

Comparison of two twice-daily doses of budesonide/formoterol maintenance and reliever therapy

An open, randomised pan-European clinical trial

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Abstract

The aim of this study was to compare two budesonide/formoterol maintenance doses within the budesonide/formoterol maintenance and reliever therapy concept, and to identify possible patient characteristics at baseline which would predict a better response to a higher than standard maintenance dose (NCT00463866).

A total of 8424 patients with symptomatic asthma when using an inhaled corticosteroid (ICS) with or without a long-acting β_2 -agonist (LABA) were randomised to budesonide/formoterol 160/4.5 μg 1 (1x2) or 2 (2x2) inhalations bid. Patients used the same inhaler as needed for symptom relief. The primary outcome variable was time to first severe asthma exacerbation.

In the total study population the time to first severe asthma exacerbation was prolonged by 18% with 2x2 vs 1x2 (hazard ratio 0.82; $p=0.03$). Lung function (peak expiratory flow) was the only statistically significant predictor for a better response to 2x2. The mean daily ICS doses were 737 and 463 μg in the 2x2 and 1x2 groups, respectively.

In a real life setting budesonide/formoterol maintenance and reliever therapy at the 2x2 maintenance dose did prolong time to first severe exacerbation but at a higher medication load. Patients with low lung function benefited most from the higher maintenance dose.

Introduction

Budesonide/formoterol (Symbicort[®] Turbuhaler^{®†}) maintenance and reliever therapy (Symbicort SMART^{®‡}) is established as a useful treatment for appropriate patients with asthma [1,2]. In clinical studies this treatment concept has consistently shown a reduction in the rate of asthma exacerbations compared with higher doses of budesonide [3-5], or fluticasone [6]. Superiority of budesonide/formoterol maintenance and reliever therapy has also been demonstrated versus the same [7] or higher [8] maintenance doses of budesonide/formoterol or salmeterol/fluticasone [8-10] with a SABA [7-10] or formoterol [7] as reliever. In addition, preventing exacerbations with this concept has been achieved at a lower total corticosteroid load [1,2].

When using fixed ICS/LABA regimens, the choice of steroid maintenance dose for the individual patient will depend on asthma severity, similar to ICS monotherapy. A recent study using fluticasone/salmeterol for maintenance treatment and SABA for symptom relief showed that 25% of the patients, who did not obtain control on the starting ICS dose level, achieved control when the ICS dose was doubled [11]. When prescribing budesonide/formoterol as both maintenance and reliever therapy patients will inhale additional ICS doses when symptoms appear, which may allow for a lower maintenance dose without loss of efficacy.

In previous budesonide/formoterol maintenance and reliever trials one or two maintenance doses were given twice daily. A study with a one dose once daily maintenance regimen plus additional doses as needed showed less asthma control days compared to one dose twice daily [12]. Therefore two doses per day are considered the lowest recommended maintenance dose within the budesonide/formoterol maintenance and reliever therapy concept. However, there are no comparative studies to date evaluating the potential benefit of increasing the maintenance dose from 2 to 4 inhalations per day.

[†] Symbicort[®] and Turbuhaler[®] are trademarks owned by AstraZeneca. The Symbicort dry powder formulation Turbuhaler is not currently approved in the US.

[‡] Symbicort SMART[®] is a trademark owned by AstraZeneca. The Symbicort SMART posology is currently not approved in the US.

The aim of this study was therefore to evaluate the impact of double the maintenance dose of the budesonide/formoterol maintenance and reliever therapy concept by comparing a standard dose, 160/4.5 µg one inhalation bid plus as needed, with the highest recommended maintenance dose, 160/4.5 µg two inhalations bid plus as needed. Furthermore, analyses were planned to identify baseline patient characteristics which would predict a better response to the higher maintenance dose in terms of the primary outcome measure, time to first severe asthma exacerbation. A data collection plan to enable this was developed prospectively.

