REGULAR VERSUS RESCUE BUDESONIDE AND FORMOTEROL COMBINATION FOR MODERATE ASTHMA: A NON INFERIORITY RANDOMISED CLINICAL TRIAL

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ABSTRACT

Background. Treatment guidelines recommend regular inhaled corticosteroid and long-acting β_2 agonist combination plus PRN rapid-acting bronchodilators for patients with moderate persistent asthma. We investigated whether PRN symptom-driven budesonide/formoterol combination would be as effective as regular budesonide/formoterol combination plus PRN symptom-driven terbutaline.

Methods. After a six-week run-in period of regular budesonide/formoterol plus PRN terbutaline, 866 patients with stable moderate asthma were randomly assigned according to a list prepared with the use of a random-number generator and a balanced-block design stratified according to centre to receive placebo twice daily plus PRN combination of 160 μg budesonide/4·5 μg formoterol (PRN budesonide/formoterol therapy) or twice-daily 160 μg budesonide/4·5 μg formoterol combination plus symptom-driven 500 μg terbutaline (regular budesonide/formoterol therapy) for one year. The primary outcome was time to first treatment failure during the one year treatment, and the power of the study was calculated on the rate of treatment failure, and the analysis was performed on the intention to treat population.

Findings. Compared to regular budesonide/formoterol therapy, PRN budesonide/formoterol therapy was associated with lower probability of patients with no treatment failure (Kaplan Meier estimates, 53·6% *vs* 64·0%; difference: 10·3%, 95% CI: 3·2%, 17·4%, predefined non-inferiority limit: 9%); earlier treatment failure (first quartile, 11·86 versus 28·00 days); higher drop-out rates (Kaplan Meier estimates, 34·0% *vs* 25·9%, p=0·009).The difference in treatment failures was largely due to nocturnal awakenings (82 patients in the PRN budesonide/formoterol group and 44 in the regular budesonide/formoterol group). PRN budesonide/formoterol therapy was also inferior in most secondary outcomes. Both treatment regimens were well tolerated.

Interpretation. In patients with moderate asthma, PRN budesonide/formoterol therapy is less effective than the guidelines-recommended regular budesonide/formoterol therapy, even if the differences are small. (ClinicalTrials.gov number NCT00849095).

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INTRODUCTION

The 2014 revision of the Global Initiative for Asthma (GINA) guidelines recommends first assessing the level of asthma control and then planning treatment accordingly.[1] For patients not controlled by low-dose inhaled corticosteroid (ICS), guidelines recommend a combination of low-dose ICS and a long-acting β_2-agonist (LABA) plus a rapid-acting β_2-agonist for symptom relief, or inhaled ICS/rapid-acting LABA combination both regular and for symptom relief. This approach, called same maintenance and reliever therapy (SMART), achieves similar asthma control but more effective reduction of exacerbations in moderate to severe asthmatics.[2-10]

The symptom-driven use of an ICS/short-acting β_2-agonist (SABA) or an ICS/LABA combination in the absence of any regular maintenance treatment are considered effective alternatives to regular ICS plus PRN SABA in patients with intermittent or mild asthma.[11-12] In subjects with mild persistent asthma, i.e., controlled by regular low-dose ICS, the PRN combination of beclomethasone (BDP) and the SABA salbutamol with no regular treatment is non inferior to regular low-dose BDP plus PRN salbutamol.[13] The rationale for preferring a symptom-driven approach is that it allows titration both the ICS and the LABA according to the needs of the patient, and is associated with lower cumulative exposure to both bronchodilators and ICS, and might reduce the impact of low adherence to regular treatment commonly found in "real life".[11,12,14] In addition, treatment with a steroid together with a bronchodilator for symptom relief may be more effective that a bronchodilator alone, as it may reverse not only bronchoconstriction but also the transient acute airway inflammation[15-18] associated with the development of symptoms[11,19-22] and thus it may improve asthma control and reduce the need for regular treatment.

No previous study has investigated whether moderate asthmatics, i.e. patients whose asthma is not controlled by low-dose ICS but is adequately controlled by an ICS/LABA combination, can

be equally controlled by a symptom-driven ICS/LABA combination in the absence of regular maintenance treatment.

In this one-year study, we investigated whether treatment failure could be prevented in moderate asthmatics receiving regular placebo plus PRN budesonide/formoterol combination versus the regular budesonide/formoterol combination plus PRN terbutaline.

