

A Comparison of Short-Term Growth During Treatment with Two Dry Powder Combinations of Inhaled Corticosteroids and Long-Acting β_2 -Agonists

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Abstract

Background: A combination of the inhaled corticosteroid budesonide and the long-acting β_2 -agonist formoterol has been formulated in a novel dry powder inhaler, Spiromax[®]. The objective was to compare lower leg growth in children with asthma treated with inhaled budesonide + formoterol (BF) delivered from the Spiromax inhaler with BF from the Symbicort Turbohaler[®].

Methods: Prepubescent children with persistent asthma ($n=75$, aged 6–11 years) were included in a randomized, double-blind, double-dummy, placebo-controlled, three-way crossover study with active treatment and placebo periods of 2 weeks duration. Lower leg length was measured every second week. As a secondary outcome parameter, 24-hr urine was collected for assessment of free cortisol. Interventions were dry powder BF 160 + 9 μg twice daily (b.i.d.; delivered dose) from the Spiromax inhaler and dry powder BF 200 + 12 μg b.i.d. (metered dose) from the Symbicort Turbohaler.

Results: The least squares mean difference in lower leg growth rates (LLGR) between BF Spiromax and Symbicort Turbohaler was -0.086 mm/week [95% confidence interval (CI) -0.203 , 0.032]. The pre-specified non-inferiority margin was -0.200 mm/week, so the lower limit of the 95% CI was just outside this margin. The difference between BF Spiromax and placebo was -0.20 mm/week (95% CI: -0.322 , 0.086); $p < 0.001$, between Symbicort Turbohaler and placebo -0.118 mm/week (95% CI: -0.236 , -0.001 ; $p = 0.048$). No statistically significant differences were seen in urine free cortisol assessments.

Conclusions: As the lower limit of the CI of LLGR was marginally outside of the pre-specified non-inferiority margin between BF Spiromax 160 + 9 μg b.i.d. and Symbicort Turbohaler 200 + 12 μg b.i.d., non-inferiority could not be demonstrated. Further studies may be needed for comparison of systemic activity of BF Spiromax and Symbicort Turbohaler in children before firm conclusions about their comparability may be drawn.

Key words: adrenal function; asthma; inhaled therapy; knemometry; systemic activity

Introduction

CONTROLLER TREATMENT WITH AN INHALED corticosteroid is considered the mainstay of anti-asthma treatment in school-age children by current guidelines.^(1,2) Long-acting inhaled β_2 -agonists are primarily used as add-on therapy in children whose asthma is insufficiently controlled by medium doses of inhaled corticosteroids. In such cases, combination products containing an inhaled corticosteroid and a long-acting β_2 -agonist are preferred to inhaled corticosteroids and long-acting β_2 -agonists administered by separate inhalers

because the fixed combinations ensure that long-acting β_2 -agonists are always taken with an inhaled corticosteroid. The fixed combination of the inhaled corticosteroid budesonide and the long-acting β_2 -agonist formoterol administered by a dry powder inhaler (DPI; Symbicort[®] Turbohaler[®]) was approved for long-term, twice-daily maintenance treatment of asthma in the European Union in 2000.⁽³⁾

Recently, Teva Branded Pharmaceutical Products Research and Development, Miami, FL, USA, developed a dry powder formulation of the combination of budesonide + formoterol (BF) that is designed to be comparable to Symbicort Turbohaler. The

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BF combination is delivered using a novel inhalation-driven, multi-dose DPI (MDPI) technology, Spiromax[®].⁽⁴⁾ Since systemic activity of inhaled corticosteroids may vary between devices, and as treatment with Symbicort Turbohaler has been found to be associated with suppressive effects on longitudinal height growth, demonstration of comparable systemic activity between the two products in children is mandatory.⁽⁵⁾ The aim of the present study was to assess the relative effects of the administration of BF from the Spiromax and Symbicort Turbohaler dry powder devices on short-term lower leg growth as measured by knemometry in prepubescent children with persistent asthma. As a secondary aim, hypothalamic-pituitary-adrenal function was also assessed.