Methods

Study design and patients

This was an open, randomised, parallel-group, 6-month multicentre study in patients with moderate to severe asthma who were symptomatic despite daily use of an ICS with or without LABA. Patients should be 18 years or older and have at least a 6-month documented history of asthma according to the American Thoracic Society definition [13]. Patients were required to be symptomatic, as indicated by a history of SABA use for symptom relief during the last month, despite ICS (with or without LABA maintenance therapy) for at least one month at a constant daily dose of ≥ 500 µg beclomethasone dipropionate (BDP), or other ICS at equivalent doses.

The study started with a 2-week run-in period when patients continued their current asthma maintenance treatment and used terbutaline (Bricanyl® Turbuhaler®, AstraZeneca, Södertälje, Sweden) as reliever medication.

To be randomised, patients treated with ICS and no LABA should have used at least one terbutaline inhalation for symptom relief on at least four of the last seven days of the run-in period, and those treated with both ICS and LABA should have used as-needed terbutaline for symptom relief on at least two of the last seven days of the run-in period. No change in asthma maintenance treatment was allowed during run-in and patients with exacerbations during run-in were excluded.

Study entry criteria were broad to reflect the situation in real life. No withdrawal of SABA or LABA was requested before the reversibility test. Smokers could be enrolled, but not those older than 40 years with a smoking history of 10 pack-years or more, nor people with a diagnosis of chronic obstructive pulmonary disease. After the run-in period, eligible patients were randomly allocated to one of the following two treatments; budesonide/formoterol (Symbicort Turbuhaler®, AstraZeneca, Södertälje, Sweden) 160/4.5 µg bid (1x2) or 2x160/4.5

µg bid (2x2). By definition of the treatment concept, budesonide/formoterol was also used as reliever medication.

Randomisation was performed via an Interactive Web Response System developed by AstraZeneca, Lund, Sweden. There were four visits in the study, the first before and the second after the 2-week run-in period (visit 1 and 2), one after 3 months treatment (visit 3) and the last after 6 months treatment (visit 4).

The first patient entered the study in March 2007 and the last patient completed the study in December 2008.

Assessments

Demographic, life-style and clinical data were collected at baseline. During the 2-week run-in period, and during 2-week periods prior to visits 3 and 4, patients recorded in a notebook the number of inhalations taken as maintenance medication, the number of reliever inhalations used, asthma symptoms (yes/no) and night-time awakenings (yes/no) due to asthma. At randomisation (visit 2) and at study end (visit 4) lung function assessments were performed; peak expiratory flow (PEF) and, if available due to the real life setting of the study, spirometry (forced expiratory volume in one second, FEV₁).

The five-question asthma control questionnaire (ACQ₅) [14,15] excluding FEV₁ (as FEV₁ was not measured at all clinics) and use of SABA (as budesonide/formoterol should be used as reliever medication) was filled in via self-administration at visits 2, 3 and 4. The scale of each ACQ component is from 0 to 6 with 0 as the best. The ACQ total scores were reported in three groups: mean scores <0.75 (well controlled asthma), 0.75-1.5 (intermediate group) and >1.5 (poorly controlled asthma). These intervals were based on data from a previous large clinical study [16].

The primary variable of efficacy was time to first severe asthma exacerbation, defined as deterioration in asthma leading to a need for oral or systemic corticosteroids either for at least three days, and/or associated with hospitalisation, emergency room visit or other patient-initiated unscheduled visits to a health-care centre. A secondary efficacy variable was the total number of severe asthma exacerbations and the time to first and total number of exacerbations leading to hospitalisation or an emergency room visit because of asthma, requiring treatment with systemic corticosteroids. Compliance with treatment was not formally monitored to allow patient behaviour to be as close to real-life as possible. Safety was evaluated by reporting serious adverse events and adverse events leading to discontinuation from the study.

Patient characteristics at baseline and run-in diary variables, which would potentially be used to predict phenotypes that would achieve a better response with higher maintenance dose, were: age, gender, body mass index (BMI), dose of ICS, smoking, exacerbations during the past 12 months, years with asthma, ACQ₅, number of as-needed inhalations, days with symptoms and night-time awakenings and pre- and postbronchodilator lung function values (PEF, FEV₁). These easily accessible factors were considered to be of potential use to clinicians when managing patients in a real-life setting.