METHODS

Design and study population

This was a multicentre, randomised, placebo-controlled, double-blind, parallel group study (eFigure 1, Appendix). The study population consisted of adults with moderate persistent asthma, i.e., according to 2006 GINA guidelines,[23] who were either not controlled by low-dose ICS (≤500µg BDP/day or equivalent; 72·7%) or controlled by a fixed combination of low-dose ICS+LABA b.i.d during the 2 months before the study (27·3%). Asthma was considered not adequately controlled with low-dose ICS if patients reported > two/week daytime symptoms, > two/week need for rescue treatment, any nocturnal symptoms or awakening, any limitation of activities, and use of oral corticosteroids in the last month before enrolment. By contrast, asthma was considered adequately controlled in the patients who had initiated treatment with low-dose ICS/LABA combination in the last year because asthma was not controlled by low-dose ICS, and that in the two month before the study reported ≤ two/week daytime symptoms, ≤ two/week need for rescue treatment, no nocturnal symptoms or awakening, no limitation of activities, and no use of oral corticosteroids. Main exclusion criteria were: inability to carry out pulmonary function testing; moderate severe asthma associated with reduced lung function; history of near-fatal asthma and/or admission to intensive care unit because of asthma; three or more courses of oral corticosteroids or hospitalisation for asthma during the previous year; diagnosis of COPD as defined by the GOLD guidelines; evidence of severe asthma exacerbation or symptomatic infection of the airways in the previous 8 weeks; current smokers or recent (<1 year) ex-smokers, defined as smoking at least 10

pack/years; history or current evidence of heart failure, coronary artery disease, myocardial infarction, severe hypertension, or cardiac arrhythmias; diabetes mellitus. Further details of entry and exclusion criteria are given in eTable 1 of the Appendix.

Eligible patients entered a six-week run-in period, during which they received open-label b.i.d. 160/4·5 µg budesonide/formoterol combination plus PRN 500 µg terbutaline. At the end of run-in, patients with controlled asthma during the last 14 days of the run-in were randomised to receive either b.i.d. placebo plus PRN 160/4·5 µg budesonide/formoterol combination (PRN budesonide/formoterol) or b.i.d. 160/4·5 µg budesonide/formoterol combination plus PRN 500 µg terbutaline (regular budesonide/formoterol). Patients were not given a written plan of action to guide the as-needed use of study drugs but were simply instructed orally to use them any time they were needed for relief of symptoms. Patients were not supplied with OCS or additional ICS to keep at home for self-administration in case of asthma deterioration, but instructed, as per current clinical practice, to seek for medical attention/investigator contact (unscheduled visit) in case of uncontrolled clinical condition. At the end of one year of treatment, patients underwent a 6-week follow-up open-label SMART therapy with 160/4·5 µg budesonide/formoterol with the aim of assessing whether maximizing treatment would modify the level of control observed at the end of the study (eFigure 1, Appendix). Up to eight additional PRN inhalations/day were allowed for the entire study duration. No other anti-asthma drug was allowed. All drugs were prepared and given by the dry-powder inhaler Turbohaler. Treatment compliance was assessed by the clinical investigator at each visit by asking the patients to return study drug devices and diary cards. Diary cards were reviewed and correct use of the device was assessed at each visit. Compliance to medication was checked by counting the remaining doses (dose-counter) in each returned DPI at the end of the study period (visit 9) and reporting the number in the CRF. Compliance to treatment was expressed as % of expected number of doses actually taken in the last 8 weeks.

As specified in the protocol, patients were allowed to receive by the investigators or by the family doctor additional medication for the treatment of the worsening asthma, including additional

"open label" courses of inhaled bid and/or oral/systemic corticosteroids. Patients were also recommended to stop study medication during exacerbations. Investigators were asked to annotate in the CRF the treatments they received for the exacerbations. Patients were not withdrawn from the study after the exacerbation, unless decided by the patient, family physician, investigator.

Efficacy outcomes

The primary outcome of the study was the time to treatment failure and the power of the study was based on the rate of treatment failure at one year (vide infra). Treatment failure was defined as the occurrence of one of the following: hospitalisation, unscheduled medical visits for asthma, use of systemic corticosteroids or open-label use of ICS for asthma prescribed by a physician, two nocturnal awakenings on two consecutive days, ≥4 additional puffs/day compared with baseline on two consecutive days, refusal of the patient to continue because of dissatisfaction with treatment, or treatment stopped by the physician for safety reasons. Secondary outcomes were: time to treatment failure, time to drop-out, use of rescue medication, asthma control, quality of life, daily morning/evening PEF, measured by the patient; pre-bronchodilator forced vital capacity (FVC), FEV_1, FEV_1/vital capacity, and FEV_1/FVC; post-bronchodilator FEV_1; asthma symptom scores; rescue medications; Asthma Control Questionnaire[24]; and Asthma-Related Quality of Life Questionnaire.[25] Secondary safety outcomes were adverse events and morning serum cortisol (Appendix).