Materials and Methods

The study was powered to demonstrate non-inferiority between lower leg growth rates (LLGR) during treatment with BF Spiromax 160+9 μg and Symbicort Turbohaler 200+12 μg twice daily (b.i.d.).⁽⁶⁾ A power calculation based on the standard deviation on the difference in LLGR from previous knemometry studies (0.275 mm/week) showed that to be able to demonstrate with 90% power that the lower end of the one-sided 97.5% confidence interval (CI) for the difference in LLGR between BF Spiromax 160+9 μg and Symbicort Turbohaler 200+12 μg b.i.d. would be above -0.20 mm/week, 72 subjects had to complete the study.^(6,7) Estimating a withdrawal rate of around 10%, a total of 81 children were enrolled.⁽⁷⁾

Inclusion criteria

Male and female pre-pubertal (Tanner stage 1 of puberty development) patients (aged 5 to 11, inclusive) with a documented history and confirmed diagnosis of asthma;⁽⁸⁾ normal growth development (height between 3- and 97-percentiles according to Danish standard height growth charts); current use of either short-acting β_2 -agonist and/or $\leq 400 \mu\text{g}$ inhaled corticosteroid daily; ability to use a peak-flow meter correctly; demonstrated satisfactory technique in the use of pressured MDIs (pMDIs) and spacer; willingness and ability to complete patient diary cards accurately with assistance from their parents/guardians; capability of reading and understanding informed consent (assent for those under the legal contractual age of consent) and the patient information leaflet by each patient and both parents/guardians; written informed consent by both parents/guardians with assent from each patient before any trial procedure was carried out.

Exclusion criteria

Patients who had entered puberty; current or prior (i.e., in the 4 weeks preceding visit 1), use of $>400 \mu\text{g}$ inhaled corticosteroids daily; concomitant severe diseases and diseases which the investigator believed were contraindications to the use of bronchodilators or which could affect study outcome measures, including malignancies; chronic systemic or lung diseases (i.e., cystic fibrosis); in-patient hospitalization for acute therapy of asthma during 3 months preceding visit 1; current or recent (within 3 months before visit 1) systemic (oral, parenteral or depot) corticosteroid therapy or receipt of more than three short courses of systemic corticosteroid therapy in the preceding year; continuous use of long-acting

β_2 -agonists (inhaled, oral or otherwise) for asthma symptoms; asthma exacerbation or respiratory tract infection requiring antibiotic treatment during 6 weeks before visit 1; known or suspected hypersensitivity of any inhaled corticosteroid or any one of the excipients of the dry powder inhalers; inability to perform lung function tests; a suspicion of patients being unlikely to be compliant, take their medication as directed, complete the lung function testing procedures, or attend scheduled clinic visits; participation in an investigational drug trial during 30 days preceding visit 1. Furthermore, peak expiratory flow rate (PEFR) and forced expiratory volume in 1 sec (FEV₁) was to be $>80\%$ of expected values at the screening visit. A decrease in pulmonary function by 25% or more of the value would lead to exclusion from the study.

Description of procedures

The study was conducted in accordance with international guidelines issued by the European Commission in 1990 and the Declaration of Helsinki and approved by the local ethics committee.⁽⁹⁾ Informed consent and assent, respectively, were obtained from all parents and children. International Conference on Harmonization for Good Clinical Practice guidelines for clinical studies was followed.⁽¹⁰⁾ Registration numbers were: EudraCT 2010-019082-29, Danish Medicine Agency 2612-4325, Ethics Committee Region Midtjylland M-20100110, Danish Data Protection Agency 2010-41-4786.

The study was a randomized, double-blind, double-dummy, placebo-controlled, three-way crossover study with a run-in, two wash-out and two active and placebo treatment periods of 2 weeks duration each (Fig. 1). At the first visit (screening visit), the child and his or her parents were informed about the study and consent to participate was obtained. Diary cards were presented and handed out. Eligibility was evaluated, and demography and pubertal development using the Tanner staging system were recorded by a doctor if the patient was eligible.⁽⁸⁾ At the second visit, the patients were randomized. The total study duration for each patient was 12 weeks. The patients attended the clinic on the first and last day of each period at the same time in the afternoon between 13:00 h and 19:00 h ± 1 h.⁽⁷⁾ Knemometry and pulmonary function tests, inspection of the oral cavity, and measurement of heart rate and blood pressure were performed at each visit; 24-h urine collection was performed at the end of each active and placebo treatment periods. The study was conducted at The Children's Clinic Randers, Randers, Denmark, from September 2010 to January 2011.