The study was performed according to Good Clinical Practice and the Declaration of Helsinki. by All local ethics committees approved the study protocol. All patients gave their written informed consent for participation. The study was performed in 14 European countries. The clinical trial registration number is NCT00463866.

Determination of sample size

With a sample size of 4000 patients in each group and with a significance level of 5% the study had a 90% power to detect a reduction from 10% to 7.9% (a 21% risk reduction) in the proportion of patients experiencing a severe asthma exacerbation during the 6-month study.

Statistical analysis

Times to first asthma exacerbation were compared using Cox proportional hazard model, stratified by country and with treatment as factor. The total number of exacerbations was compared between the treatments using a Poisson regression model controlling dispersion with country and treatment as factors and total time in study as an offset variable.

Baseline predictors which potentially could identify groups of patients that benefit on 2x2 compared to 1x2 was investigated in a Cox regression model in two ways; a univariate approach and a multi-variate backward selection approach. Both calculations were based on the total randomised population.

The change in ACQ scores, day-time symptoms, awakenings and lung function was analysed using an analysis of variance (ANCOVA) model with treatment and country as factors and baseline value as covariate.

Results

A total of 9695 patients were enrolled and 8424 randomised. A flow chart is shown in figure 1. Baseline characteristics of the randomised study population are shown in table 1. There

were 1239 patients older than 65 years (15.4% of the study population) and 11% were current smokers with a mean smoking history of 5.7 pack-years. Mean duration of asthma since diagnosis was 15.5 years. A total of 92% of the patients in both groups completed the 6-month study.

Exacerbations

Time to first severe asthma exacerbation (the primary variable) was prolonged in the 2x2 group by 18% vs the 1x2 group (hazard ratio 0.82; $p=0.03$) (fig.2). Before the study the patients had a self-reported history of 145 exacerbations per 100 patients per year. During the 6-month study there were 322 exacerbations in 264 patients in the 1x2 group and 266 exacerbations in 219 patients in the 2x2 group, corresponding to a 18% difference in the total number of exacerbations ($p=0.0176$). This translates to an incidence of 9.7 exacerbations in the 1x2 group and 8.0 exacerbations in the 2x2 group per 100 patients, i.e. 19.4 and 15.9 exacerbations per 100 patients per year. Few exacerbations leading to hospitalisation were reported; 48 in the 1x2 and 37 in the 2x2 group (difference not significant). The vast majority of all exacerbations (95%) were managed with oral corticosteroids without hospital admission.

Use of medication

The patients in the 1x2 group used a mean total of 463 µg budesonide per day (318 µg as maintenance and 145 µg as reliever medication). The patients in the 2x2 group used a mean total of 737 µg/day (635 µg as maintenance and 102 µg as reliever medication). In total, 0.91 and 0.64 inhalations per day of reliever medication were used in the 1x2 and 2x2 groups respectively ($p<0.001$ between groups).

Asthma control questionnaire

At baseline, 61% of the patients had an ACQ score >1.5 indicating poorly controlled asthma and 12% a score <0.75 indicating well controlled asthma. During treatment there was a gradual decrease in ACQ scores over time (fig.3). The difference between the 1x2 and 2x2 groups was statistically significant ($p<0.001$) but clinically not important (a mean difference of 0.1 score).

During the study, the number of patients with poorly controlled asthma decreased from 61% to 30% and 27% for 1x2 and 2x2, respectively, while the number of patients with well-controlled asthma simultaneously increased from 12% to 42% and 47% at study end. The clinically relevant changes of >0.5 scores in ACQ₅ are illustrated in fig. 4. In the 1x2 group 51% of the patients reported an improvement compared with 56% in the 2x2 group. This difference in score changes was statistically significant; $p<0.001$.

