70	853	853	0	0.72	0.72	0	160+ 18; 160; 640+18; 640	BUD TBH vs [BUD TBH plus FORM TBH]
37-3041	12 months	19	69	60	60	0	0.05	0.05	0	160+ 18; 640	BUD TBH vs [BUD TBH plus FORM TBH]
SD-037-0345	12 months	11	82	1970	1731	239	1.76	1.55	0.21	160+ 9; 160	BUD TBH vs [BUD TBH plus FORM TBH] vs PLA
RofleponideTurbuhaler trials											
SD-050-0437	3 months	18	70	472	240	232	0.10	0.05	0.05	160;960	Rofleponide TBH vs BUD TBH
Total				**42686**	**33496**	**9190**	**24.0**	**18.9**	**5.2**		

Double-blind controlled COPD trials included in the dataset

Studycode	Duration	Age min	Age max	Number of patients			Total exposure (1000 treatment years)			Total daily delivered doses of budesonide or budesonide/formoterol («g)	Comparison
				Total	ICS	Non-ICS	Total	ICS	Non-ICS		
Budesonide Turbuhaler trials											
04-2268	1 year	48	81	75	38	37	0.06	0.03	0.03	1280	BUD TBH vs PLA
04-3002	3 years	25	66	1175	593	582	1.09	0.55	0.54	640	BUD TBH vs PLA
04-7201	3 years	30	70	290	145	145	0.26	0.13	0.13	640	BUD TBH vs PLA
Budesonide/formoterol Turbuhaler trials											
SD-039-0629	1 year	40	92	812	406	406	0.64	0.33	0.31	640; 640/18	BUD/FORM TBH vs PLA;BUD;FORM
SD-039-0670	1 year	41	86	1022	511	511	0.73	0.39	0.35	640; 640/18	BUD/FORM TBH vs PLA;BUD;FORM
Budesonide/formoterol pMDI trials											
D5899C00001	12 months	40	89	1964	988	976	1.57	0.82	0.75	640/18; 320/18	BUD/FORM HFA (2 strengths) vs FORM TBH (18μg) vs PLA
D5899C0000	6 months	40	90	1704	1120	584	0.75	0.51	0.25	640; 320/18; 640/18; 640+18	BUD/FORM HFA (2 strengths) vs BUD HFA vs FORM TBH (18μg) vs PLA
D589CC00003	12 months	40	87	1217	815	402	0.97	0.66	0.31	640/18; 320/18	BUD/FORM HFA (2 strengths) vs FORM TBH (18μg)
Total				**8259**	**4616**	**3643**	**6.07**	**3.42**	**2.67**		