Statistics

All statistical analyses and data processing were performed using Statistical Analysis Systems (SAS®) Software (release 9.2) on a Windows 7 operating system.

The rate of patients in the regular budesonide/formoterol group with treatment failure at one year was estimated at 35%, and a non-inferiority margin of 9% at one year was considered clinically acceptable, based on an estimated effect size of 17%.[7,26] A total of 355 treatment failures (in patients with at least one) were required to test the non-inferiority (one-sided test at 0·025 significance level) of the time to treatment failure of the PRN budesonide/formoterol group versus

the regular combination group, with a power of at least 80%. A total of 860 evaluable patients, 430 in each group, were required to satisfy the above hypothesis.

Kaplan-Meier estimates were used to evaluate the time to treatment failure and the probability of patients with no treatment failure at 1 year. Time to treatment failure was also analysed by using a Cox proportional hazards regression model, including only treatment in the model.

Methods for the sensitivity analyses of the primary outcome, and ANCOVA models for secondary quantitative endpoints are described in the Appendix. A post-hoc analysis was performed to evaluate the effects of baseline risk factors/covariates on the probability of treatment failure by means of a logistic analysis. The primary endpoint was assessed both in the ITT and PP population, where the ITT analysis included all randomized patients who received at least one administration of the study medication and who had at least one available post-baseline efficacy evaluation and the PP population excluded from the ITT the efficacy data collected after the start date of the major protocol deviation. All secondary endpoint were analysed in the ITT population.

Randomisation and masking

Patients were randomly assigned to a treatment group according to a list prepared with the use of a random-number generator and a balanced-block design (block size = 4) stratified according to centre.

DPI devices were identical in shape and used in all groups to ensure a double-blind design. The inhalation devices containing regular treatment (budesonide/formoterol combination or placebo) were white, whereas those for as-needed treatment (terbutaline or budesonide/formoterol combination) were yellow.

A package insert written in Italian containing the instructions for use was included in each test treatment. Patients were instructed to take one inhalation in the morning and one inhalation in the evening from the white device, and one or more inhalation when needed for symptoms relief

from the yellow device. Patients were individually instructed to use the DPIs with the support of the package insert.

The protocol was approved by the institutional review board for each centre, and all participants provided written informed consent. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The clinical trial is registered with ClinicalTrials.gov (NCT00849095).

Role of the funding source

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Data were collected by the clinical investigators, analysed by CROS NT (Verona, Italy), and discussed by the clinical investigators. AstraZeneca had no role in data collection and analyses, and in drafting the manuscript, nor was informed of the results of the study. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

A total of 1,010 patients were screened, and 866 were randomised (424 in the PRN budesonide/formoterol group and 442 in the regular budesonide/formoterol group). Figure 1 shows the disposition of patients. The number of patients who actually received treatment (safety population) was 419 in the PRN budesonide/formoterol group and 437 in the regular budesonide/formoterol group. The intention-to-treat (ITT) population included 394 and 423 patients, respectively, and the per protocol (PP) population included 393 and 422 patients, respectively.

Treatment groups were well matched in demographic and clinical characteristics at baseline (Table 1). Compliance to treatment at the end of the study period (visit 9) was of 85 % (SD: 27%) and of 83% (SD: 26%) in the PRN and regular budesonide/formoterol groups, respectively.

Primary efficacy outcome

Compared to regular budesonide/formoterol therapy, patients in the PRN budesonide/formoterol group had shorter time to treatment failure (Table 2 and Figure 2) and higher probability of treatment failure (Kaplan Meier estimates, 53·6% *vs* 64·0%; difference: 10·3%, 95% CI: 3·2%, 17·4%, pre-defined non-inferiority limit: 9%) at one year (Table 2 and Figure 2) in the ITT population analysis . The hazard ratio between the two groups was 1·49 (95% CI, 1·19 to 1·87). The two curves for the 2 groups were resulted to be parallel and this confirmed the proportional hazards assumption. In addition we tested the correlation of the scaled Schoenfeld residuals on functions of time for both the ITT and PP population. The Pearson correlation was not statistically significant and for this reason there was not a violation of the proportional hazard assumption.

The cumulative number of patients experiencing treatment failure during the one-year study period was 170 (43·1%) in the PRN budesonide/formoterol group and 139 (32·9%) in the regular budesonide/formoterol group.

The results observed in the PP analysis were consistent with those in the ITT population (eTable 2, Appendix). The pre-planned sensitivity analyses, which treated drop-outs as treatment failures (eFigure 2, Appendix), confirmed the robustness of the results of the primary outcome. The most common reason for treatment failure was two nocturnal awakening on two consecutive days (82 patients in the PRN budesonide/formoterol group and 44 in the regular budesonide/formoterol group). This was the only component of the composite primary outcome that differed significantly between groups ($p<0·001$) (Table 2a). The mean percentage of days with nocturnal awakenings was 16·17 (SD: 23·94) and 7·94 (SD: 16·07) in the PRN budesonide/formoterol and in the regular budesonide/formoterol group respectively. Female sex and smoking habit in the PRN

budesonide/formoterol group, and baseline Asthma Control Questionnaire score overall and in both groups, were the factors significantly associated with higher risk of failure (Figure 3).