Daytime asthma symptoms and night-time awakenings

The number of days per week with symptoms was reduced in both treatment groups, from 4.38 to 2.8 in the 1x2 group and from 4.39 to 2.3 in the 2x2 group ($p < 0.0001$ for 2x2 vs 1x2). The number of night-time awakenings per week was reduced during treatment, from 1.10 to 0.65 in the 1x2 group and from 1.15 to 0.58 in the 2x2 group ($p < 0.001$ for 2x2 vs 1x2).

Lung function

A total of 99% of the patients had baseline PEF values recorded. Two thirds of them had baseline postbronchodilator PEF values $\geq 80\%$ PN. During treatment mean prebronchodilator PEF improved by 16.7 L/min (1x2) and 19.4 L/min (2x2) and postbronchodilator mean values by 9.3 L/min (1x2) and 11.8 L/min (2x2). The differences in improvements between the groups were not statistically significant ($p = 0.145$ and 0.159 , respectively).

FEV₁ was measured in 75% of the study population. The increase in prebronchodilator FEV₁ was 0.092 L (1x2) and 0.129 L (2x2) and in postbronchodilator FEV₁ 0.059 L (1x2) and 0.086 L (2x2). The difference in change between the 1x2 and 2x2 doses was statistically significant for both pre- and postbronchodilator FEV₁ ($p < 0.001$).

Predictor of response to the higher maintenance dose

The results when analysing patients' baseline characteristics in relation to the difference in time to first severe asthma exacerbation (primary efficacy variable) between 1x2 and 2x2 are shown in table 2. The only statistically significant single predictors of a better response to 2x2 were pre- and postbronchodilator PEF. PEF post-bronchodilation came out as the strongest predictor for dose selection with both univariate and multivariate backward selection approaches (data only shown for the univariate analysis). A cut point of PEF post-bronchodilation of 80% PN was selected based on a spline analysis and GINA guidelines [17]. In the group with a postbronchodilator PEF $< 80\%$ PN the number of exacerbations in the 2x2 group was reduced by 26% compared to 1x2, whereas in the group with a postbronchodilator PEF $\geq 80\%$ PN a non-significant reduction in number of exacerbations of 18 % between the groups was seen (fig. 5). Although not statistically significant the next best predictor of a better response to 2x2 was the postbronchodilator FEV₁ (table 2). In the group of patients ($n = 5995$) with both FEV₁ and PEF available, it was shown that both postbronchodilator FEV₁ and PEF were significantly predictive of a better response to 2x2 ($p = 0.0122$ and 0.0028 , respectively). Thus lung function variables were better predictors than any other baseline variables in the study for a better response to 2x2.

Safety

Two deaths were reported in the 1x2 group; one intracranial haemorrhage, the other unknown. In the 2x2 group one death due to colon cancer and one death due to colon cancer plus acute heart failure were reported. Around 2% of the patients in both groups experienced a serious adverse event. The most common serious adverse event was deterioration of asthma, which occurred in 13 and 9 patients in the 1x2 and 2x2 groups, respectively.

There was no significant difference between the groups regarding time to discontinuation because of adverse events (1x2 vs. 2x2; $p=0.40$). Worsening of asthma was the most frequent reason for discontinuation, 20 and 11 patients in the 1x2 and 2x2 groups, respectively.

Discussion

The aim of this study was to compare two maintenance doses within the budesonide/formoterol maintenance and reliever therapy concept. We compared the standard maintenance dose, 160/4.5 µg 1x2, with the highest approved dose, 2x2 [1,2]. The higher maintenance dose prolonged the time to first severe exacerbation by 18% compared with 1x2. This difference was significant with a p-value just below 0.05 showing that the power calculation of the study was appropriate. The rate of severe exacerbations decreased to 15 and 19 exacerbations per 100 patients per year with 2x2 and 1x2 maintenance doses, respectively, and these figures were lower than the figures in previously reported budesonide/formoterol maintenance and reliever therapy studies with identical maintenance doses, i.e. 19 [7] and 24 [9] exacerbations per 100 patients per year with 1x2, and 24 [9] and 25 [10] with 2x2. With salmeterol/fluticasone- and a SABA as reliever the corresponding exacerbation figures were 31-38 per 100 patients per year [8-10]. Not unexpectedly, the as-needed ICS use was somewhat higher in the 1x2 group than in the 2x2 group, although importantly the total daily glucocorticoid drug load was much lower in the 1x2 group. No clinically important differences between the 1x2 and 2x2 groups were seen in changes in ACQ₅ scores, day- and night-time symptoms or in lung function values. In both treatment groups the changes from baseline in these asthma control variables were of the same or greater magnitude compared with previous budesonide/formoterol maintenance and reliever therapy studies [7-10].