Active treatments were inhaled BF 120+9 μg b.i.d. (labeled as delivered dose) from the Spiromax inhaler and BF 200+12 μg b.i.d. (labeled as metered dose) from the Symbicort Turbohaler. The children were randomized to one of six treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA) containing the following treatment arms:

- Treatment A: BF Spiromax [80/4.5 mcg; two inhalations in the morning (AM) and two inhalations in the evening (PM)]+Turbohaler placebo (two inhalations AM and two inhalations PM).
- Treatment B: Symbicort Turbohaler (100/6 mcg; two inhalations AM and two inhalations PM)+Spiromax placebo (two inhalations AM and two inhalations PM).

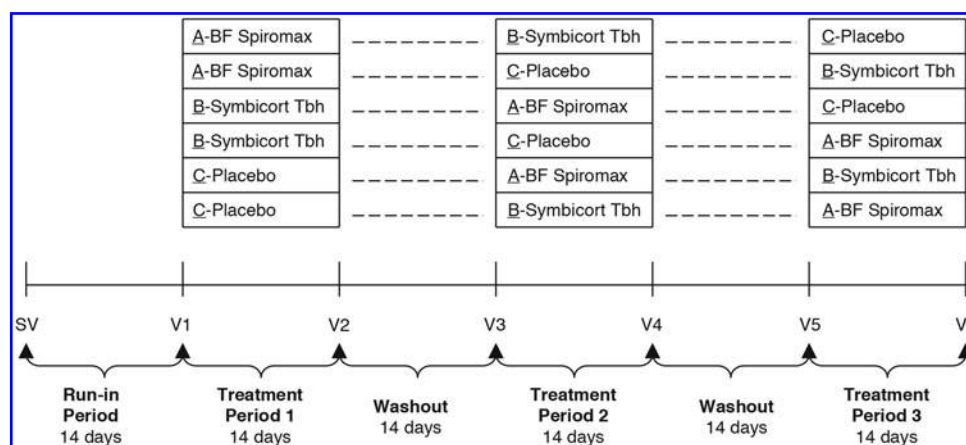


FIG. 1. Study design: A randomized, double-blind, double-dummy, placebo-controlled, three-way crossover study of BF Spiromax 160 + 9 μg b.i.d. and Symbicort Turbohaler 200 + 12 μg b.i.d. BF, budesonide + formoterol; b.i.d. twice daily; Tbh, Turbohaler; SV, screening visit; V1–V6, visit 1–6.

- Treatment C: Spiromax placebo (two inhalations AM and two inhalations PM) + Turbohaler placebo (two inhalations AM and two inhalations PM).

Treatment periods 1 and 2 were followed by a 14-day washout period. At the end of the washout period, the subject was exposed to the next treatment. Treatment sequences were determined by means of a computerized randomization scheme prepared in balanced blocks. The randomization schedule was provided by Chiltern International Ltd, Slough, UK, and test treatments were supplied by TEVA, Global Respiratory Research and Development, Horsham, PA, USA. The children took the medications at 07:00 h and 19:00 h $\pm$ 60 min. Mouth rinsing was performed after the inhalation. No drugs other than the study medication, *pro re nata* inhaled terbutaline (Bricanyl Turbuhaler[®], 0.5 mg per inhalation), oral antihistamines, and oral leukotriene receptor antagonists were allowed during the study period. Compliance to study drug administration was recorded in diaries in which the child supervised by a parent specified if medication was taken in the morning and in the evening. Furthermore, readings from the Spiromax dose counter and the Symbicort Turbohaler dose indicator were taken and the number of used puffs was calculated.