Secondary efficacy outcomes

The time to drop-out was shorter in the PRN budesonide/formoterol group (28 versus 48 days, representing the time until at least 25% of the patients [first quartile] dropped out of the study; p=0·009 between groups in the log-rank test). Appendix, eFigure 3, shows the Kaplan-Meier plot for the time to drop-out in the ITT population. The cumulative number of patients who dropped out at the end of the randomised treatment phase was 133 (31·4%) in the PRN budesonide/formoterol group and 108 (24·4%) in the regular budesonide/formoterol group; Kaplan Meier estimates, 34·0% *vs* 25·9%, p=0·009).

Table 2b shows the results of the other secondary outcomes. From baseline to the end of treatment in the randomised phase of the study, there were significant differences between the two groups, in favour of regular budesonide/formoterol therapy.

After the follow-up period with open-label SMART budesonide/formoterol therapy (eTable 3, Appendix,) only morning PEF (p=0·02), number of puffs of rescue medication (p=0·01), and percentage of days without use of rescue medication (p=0·004) were still significantly different in favour of regular budesonide/formoterol therapy.

Safety

Patients on PRN budesonide/formoterol combination used significantly more rescue medications, and the difference, albeit small, remained significant even at the end of the follow-up (Table 2b; eTable 3, Appendix). The estimated cumulative dose of budesonide (116·8 *vs* 24·5 mg/year) and formoterol (3·2 mg *vs* 0·69 mg/year) was obviously larger in patients treated with regular budesonide/formoterol combination.

Apart from the number of patients with oropharyngeal pain, he number of patients with treatment-emergent adverse events (TEAEs) was no different between the two groups (Table 3). Similarly, there were no differences in the number of patients with adverse reactions. Worsening of asthma was the most common TEAE: 48 patients (11·5%) in the PRN budesonide/formoterol group

and 40 (9·2%) in the regular budesonide/formoterol group (Table 3). From baseline to the end of the treatment period, morning serum cortisol showed no evidence of adrenal suppression in either group (data not shown).

DISCUSSION

In this one-year, randomised, double-blind, clinical trial conducted in moderate asthmatics, PRN budesonide/formoterol was inferior to regular budesonide/formoterol combination plus PRN terbutaline in preventing treatment failure. These results confirm the guideline recommended regular LABA/ICS combination treatment for patients not adequately controlled by regular ICS.[1]

Nocturnal awakenings were the only component of treatment failure that was not protected by the PRN budesonide/formoterol therapy, most likely either because of lack of protection offered by the regular treatment or lack of prompt reversal of nocturnal symptoms by the PRN budesonide/formoterol combination treatment The overall increased number of nocturnal awakening in the PRN budesonide/formoterol group was 38 episodes of nocturnal awakening in two consecutive nights in one year for the 394 patients in the ITT population, i.e. an average risk of one episode of nocturnal awakening in two consecutive night per patient in ten years, which may be considered of limited clinical relevance. The other difference between the two treatments was the higher drop-out from the study in patients on PRN budesonide/formoterol treatment (41·3% in the PRN budesonide/formoterol group and 31·2% in the regular budesonide/formoterol group). The drop-out was reported to be not related to efficacy or safety reasons, but mainly to consent withdrawn (11·5% *vs* 14·6%) and other logistic reasons. In a relatively young and actively working population, it is not totally surprising that the willingness (and possibility) to follow the strict rules-visit intervals- of a RCT for one entire year may be too demanding, and thus patients withdrew their consent (the main dropout reason; the same for logistic reasons), especially in a non-sponsored study, like the present one, where patients received no payment nor expense reimbursement for the participation to the study. However, the difference between the two groups (5·4% *vs* 8·0%) further suggest inferiority of the PRN budesonide/formoterol treatment. The results of the sensitivity analyses that took into account the

study drop-outs confirmed the results of the primary analysis, excluding that they might have been affected by the different drop out.

Because of the characteristics of the population examined, i.e., patients with moderate asthma well controlled by the regular ICS/LABA combination—hence, not at high risk of exacerbations—the primary outcome of our study was rate to treatment failure. Indeed there were only 117 severe exacerbations (defined as treatment with steroids and/or admission to the emergency room/hospital[7]) in 817 patients during the one-year study (0·143 per patient per year): 53 (none hospitalized) in the PRN budesonide/formoterol group (0·135 per patient per year) and 64 (4 hospitalized) in the regular budesonide/formoterol group (0·151 per patient per year). Thus, both therapies were associated with a very low incidence of severe exacerbations, possibly because they were both effective in controlling exacerbations.