No safety concerns were raised in the study, which is in line with the results of other budesonide/formoterol maintenance and reliever therapy studies [18]. We could conclude that the higher 2x2 maintenance dose was superior and this dose should normally be of no concern from a safety point of view [18]. However, in most countries, 1x2 is considered the standard maintenance dose and both patients and clinicians hold concerns about intake of high doses of ICS if not deemed necessary. Therefore we investigated what baseline factors might predict a better response to 2x2 and hypothesized that smoking, a history of exacerbations, a longer duration of asthma, a higher ICS dose and poor asthma control might be the most relevant predictors. However, none of the postulated factors were predictors of a better response to 2x2. Instead, baseline pre- and postbronchodilator PEF were the only statistically significant predictors of a better response to 2x2. FEV₁ postbronchodilation showed a similar trend in the analysis of the total population, and in the subgroup of patients with both FEV₁ and PEF available, FEV₁ postbronchodilation was shown to be a statistically significant in predicting response to a higher maintenance dose. For patients with a postbronchodilator PEF value $\geq 80\%$ PN, comprising two thirds of the population in this study, the maintenance dose of budesonide/formoterol did not significantly affect the risk of having an exacerbation.

It was unexpected that a low PEF value was the only variable predicting a better response to 2x2. Plausible explanations include differences in airway inflammation and lung deposition of ICS between the groups and in formoterol doses. It could be that due to the more severe airway obstruction in patients with a low lung function compared with the rest of the study population, the lung deposition is impaired and therefore a higher lung dose may result in a better response [19]. It could also be that patients with less good lung function have a more severe inflammatory process in their airways and therefore require a higher ICS dose. Against this hypothesis, however, speaks the fact that patients with a high baseline dose of ICS did not behave differently when randomised to 1x2 compared with 2x2, indicating that treatment with a high ICS dose may not necessarily reflect asthma severity and also, that overtreatment with ICS at baseline cannot be excluded. Regarding the effects of the formoterol doses the patients with a lower PEF had of course more room for improvements in lung function and thus a higher bronchodilator dose might have been of clinical importance. The ACQ₅ scores showed that only 12% of the patients had well-controlled asthma at baseline (ACQ₅ <0.75). The clinically relevant improvements in ACQ₅ scores, e.g. changes of >0.5 scores during the study, were quite clear in both groups. The proportion of patients with a score <0.75 increased and the proportion of patients with scores >1.5 decreased, with a statistically significant but clinically not important mean difference of 0.1 score in change between the two groups. Only a 5% difference in the proportion of patients reporting improvement in their asthma was seen.

We found that the changes from baseline in ACQ₅ scores were very similar to previous controlled budesonide/formoterol maintenance and reliever studies with the 1x2 [7] and the 2x2 maintenance dose [9,10]. The reduction in symptom scores and awakenings were greater than in the cited studies [7-10] and similarly the reduction in use of reliever medication [7-10].

Our study indicates that most patients benefit from the standard dose budesonide/formoterol. Considering the outcomes in the study with the lower corticosteroid load and the lower costs with the 1x2 dose [20,21] it seems appropriate to recommend this dose for initial use and to increase the maintenance dose to 2x2 in patients not fully controlled with this standard dose. This treatment approach would be particularly warranted in patients with persistent low lung function despite the standard maintenance dose.

