Evaluation of the efficacy and safety of a fixed-dose, single-capsule budesonide-formoterol combination in uncontrolled asthma: a randomized, double-blind, multicenter, controlled clinical trial*

Avaliação da eficácia e segurança da associação de budesonida e formoterol em dose fixa e cápsula única no tratamento de asma não controlada: ensaio clínico randomizado, duplo-cego, multicêntrico e controlado

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Abstract

Objective: To evaluate the efficacy and safety of a fixed-dose, single-capsule budesonide-formoterol combination, in comparison with budesonide alone, in patients with uncontrolled asthma. **Methods:** This was a randomized, double-blind, multicenter, phase III, parallel clinical trial, comparing the short-term efficacy and safety of the combination of budesonide (400 µg) and formoterol (12 µg), with those of budesonide alone (400 µg), both delivered via a dry powder inhaler, in 181 patients with uncontrolled asthma. The age of the patients ranged from 18 to 77 years. After a run-in period of 4 weeks, during which all of the patients received budesonide twice a day, they were randomized into one of the treatment groups. The treatment consisted of the administration of the medications twice a day for 12 weeks. The primary outcome measures were FEV_1, FVC, and morning PEF. We performed an intention-to-treat analysis of the data. **Results:** In comparison with the budesonide-only group patients, those treated with the budesonide-formoterol combination showed a significant improvement in FEV_1 (0.12 L vs. 0.02 L; p = 0.0129) and morning PEF (30.2 L/min vs. 6.3 L/min; p = 0.0004). These effects were accompanied by good tolerability and safety, as demonstrated by the low frequency of adverse events, only minor adverse events having occurred. **Conclusions:** The single-capsule combination of budesonide-formoterol appears to be efficacious and safe. Our results indicate that this formulation is a valid therapeutic option for obtaining and maintaining asthma control. (ClinicalTrials.gov Identifier: NCT01676987 [http://www.clinicaltrials.gov/])

Keywords: Asthma; Budesonide; Adrenergic beta-2 receptor agonists.

Resumo

Objetivo: Avaliar a eficácia e a segurança da associação de budesonida e formoterol em dose fixa e cápsula única, em comparação ao uso de budesonida isolada em pacientes com asma não controlada. **Métodos:** Ensaio clínico randomizado, duplo-cego, multicêntrico, de fase III, com grupos paralelos, comparando a eficácia de curto prazo e a segurança da formulação em pó de budesonida (400 µg) e formoterol (12 µg) com a formulação em pó de budesonida (400 µg) em 181 participantes com asma não totalmente controlada. A idade dos participantes variou de 18-77 anos. Após um período de *run-in* de 4 semanas, durante o qual todos os participantes receberam budesonida duas vezes por dia, houve a randomização para um dos tratamentos do estudo. O tratamento foi administrado duas vezes ao dia por 12 semanas. Os principais desfechos foram VEF_1, CVF e PFE matinal. Os dados foram analisados por intenção de tratar. **Resultados:** O grupo tratado com a associação, quando comparado ao grupo budesonida isolado, teve uma melhora significativa no VEF_1 (0,12 L vs. 0,02 L; p = 0,0129) e no PFE matinal (30,2 L/min vs. 6,3 L/min; p = 0,0004). Esses efeitos foram acompanhados por boa tolerabilidade e segurança, como demonstrado pela baixa frequência de eventos adversos menores. **Conclusões:** A associação em cápsula única de budesonida e formoterol mostrou ser eficaz e segura. Os resultados demonstram que essa formulação é uma opção terapêutica válida para a obtenção e manutenção do controle da asma. (ClinicalTrials.gov Identifier: NCT01676987 [http://www.clinicaltrials.gov/])

Descritores: Asma; Budesonida; Agonistas de receptores adrenérgicos beta 2.

Introduction

The treatment of persistent asthma involves continued use of controller medications.[1-3] Current evidence shows that the use of an inhaled corticosteroid (ICS) in combination with a long-acting β_2 agonist (LABA), when compared with the use of an ICS alone, results in better disease control and reduces future risks.[4,5] In addition, these effects are obtained with lower ICS doses, and asthma treatment is facilitated by a reduction in the number of daily inhalations.[6]

Various ICS-LABA combinations, delivered via different inhalers, have been approved and are available for the treatment of asthma in Brazil. The budesonide-formoterol combination can be delivered via a multiple-dose dry powder inhaler (Turbuhaler) or via a single-dose inhaler with two separate capsules containing budesonide and formoterol (Aerolizer) or with a single capsule containing the budesonide-formoterol combination (Aerocaps). The medical literature has not provided sufficient evidence to support the use of a fixed-dose, single-capsule ICS-LABA combination delivered via Aerocaps. Therefore, the objective of the present study was to evaluate the efficacy and safety of a fixed-dose, single-capsule budesonide-formoterol combination, in comparison with budesonide alone, in patients with uncontrolled persistent asthma.