Poor adherence in the regular treatment might have reduced the difference in medication use between the two groups, thereby contributing the small differences in outcomes at the end of the study. In fact, Patel et al[8] recently reported that adherence is lower in regular compared to SMART treatment and falls progressively over six and 12 months, suggesting that poor adherence to regular maintenance treatment might have influenced the small differences in outcomes that we observed in our study. However, the differences observed in our study likely reflect what would happen in real life by adopting the two different strategies compared in this study.

After the one-year randomised treatment, both groups of patients received a six-week SMART treatment with both maintenance and reliever budesonide/formoterol therapy to reverse uncontrolled components of asthma, if any. Both groups improved clinically and in most measurements of lung function made in the clinic (FVC, FEV_1, and PEF). These values returned to baseline, suggesting there had been no irreversible decline in lung function. However, morning PEF measured by the patient at home decreased significantly in the PRN budesonide/formoterol group and did not return to baseline after six weeks of SMART treatment. The reasons for the discrepancy

between measurements of lung function made by the patient and in the clinic remain unclear.[27] Although the decrease in morning PEF may suggest that the PRN budesonide/formoterol therapy may be associated with a decline in pulmonary function that was not reversible even after six weeks of SMART treatment with budesonide/formoterol, the fact that such a decline was not observed in clinically assessed PEF, FVC and FEV_1 is reassuring.

The use of rescue medication and the percentage of days without the use of rescue medication remained significantly different between groups at the end of the six-week SMART follow-up therapy, suggesting that long-term PRN therapy may be associated with some persistent small reduction of control.

As expected, the number of patients with adverse reactions was low in both groups and, apart from the predictable oropharyngeal pain possibly related to the regular use of inhaled steroids, there were no other difference between groups, suggesting that safety is not an issue in considering the two alternative therapies, at least from a one-year perspective. In particular, the use of a less intensive regimen in the PRN budesonide/formoterol group did not result in a lower risk of adverse events compared to the regular budesonide/formoterol group.

The study had some weaknesses. Two centers that initially agreed to participate in the study withdrew afterwards their willingness to participate/participation for logistic at local reasons. No patients were randomized in these centers and entered in the analysis. Also, due to the limited budget, monitoring of the centers was mainly made via teleconferences/internet and not with direct site-visits as usually performed in pharmaceutically sponsored randomized clinical trials. Moreover, paper diary card consisted a limitation for the completeness of the data related to PEF/symptoms data. This problem is well known in clinical research and the use of ePRO is more frequent to limit this aspect. The limitation of the budget was not allowing though the use of these tools.

In conclusion, the results of this study show that PRN budesonide/formoterol is inferior to regular budesonide/formoterol plus PRN terbutaline in preventing treatment failure and in maintaining control. However, because the differences were small and the level of control remained above partially controlled asthma,[1,23] we speculate that in recommending the regular combination

treatment according to guidelines, the results of this study could be discussed with the patient, particularly reinforcing the recommendation of regular treatment with LABA/ICS combination to female patients and to patients with a significant smoking history who have a higher risk of loss of asthma control with PRN combination treatment[28] (Figure 3). Other patients could be presented with the advantages of a PRN treatment (convenience, lower cumulative dose of medications, potential long-term safety) to balance the disadvantages (lower level of control of asthma with occasional nocturnal awakening, increased use of rescue medication).

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AUTHOR CONTRIBUTIONS

The study was designed by two academic authors, AP (Study Coordinator) and LMF, assisted by BM (Study Manager) and BB. Data were collected by the clinical investigators, analysed by Paolo Morelli and Marco Pannacci, (CROS NT, Verona, Italy), who also contributed to the study design and to the statistical analysis. NS, Piero Maestrelli, PP, MS, SN, IF, GB, SB, MC, MPFB, AS, NS, and MA recruited the patients and contributed to the study design. Mario Plebani conducted the laboratory analyses. The first draft of the manuscript was written by AP and LMF assisted by BM and BB. All authors discussed and approved all drafts of the manuscript and agreed to submit it. All authors had access to the data and vouch for the accuracy of the reported data and for the fidelity of this report to the study protocol.