All lower leg length measurements (the distance from the surface of the right flexed knee to the bottom of the sole) were performed by the same trained observer without reference to previous recordings. At each visit, four independent estimations were made and the first was discarded.⁽⁷⁾ The children were sitting 10 min before and refrained from physical activity on the days the measurements were made. LLGR were calculated for each period by the conventional method as previously described:⁽¹¹⁾ the change in lower leg length in a given period divided by the length of the period expressed in mm/week. The technical error (i.e., the standard deviation of each measurement) of the knemometer was 0.09 mm.⁽⁷⁾

The children were instructed in collecting 24-h urine for assessment of cortisol at the end of the placebo and the two active treatment periods. The patient voided in the toilet before bedtime at the latest at midnight. In the following 24 h, the urine was collected in a plastic container, the last void in the container was prior to bedtime at the latest at midnight. Frozen aliquots of the urine samples were thawed. All col-

lections from one subject were processed in one batch. Urine free cortisol was measured by radioimmunoassay after dichloromethane extraction.⁽¹²⁾ Creatinine was measured on an INTEGRA Auto Analyzer using Jaffe alkaline picrate method. As recommended in pediatric populations, cortisol concentrations were corrected for creatinine excretion.⁽¹³⁾

Inspiratory flow rates (IFR) were measured (best of three) at each visit throughout the study by the In-Check Dial device (Clement Clarke International Ltd, Harlow, UK). Peak flow (PEF) were measured (best of three) in the morning and in the evening at home by the Mini Wright Peak Flow Meter (Spiropharma, Copenhagen, Denmark) before the intake of study medications and entered into diary cards. The use of rescue medication were also recorded twice daily in diaries. For clinical monitoring purposes at each visit, FEV₁ was measured by the Vitalograph[®] spirometer (Spiropharma, Copenhagen, Denmark). FEV₁ data were only recorded in the patient notes and they were not processed. Exacerbations in asthma requiring intensified treatment with systemic or inhaled glucocorticoids or other medications would lead to withdrawal from the study.

Statistics

The primary endpoint, the short-term LLGR as measured by knemometry of the right lower leg (mm/week), was compared between BF Spiromax and Symbicort Turbohaler by a 97.5% one-sided CI derived for treatment difference from a crossover analysis of variance (ANOVA) model allowing for fixed effects due to treatment, sequence, and period, and a random effect of subject within sequence.

A non-inferiority analysis was performed to test if BF Spiromax was not inferior to Symbicort Turbohaler in short-term LLGR. Non-inferiority was demonstrated if the lower limit of the 97.5% one-sided CI for the treatment difference in short-term LLGR (BF Spiromax minus Symbicort Turbohaler) was greater than -0.20 mm/week. The 0.20 mm/week level was chosen to be two standard deviations away from a minimum clinically relevant difference. Comparisons of LLGR, urine cortisol, IFR, PEF, and rescue medication-free days during active treatments with placebo were analyzed by an