We conclude that in a real life setting budesonide/formoterol maintenance and reliever therapy at the 2x2 maintenance dose did prolong time to first severe exacerbation and reduced symptoms, but at a higher medication load. Patients with low lung function benefited most from the higher maintenance dose.

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Figure legends

Figure 1. Flow chart of patients.

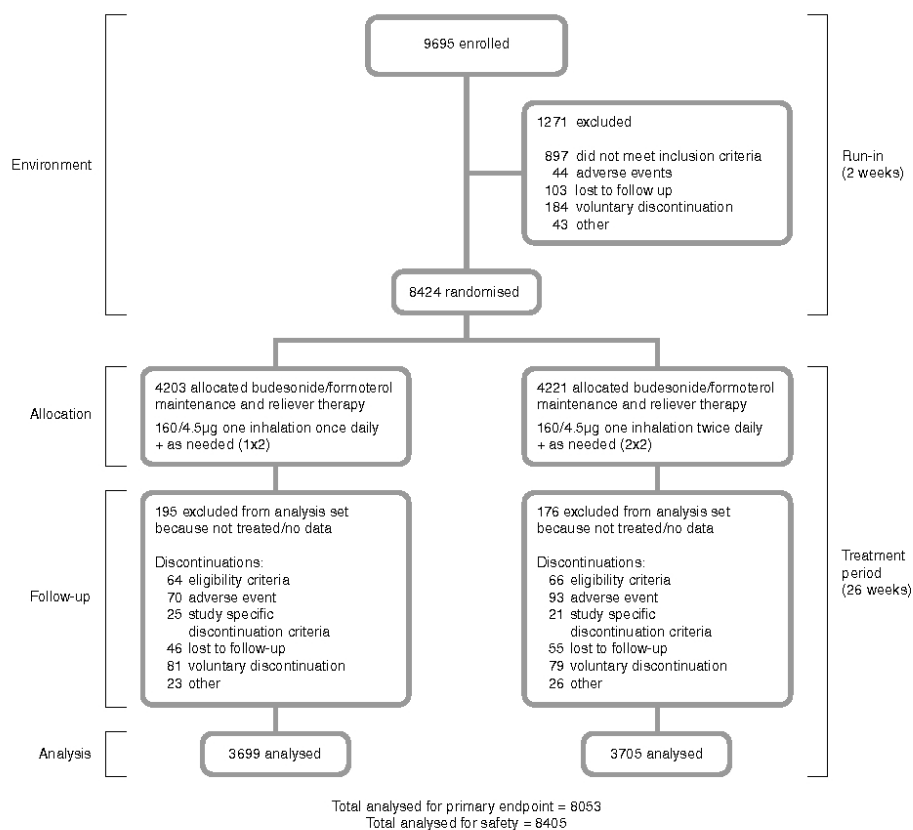


Figure 2. Time to first severe asthma exacerbation.