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Table 1. Demographic and clinical characteristics of patients at baseline (ITT population)

	PRN budesonide/formoterol (N=394)	**Regular budesonide/formoterol (N=423)**
Sex, N (%)		
Males	153 (38·8%)	185 (43·7%)
Females	241 (61·2%)	238 (56·3%)
Age, *years* (mean ± SD)	42·1 ± 12·8 (N=392)	43·2± 12·6 (N=423)
Ethnic origin, N (%)		
White	382 (97·0%)	415 (98·1%)
Asian	5 (1·3%)	3 (0·7%)
Black	4 (1·0%)	1 (0·2%)
Other	3 (0·8%)	3 (0·7%)
Missing	0 (0·0%)	1 (0·2%)
Weight, *kg* (mean ± SD)	71·93 ± 16·33 (N=393)	73·10± 16·01 (N=422)
Height, *cm* (mean ± SD)	166·6 ± 9·60 (N=393)	166·5± 9·80 (N=422)
BMI, kg/m^2 (mean ± SD)	25·87 ± 5·35 (N=393)	26·31± 5·09 (N=422)
Asthma duration, *years* (mean ± SD)	10·95 ± 10·27 (N=393)	10·99 ± 10·68 (N=419)
Morning PEF, *L/min* (mean ± SD)	402·02 ± 121·50 (N=363)	414·11 ± 120·08 (N=395)
Evening PEF, *L/min* (mean ± SD)	406·51 ± 121·66 (N=362)	419·99 ± 121·03 (N=393)
Pre-bronchodilator FEV_1, *L* (mean ± SD)	2·91 ± 0·84 (N=393)	2·95± 0·81 (N=419)
Pre-bronchodilator FEV_1 Pred, *%* (mean ± SD)	93·59 ± 21·54 (N=393)	94·58± 14·33 (N=418)
Post-bronchodilator FEV_1, *L* (mean ± SD)	3·01 ± 0·85 (N=379)	3·06± 0·83 (N=406)
Post-bronchodilator FEV_1 Pred, *%* (mean ± SD)	96·70 ± 22·00 (N=379)	97·73± 14·76 (N=405)
Pre-bronchodilator FVC, *L* (mean ± SD)	3·86 ± 1·03 (N=393)	3·92± 1·02 (N=419)
Asthma symptoms, *score* (mean ± SD)	0·11 ± 0·30 (N=364)	0·06± 0·18 (N=388)
Rescue medication, puffs/day (mean ± SD)	0·13 ± 0·52 (N=352)	0·06± 0·21 (N=377)
ACQ, *score* (mean ± SD)	0·57 ± 0·68 (N=375)	0·52± 0·64 (N=401)
AQLQ, *score* (mean ± SD)	6·03 ± 0·94 (N=363)	6·00± 0·81 (N=401)
Use of regular LABA/ICS combination therapy in the last year, N (%)	104 (26·4%)	119 (28·1%)

N = number of patients; ACQ = Asthma Control Questionnaire; AQLQ = Asthma-Related Quality of Life Questionnaire.

Table 2. Primary and secondary outcomes

Table 2a. Primary outcome: time to treatment failure in the ITT population

	PRN budesonide/ formoterol (N=394)	**Regular budesonide/ formoterol (N=423)**
Probability of no treatment failure at 1 year, Kaplan Meier estimate (SE)	0·536 (0·026)	0·640 (0·025)
Difference between the PRN budesonide/formoterol therapy and the regular budesonide/formoterol therapy	0·103	
Two-sided 95% CI	0·032, 0·174	
Time to treatment failure during treatment period Hazard ratio	1·491	
Two-sided 95% CI	1·192, 1·866	
Patients who experienced at least one treatment failure	170 (43·1%)	139 (32·9%)
Reasons for first treatment failure (N)		
Hospitalisation	0	3
Treatment stopped for safety reasons (physician's judgment)	24	23
Refusal to continue because of patient dissatisfaction with treatment	6	4
Episodes of wo nocturnal awakenings on two consecutive days	82	44
Unscheduled medical visit for asthma worsening	6	8
Use of rescue medication	17	18
Use of systemic CS or ICS for asthma worsening	51	59
Use of systemic CS for asthma worsening	31	31
Use of ICS for asthma worsening	20	28

Table 2b. Secondary outcomes (ITT population)