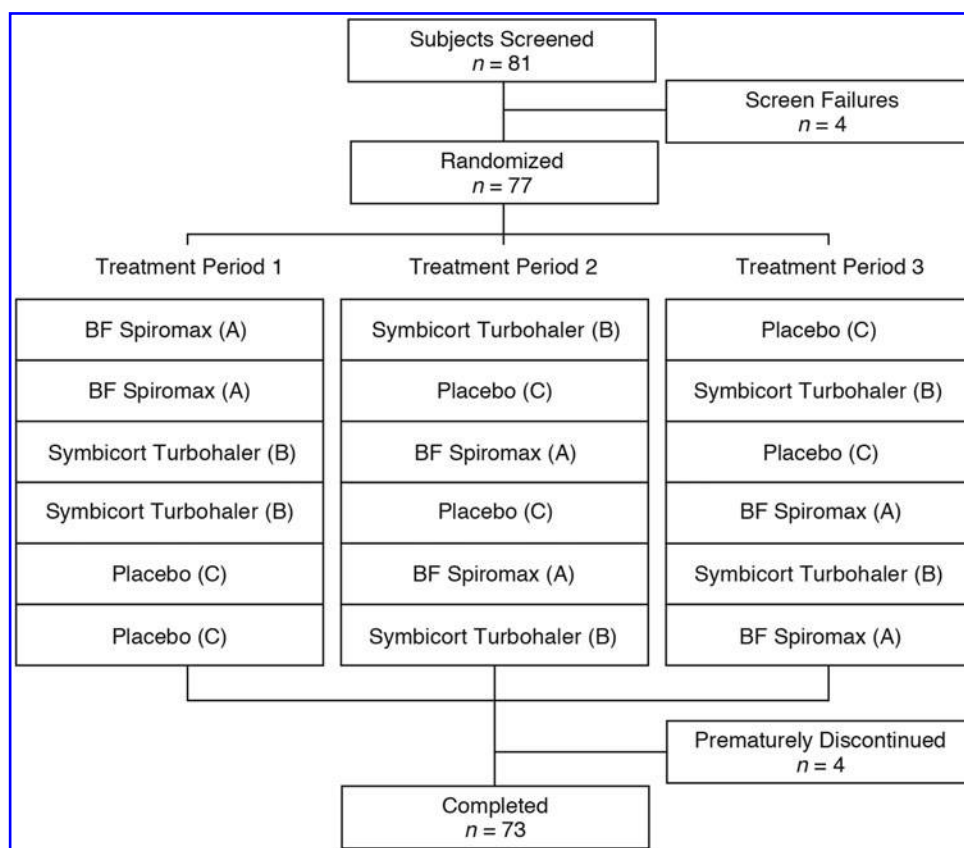


FIG. 2. Patient entry and participation in the study.

ANOVA, including treatment and period as fixed effects and subject as a random effect. All data were tested for period and carry over effects, none were found. The SAS procedure Proc Mixed was used. The 5% level of significance was used.

Results

All children were recruited from a secondary referral center. There were four screening failures (Fig. 2). The study

population consisted of 46 boys and 31 girls, all Caucasians, with mean age 8.6 years (range 6–11 years). Mean height was 133.8 cm [range 116–157 cm (53rd percentile; +0.15 standard deviation [SD])], mean weight 31.7 kg [range 20–54 kg (+0.6 SD)]. All children were prepubertal (Tanner stage 1 of pubertal development). Mean asthma duration was 5.5 years (range 8 months–11.9 years). All children had mild-to-moderate persistent asthma that was treated with inhaled *pro re nata* β_2 -agonists or inhaled dry-powder budesonide

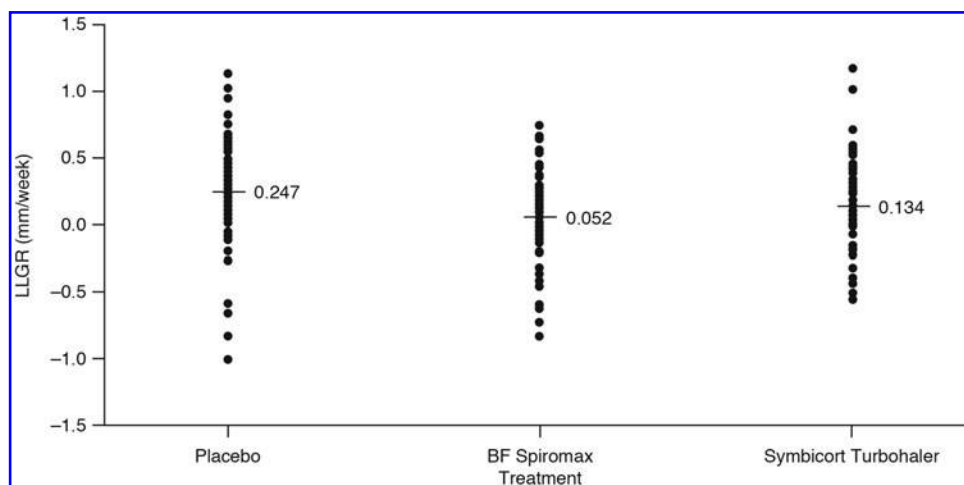


FIG. 3. Individual and mean (---) LLGR in children with asthma during 2 weeks' placebo and treatment periods with BF Spiromax 160+9 μ g b.i.d. and Symbicort Turbohaler 200+12 μ g b.i.d. LLGR, lower leg growth rates.