Methods

This was a randomized, double-blind, multicenter (four centers), phase III, parallel clinical trial conducted in Brazil and comparing the efficacy and safety of a fixed-dose, single-capsule combination of budesonide 400 μg and formoterol 12 μg (Alenia®; Biosintética Farmacêutica Ltda., São Paulo, Brazil) with those of budesonide 400 μg alone (Busonid Caps®; Aché Lab Farm S.A., Guarulhos, Brazil) in adults with partially controlled asthma, as determined on the basis of the classifications proposed by the Global Strategy for Asthma Management and Prevention and the Fourth Brazilian Guidelines for Asthma Management.[1,3] After a run-in period of 4 weeks, during which all of the patients received 400 μg of inhaled budesonide twice daily, they were randomized into one of the treatment groups. The randomization scheme, i.e., permuted blocks of size 4 at a 1:1 ratio,

was generated by the Statistical Analysis System, version 9.1.3 (SAS Institute, Gary, NC, USA).

Both treatments consisted of inhaled administration of the medications (identical dry powder capsules) twice daily for 12 weeks. The primary outcome measures were changes in FEV_1, FVC, and morning PEF. Secondary outcome measures included the effects of treatment on afternoon PEF, the FEV_1/FVC ratio, the percentage of symptom-free days, the frequency of nocturnal awakenings due to asthma, and the frequency of use of rescue medication.

Concomitant use of other asthma treatments was not allowed, except for rescue albuterol use and oral corticosteroid use during exacerbations (courses of oral corticosteroid therapy consisting of prednisone 40 mg for 3 days, 20 mg for 3 days, and 10 mg for another 3 days).

All of the participants had been diagnosed with asthma at least one year prior, had never smoked or had stopped smoking more than one year prior (with a smoking history of fewer than 20 pack-years), and had no other respiratory diseases or comorbidities that could affect the results of the study. None of the participants had received oral corticosteroids or had been hospitalized in the previous month. The study was approved by the human research ethics committees of each participating center, and all of the participants gave written informed consent.

The study consisted of six consecutive visits, which took place in the morning (Figure 1). At the first visit (V_{-2}), eligible patients gave written informed consent, underwent spirometry, and received information about the study. On the following week (V_{-1}), the participants returned to receive the run-in medication (budesonide 400 μg twice daily for 4 weeks); at the subsequent visit (V_0), the patients were randomized into one of
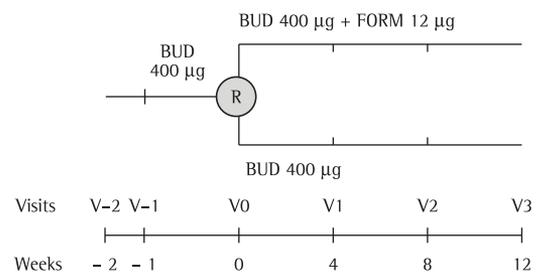

Figure 1 – Study design. BUD: budesonide; FORM: formoterol; R: Randomization; and V: visit.

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the treatment groups. The other visits (V_1, V_2, and V_3) took place every 4 weeks. The spirometry results obtained at V_0 were considered baseline values. The first spirometry was performed no later than 10:00 a.m., subsequent spirometry tests having been performed ± 2 h after the first spirometry, no later than 11:00 a.m. For the evaluation of safety, blood samples were collected at V_{-2}, V_0, and V_3. Symptoms, use of rescue medication, and daily measurements of PEF with a Mini-Wright® meter (Clement Clarke International, Essex, England) prior to the use of the study medications were recorded by the participants in a diary.

Spirometry was performed with a computerized spirometer (Koko®; PDS Instrumentation, Louisville, CO, USA), in accordance with the Brazilian Thoracic Association guidelines.[7] The predicted normal values were those proposed by Knudson et al. in 1976[8] and 1983.[9]

Adherence to treatment was measured at each visit by counting the number of capsules left. Participants with adherence below 70% were discontinued from the study.