	PRN budesonide/formoterol (N=394)	Regular budesonide/formoterol (N=423)	Difference between adjusted means (Regular vs PRN)
Pulmonary function			
Morning PEF, L/min(N)*	**191**	**234**	
Mean change ± SD	**–22·73 ± 55·26**	**–2·61 ± 41·89**	**23·127**
95% CI	**–31·18 to –14·29**	**–8·25 to 3·04**	**13·406, 32·847**
P-value			**p<0·001**
Evening PEF, L/min (N)*	**190**	**230**	
Mean change ± SD	**–21·39 ± 56·27**	**–4·21 ± 43·62**	**19·882**
95% CI	**–30·01 to –12·76**	**–10·15 to 1·74**	**9·766, 29·998**
P-value			**p<0·001**
FEV1, L (N)	**244**	**305**	
Mean change ± SD	**–0·16 ± 0·37**	**–0·01 ± 0·34**	**0·146**
95% CI	**–0·20 to –0·11**	**–0·05 to 0·03**	**0·088, 0·204**
P-value			**p<0·001**
FEV1 pred, % (N)	**244**	**305**	
Mean change ± SD	**–3·47 ± 12.40**	**–0·02 ± 11·95**	**3·605**
95% CI	**–5·03 to –1·91**	**–1·38 to 1·33**	**1·715, 5·494**
P-value			**p<0·001**
Post-bd FEV1, L (N)	**232**	**294**	
Mean change ± SD	**–0·08± 0·31**	**0·06 ± 0·34**	**0·137**
95% CI	**–0·12 to –0·04**	**0·02 to 0·10**	**0·080, 0·194**
P-value			**p<0·001**
Post-bd FEV1 pred, % (N)	**232**	**293**	
Mean change ± SD	**–0·81 ± 12.76**	**2·33 ± 12·65**	**3·082**
95% CI	**–2·48 to 0·86**	**0·85 to 3·81**	**0·998, 5·166**
P-value			**p=0·004**
FVC, L (N)	**244**	**305**	
Mean change ± SD	**–0·10 ± 0·39**	**–0·02 ± 0·38**	**0·079**
95% CI	**–0·15 to –0·05**	**–0·06 to 0·03**	**0·015, 0·142**
P-value			**p=0·015**
PEF, L/min (N)**	**244**	**305**	
Mean change ± SD	**–33·96 ± 97·22**	**–13·64 ± 99·40**	**20·863**
95% CI	**–46·22 to –21·70**	**–24·91 to –2·36**	**6·921, 34·804**
P-value			**p=0·003**
Asthma symptoms			
Symptoms score (N)*	**194**	**225**	
Mean change ± SD	**0·14 ± 0·43**	**0·05 ± 0·29**	**–0·103**
95% CI	**0·07 to 0·20**	**0·01 to 0·10**	**–0·177, –0·029**
P-value			**p=0·006**
% of days without symptoms (N)*	**194**	**225**	
Mean change ± SD	**–15·46 ± 37·29**	**–4·95 ± 27·75**	**11·886**
95% CI	**–21·14 to –9·78**	**–8·81 to –1·09**	**5·409, 18·363**
P-value			**p<0·001**
Use of rescue medication			
Rescue medication, puffs/day (N)*	**187**	**219**	
Mean change ± SD	**0·42 ± 0·82**	**0·12 ± 0·52**	**–0·304**
95% CI	**0·29 to 0·55**	**0·05 to 0·19**	**–0·499, –0·159**
P-value			**p<0·001**
% of days without rescue (N)*	**187**	**219**	
Mean change ± SD	**–23·80 ± 38·51**	**–6·38 ± 25·33**	**18·036**
95% CI	**–29·83 to –17·77**	**–9·95 to –2·82**	**11·292, 24·779**
P-value			**p<0·001**
Asthma control			
ACQ, score (N)	**231**	**293**	
Mean change ± SD	**0·25 ± 0·92**	**0·06 ± 0·74**	**–0·207**
95% CI	**0·12 to 0·37**	**–0·03 to 0·15**	**–0·337, –0·077**

P-value			**p=0·002**
% of days of asthma control (N)*	**185**	**217**	
Mean change ± SD	**–21·65 ± 40·85**	**–6·53 ± 29·67**	**16·859**
95% CI	**–28·07 to –15·23**	**–10·74 to –2·32**	**9·646, 24·072**
P-value			**p<0·001**
Quality of life			
AQLQ, score (N)	**236**	**292**	
Mean change ± SD	**–0·11 ± 1·01**	**0·07 ± 0·75**	**0·220**
95% CI	**–0·25 to 0·02**	**–0·02 to 0·16**	**0·086, 0·354**
P-value			**p=0·001**

*in the 2 weeks preceding the medical visit.
**measured at sites.

Data are expressed as changes from baseline to the end of randomised treatment (week 52). All measurements were performed pre-bronchodilator unless otherwise indicated.

N = number of patients; ACQ = Asthma Control Questionnaire; AQLQ = Asthma-Related Quality of Life Questionnaire.

Morning PEF, Evening PEF, Asthma Symptoms Score, % days without symptoms, rescue Medication and % of Day without Rescue Medication are analysed excluding from the analysis the diary card measurements where the patients entered less than 75% data in the last 2 weeks before the visit (i.e. < 10 days over the 2 weeks preceding a study visit).