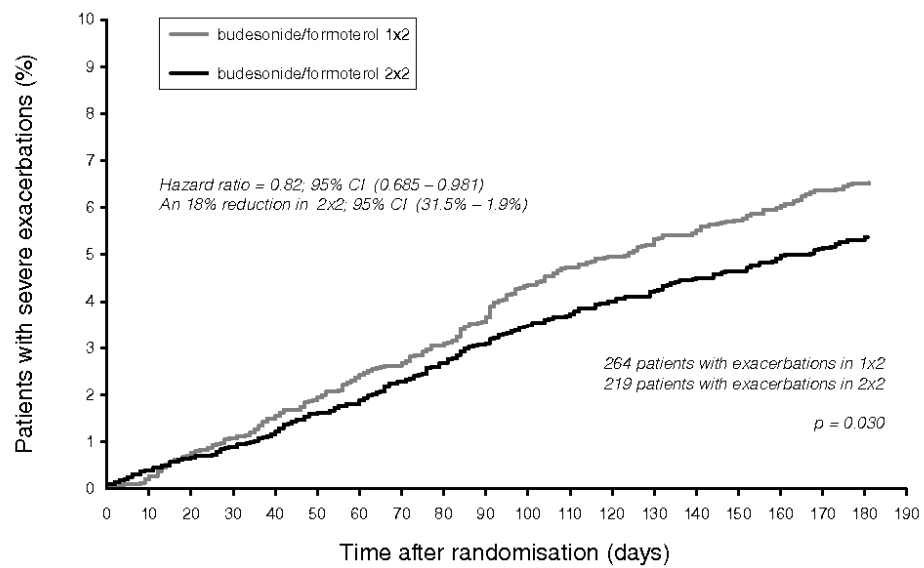


Figure 3. Mean ACQ₅ scores (95% CI) versus time in patients treated with 1x2 or 2x2 of budesonide/formoterol.

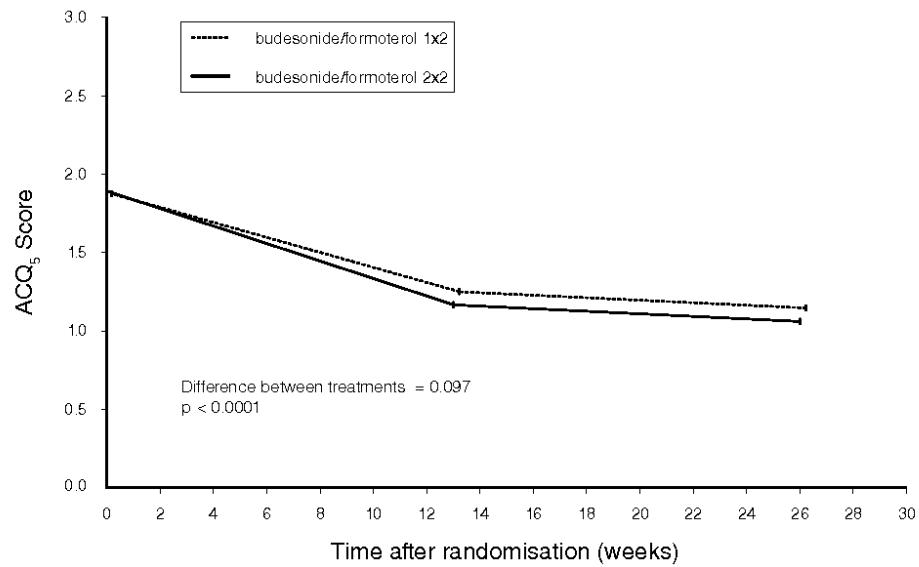


Figure 4. Clinically important shifts (change of >0.5 scores) from baseline to treatment in ACQ₅ scores in patients treated with 1x2 or 2x2 of budesonide/formoterol.