Regarding statistical analysis, the study was designed to include 100 participants in each group, a sufficient number to detect a 20-L/min difference in morning PEF between the treatments, with a power of 80% and a level of significance of 5%, assuming a standard deviation of 50 L/min. An interim analysis was planned and was performed when 40% of the participants had completed the study. The analysis showed that the intervention had had a significant effect, and recruitment was therefore stopped. A total of 181 participants completed the study.

All of the efficacy variables were evaluated for the participants who received at least one dose of the medication and who underwent at least one post-baseline evaluation of efficacy (intention-to-treat population).

The observed values of PEF were recorded in the participant diary. The baseline measurement was represented by the mean of the last 10 values recorded in the run-in period (between V_{-1} and V_0), whereas the final measurement was represented by the mean of the last 10 values recorded in the treatment period (between V_0 and V_3).

We used a covariance model to evaluate the changes in the spirometric parameters and those in PEF (i.e., the difference between final values and baseline values). In the initial adjusted model, treatment was considered a fixed factor, whereas baseline values, gender, age, and center were considered covariates, as were gender/type of treatment interactions and center/type of treatment interactions. Adjusted mean estimates and 95% CIs were calculated for the final adjusted model, non-significant interactions and covariates being excluded. The last-observation-carried-forward imputation method was used.

The efficacy variables representing counts were evaluated by a generalized linear model, the negative binomial distribution being used and the center being considered a covariate.

All calculations were performed with the Statistical Analysis System, version 9.1.3.

Results

Between April of 2009 and June of 2010, 304 adults with asthma were recruited from among those being treated at any of four research centers in Brazil. Of those 304 patients, 181 were included in the study and were randomized into one of the intervention groups; 175 participants used at least one dose of the medication (90 in the budesonide-only group and 85 in the budesonide-formoterol [BF] group), being included in the intention-to-treat analysis (Figure 2). The demographic characteristics and the baseline spirometric parameters are summarized in Table 1 and were similar between the treatment groups.

Regarding the primary outcome measures, the 12-week treatment resulted in statistically significant mean increases in FEV_1 and morning PEF—of 104 mL (95% CI: 22-186 mL) and 23.93 L/min (95% CI: 10.89-36.93 L/min), respectively—in the BF group as compared with the budesonide-only group. These results represent an estimate of the difference in change (final value – baseline value) in FEV_1 in the comparison of the two groups, calculated by the following formula:

(final FEV_1 – baseline FEV_1 (BF group)) –
(final FEV_1 – baseline FEV_1 (budesonide-only group])

In other words, these results reflect the additional effect of formoterol, when used in combination with budesonide.

There was a mean increase in FVC of 80.93 mL (95% CI: −1.28 to 163.14 mL), which was not statistically significant (Table 1 and Figure 3).

Table 1 – Treatment efficacy results in the budesonide-only and budesonide-formoterol groups.

Variable	Groups											
	Budesonide (n = 90)[a]					Budesonide-formoterol (n = 85)[a]						p[d]
	Baseline mean	Final mean	Adjusted mean change[b]	95% CI	p[c]	Baseline mean	Final mean	Adjusted mean change[b]	95% CI	p[c]	
FEV₁, L	2.25	2.23	0.02	−0.05 to 0.08	0.5997	2.32	2.40	0.12	0.05–0.18	0.0005	0.0129
FEV₁, % of predicted	75.91	74.80	−1.17	−3.23 to 0.89	0.2635	76.51	80.05	3.60	1.49–5.72	0.0010	0.0017
FVC, L	3.16	3.15	0.03	−0.03 to 0.10	0.3047	3.28	3.33	0.11	0.05–0.18	0.0013	0.0536
FVC, % of predicted	89.97	88.46	−1.70	−3.52 to 0.12	0.0672	91.86	93.84	2.18	0.30–4.05	0.0231	0.0039
Morning PEF, L/min	298.33	299.49	6.27	−3.79 to 16.32	0.2201	302.69	326.61	30.19	19.59–40.80	<0.0001	0.0004
Afternoon PEF, L/min[e]	303.75	301.64	2.31	−7.71 to 12.33	0.6492	308.49	334.28	31.34	20.72–41.95	<0.0001	< 0.0001
FEV₁/FVC, %	80.27	80.36	0.08	−1.27 to 1.44	0.9023	80.34	81.62	1.29	−0.11 to 2.69	0.0711	0.2254
Rescue medication–free days[f]	49.02 (39.52–60.79)					66.01 (52.18–83.52)					0.0673
Symptom–free days[f]	40.64 (27.27–60.56)					46.63 (29.42–73.92)					0.6579
Awakening–free nights[f]	89.33 (85.39–93.45)					91.98 (87.67–96.51)					0.3847