Table 3. Treatment-emergent adverse events (TEAEs) reported in more than 2% of patients in either group

Symptom or disease	PRN budesonide/ formoterol (N=419)	Regular budesonide/ formoterol (N=437)	P-value
	N (%)	N (%)	
Asthma worsening	48 (11·5)	40 (9·2)	0·268
Headache	27 (6·4)	30 (6·9)	0·805
Rhinitis	25 (6·0)	25 (5·7)	0·878
Bronchitis	23 (5·5)	24 (5·5)	0·999
Pyrexia	21 (5·0)	18 (4·1)	0·531
Influenza	17 (4·1)	19 (4·3)	0.832
Nasopharyngitis	11 (2·6)	22 (5·0)	0·067
Cough	15 (3·6)	16 (3·7)	0·949
Oropharyngeal pain	6 (1·4)	16 (3·7)	0·039
Back pain	11 (2·6)	10 (2·3)	0·750
Pharyngitis	9 (2·1)	5 (1·1)	0·247
Arthralgia	6 (1·4)	9 (2·1)	0·484

N = number of patients; TEAE = treatment-emergent adverse event.
Data are expressed as number (%) of patients for each TEAE (safety population).

FIGURE LEGENDS

Figure 1. Summary of patient disposition. AEs = adverse events; LR = lack of therapeutic response resulting in unacceptable risk; AR = abnormal results that constitute a risk to the patient; PV = protocol violations; EC = development of an exclusion criterion; PC = poor compliance to study drug; BI = subject's best interest (based on investigator's judgment); CW = consent withdrawn; OR = other reasons; MI = missing.

Figure 2. Kaplan-Meier plots for the time to treatment failure (ITT and PP populations). Left panel: Kaplan-Meier plot for the time to treatment failure by treatment group in the ITT population. Right panel: Kaplan-Meier plot for the time to treatment failure by treatment group in the PP population.

Figure 3. Effects of baseline risk factors or covariates on the probability of treatment failure overall and in the two groups (ITT population).

Panel

Research in context

We identified trials of the Single inhaler Maintenance and Reliever Therapy (SMART) and rescue/as needed (PRN) medication in asthma with a systematic search of Medline and handsearching of respiratory journals and meeting abstracts. We searched for ("single inhaler", "Symbicort", "Seretide", "Advair", "Viani", "Fostair", or "Clenil Forte") or ("inhaled corticosteroid", "ICS", "fluticasone", "FP", "Flixotide", "budesonide", "BUD", "Pulmicort", "beclomethasone", or "Becotide") and ("long acting beta agonist", "beta-agonist", "LABA", "salmeterol", "Serevent", "formoterol", "Oxis", "Foradil", or "Atimos"). Searches started before the study was designed and the writing of the protocol, and the search dates were from Jan 1, 1950, until Aug 31, 2014. Of the complete list of references obtained, we selected those relevant to our study, particularly those on the Single inhaler Maintenance and Reliever Therapy (SMART) and rescue/as needed (PRN) medication in asthma, and those on rescue ICS/LABA combinations in a single inhaler for mild asthma were included. Since our study is the first, to the best of our knowledge, of the rescue budesonide–formoterol combination in a single inhaler for moderate asthma, no specific reference was found. By contrast, all original studies on prn only ICS/formoterol combinations in a single inhaler for mild asthma and ICS/formoterol used as maintenance and reliever therapy (SMART therapy) for moderate to severe asthma were reviewed and the most important quoted. While all previous studies showed that prn ICS/formoterol combination was more effective as compared to prn fast-acting bronchodilator, our study showed that prn ICS/formoterol combination without any regular treatment either with ICS or ICS/LABA is less effective compared to the guidelines recommended regular treatment with ICS/LABA plus prn fast-acting bronchodilator.

Interpretation

Current guidelines recommend regular inhaled long-acting beta2-agonist/corticosteroid (LABA/ICS) plus rapid-acting β2 agonists or ICS/formoterol rescue symptom driven for the

treatment of moderate asthma not controlled by regular ICS. In this study investigated whether a simpler rescue symptom-driven (PRN) budesonide/formoterol combination would be as effective as the regular budesonide/formoterol combination plus symptom-driven terbutaline. The findings of our trial confirm this guideline recommendation by showing that the PRN inhaled budesonide/formoterol therapy is less effective than the regular budesonide/formoterol therapy in moderate asthmatic patients not controlled by ICS alone or adequately controlled by LABA(ICS combination. The idea of testing a PRN only LABA/ICS combination treatment in moderate asthma came from previous studies that showed that inhaled PRN SABA/ICS or inhaled PRN LABA/ICS combination were effective respectively to maintain under control intermittent or mild asthma and that the SMART therapy was more effective than regular LABA/ICS therapy in moderate to severe asthma.