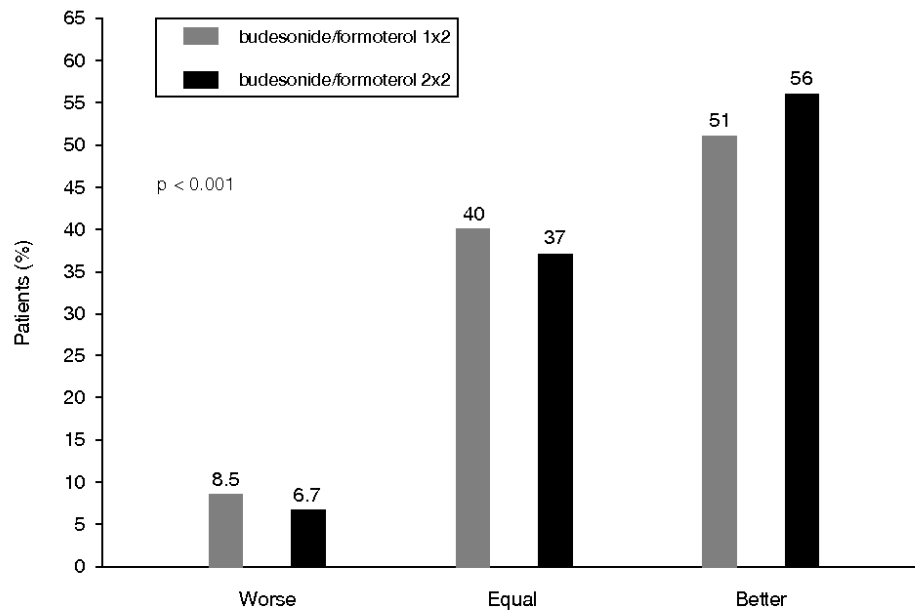
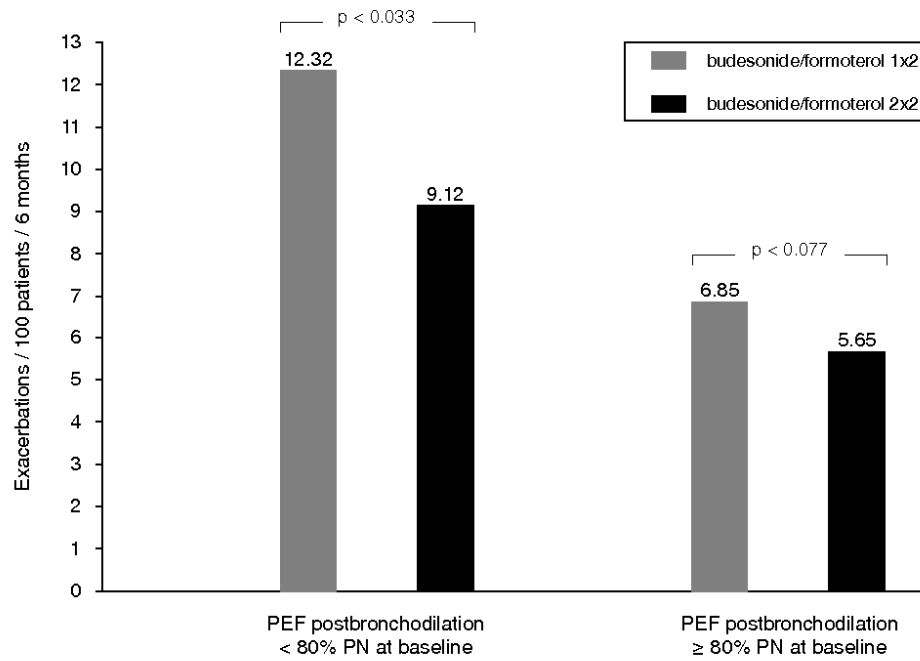


Figure 5. Exacerbation frequency in patients with baseline postbronchodilator PEF <80% and \geq 80% predicted normal treated with 1x2 or 2x2 of budesonide/formoterol.



Characteristics	Budesonide/formoterol 160/4.5 µg 1x2 <i>n</i>=4008	Budesonide/formoterol 160/4.5 µg 2x2 <i>n</i>=4045
Females, %	62	62
Mean age, years (range)	48 (18 – 96)	48 (18 – 90)
Mean FEV ₁ , % predicted	85	85
Mean reversibility, %	6	6
Mean ICS dose at entry, µg/day ¹	1046	1037
LABA use, % patients	78	77
Mean SABA use, inhalations/day	1.5	1.5
Mean % of patients with awakenings	42	43
ACQ ₅ > 1.5, % of patients	61	61
BMI, kg/m ²	27.4	27.4

¹Expressed as BDP equivalent doses

Parameter	p-value	Parameter	p-value
PEF % PN after bronchodilation	0.01	Gender	0.44
PEF % PN before bronchodilation	0.03	Awakenings	0.45
FEV ₁ % PN after bronchodilation	0.07	ACQ ₅	0.47
FEV ₁ % PN before bronchodilation	0.20	Exacerbations 1 years before	0.50
Smoking	0.26	Number of as-needed inhalations	0.61
ICS Baseline Dose	0.30	Years with asthma	0.77
<i>ICS above/below 1000 µg/d at baseline</i>	<i>0.40</i>	Day-time symptoms	0.86
BMI	0.38	Age	0.96

PN = Predicted Normal