[a]Intention-to-treat population. [b]Final value – baseline value. [c]Effect of change within the intervention group (baseline vs. final). [d]Effect of the intervention factor (budesonide-only group vs. budesonide-formoterol group). [e]One participant in the budesonide-formoterol group did not record the baseline afternoon PEF in the diary. [f]Values expressed as % (95% CI). Adjusted mean proportion of event-free days/nights in the treatment period.

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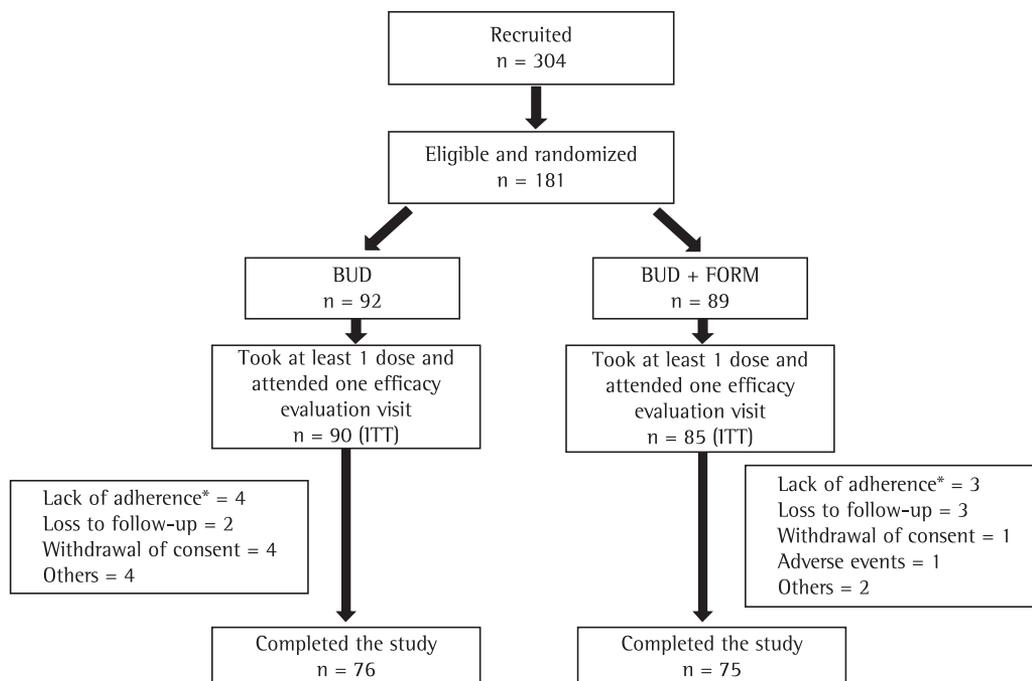a randomized, double-blind, multicenter, controlled clinical trial

Figure 2 – Flowchart of the study population. BUD: budesonide; FORM: formoterol; and ITT: intention-to-treat.

The analysis of the secondary outcome measures revealed a statistically significant mean increase in afternoon PEF of 29.02 L/min (95% CI: 16.03-42.02 L/min) in the BF group patients. There were no statistically significant differences between the groups in terms of the remaining secondary outcome measures (Table 1 and Figure 4).

Regarding adverse events, data on all randomized patients who received at least one dose of the study medications were analyzed. The use of either treatment was well tolerated, and the proportion of patients who reported adverse events was similar in the two intervention groups.

The most common adverse events were as follows: headache, in 29.8%; influenza infection, in 13.8%; upper airway infection, in 9.4%; laryngopharyngeal pain, in 7.2%; dizziness, in 7.2%; tremors, in 5.5%; nasopharyngitis, in 5.5%; nausea, in 5.0%; and upper abdominal pain, in 5.0%.

As evaluated by the investigators, 80% of the events in the BF group and 87% of those in the budesonide-only group were considered unrelated to the study medications. Changes in the treatments given were required in only 2% of the events.

Discussion

This is the first study of the efficacy and safety of the single-capsule combination of budesonide-formoterol delivered via Aerocaps to be conducted in Brazil. The effects of the budesonide-formoterol combination were found to be superior to those of budesonide alone, with the same pattern of tolerability and safety. These results are important because they confirm the efficacy of a combination that is widely prescribed for the treatment of asthma in Brazil.

The increase in FEV_1 observed in the participants who used the budesonide-formoterol combination confirms the additional controlling effect of formoterol promoted by Aerocaps, likely indicating a synergistic effect of this combination.[10,11] The mean difference of 100 mL in FEV_1 for the BF group becomes even more important when we consider that the patients included in the present study had near normal spirometric values.

Despite not being statistically significant, the trend toward improvement in FVC in the BF group can be construed as an indirect measure of deflation, possibly because of deposition and the consequent therapeutic effects on the small airways.[11,12] This suggests that the technical
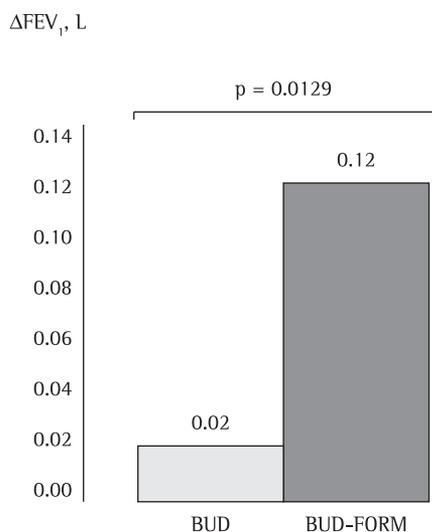
ΔFEV$_1$, L

p = 0.0129

Figure 3 – Adjusted mean change in FEV$_1$ in liters in the groups studied. BUD: budesonide; and FORM: formoterol.
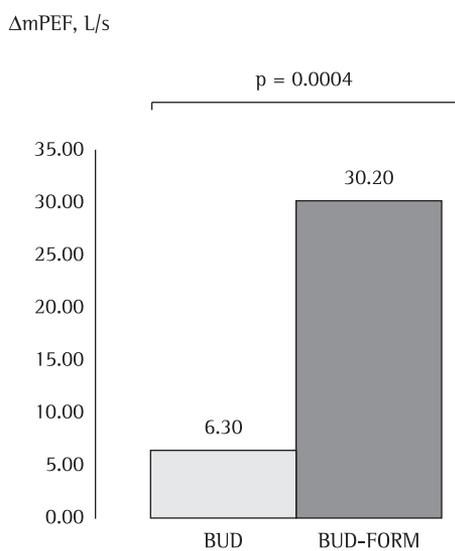
ΔmPEF, L/s

p = 0.0004

Figure 4 – Adjusted mean change in morning PEF (mPEF) in L/s. BUD: budesonide; and FORM: formoterol.

characteristics of this formulation contributed to this favorable outcome. In addition, the increase in morning PEF shows that the medication maintains its effect for the duration of the specified time period, given that this parameter was measured prior to the daily morning dose.

The scientific rigor of this study is demonstrated by its randomized, double-blind design and by the rigorous analysis of outcome measures in the intent-to-treat population. In addition, the results of the present study are in accordance

with those of previously published studies,[4,5] in which ICS-LABA combination therapy was compared with ICS treatment alone, delivered via other inhalers.

On the basis of the safety data obtained, the single-capsule combination of budesonide-formoterol was well tolerated and safe, having the same rate of serious and non-serious adverse events as did budesonide alone after 12 weeks of treatment.

The lack of significance in the results of the secondary variables (nocturnal awakenings and symptom-free days) is possibly due to the fact that the sample size was calculated to achieve a statistical significance for the primary outcome measures. However, the trend toward improvement in those parameters indicates the efficacy of the budesonide-formoterol combination in obtaining asthma control. Future studies should be designed to investigate other outcome measures (including asthma control questionnaire results), as well as other combinations and concentrations currently available on the market.

The results of the present study support the use of the single-capsule combination of budesonide-formoterol delivered via Aerocaps for obtaining and maintaining asthma control, given that this formulation proved to be efficacious and safe.

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