TABLE 1. MEAN LLGR IN CHILDREN WITH ASTHMA DURING 2 WEEKS PLACEBO AND BF SPIROMAX 160+9 µg AND SYMBICORT TURBOHALER 200+12 µg B.I.D. TREATMENT PERIODS

Treatment period	BF Spiromax		Symbicort Turbohaler
	Placebo	<i>n</i>	
	LLGR (mm/week) (1 SD)		
1	23	24	25
	0.124 (0.467)	−0.111 (0.404)	0.052 (0.393)
2	25	24	19
	0.338 (0.275)	0.092 (0.233)	0.234 (0.239)
3	22	22	26
	0.299 (0.363)	0.176 (0.314)	0.114 (0.419)

BF, budesonide-formoterol; LLGR, lower leg growth rates; SD, standard deviation.

(Spirocort®) up to 400 µg daily or equivalent treatments.⁽¹⁰⁾ The medications were withdrawn at the screening visit. Seventy-three children completed the study according to the protocol (Fig. 2). Two girls and one boy withdrew consent, and one girl was withdrawn due to an asthma exacerbation. Twelve children were allocated to the treatment sequence Spiromax–Symbicort–placebo, thirteen children to each of the other sequences. Mean peak IFR were greater than approximately 96 L/min for all treatment groups during all treatment periods. According to the diary recorded data, all children were compliant during all study periods. Mean self-reported, parental-supervised compliance rates were 92.4%, 92.4%, and 95.0% during the BF Spiromax, Symbicort Turbohaler and placebo periods, respectively. Compliance rates based on device monitoring were comparable to the diary data.

Individual and group mean LLGR during placebo and active treatments are given in Figure 3 and Table 1. Mean (SD) LLGR during placebo and BF Spiromax 160+9 µg b.i.d. and Symbicort Turbohaler 200+12 µg b.i.d. periods were 0.247 (0.39), 0.052 (0.339), and 0.134 (0.36) mm/week. The estimate of the difference [the least squares (LS) mean difference] in LLGR during BF Spiromax and Symbicort Turbohaler treatment was −0.086 mm/week (95% CI: −0.203, 0.032). The 95% CI for the treatment difference included zero, indicating that the treatments were not statistically significantly different. However, the pre-specified non-inferiority margin was −0.200, and the lower limit of the 95% CI observed was just outside this margin, the value being −0.203. Therefore, non-inferiority was not demonstrated between BF Spiromax and Symbicort Turbohaler. The difference between BF Spiromax and placebo LLGR was −0.20 mm/week (95% CI: −0.322, 0.086; $p < 0.001$), between Symbicort Turbohaler and placebo −0.118 mm/week (95% CI: −0.236, −0.001; $p = 0.048$).

Mean 24-h urine cortisol/creatinine concentrations (SD) and the results of the statistical comparison with placebo are shown in Table 2. No statistical significant effects were seen.

Mean PEF during placebo, BF Spiromax, and Symbicort Turbohaler periods are shown in Table 3. The overall effects of BF Spiromax and Symbicort Turbohaler on morning and evening PEF were similar with observed treatment differences of 2.8 L/min (95% CI: −3.1–8.7; $p = 0.347$) and 0.4 L/min (95% CI: −5.6–6.5; $p = 0.8915$), respectively. Both treatments resulted in statistically significant improvements

TABLE 2. URINE FREE CORTISOL/CREATININE (NMOL/MMOL) IN CHILDREN WITH ASTHMA DURING PLACEBO AND BF SPIROMAX 160+9 µg AND SYMBICORT TURBOHALER 200+12 µg B.I.D. PERIODS

	Placebo	BF Spiromax	Symbicort Turbohaler
<i>n</i>	64	63	64
Mean (SD)	8.90 (6.6)	8.71 (6.6)	8.28 (7.0)
LS mean	7.01	6.98	6.48
Comparison to run in:			
Estimate		0.99	0.92
95% CI		0.97–1.24	0.74–1.15
<i>p</i>		0.97	0.48

B.I.D., twice daily; BF, budesonide-formoterol; CI, confidence interval; SD, standard deviation.

in morning and evening PEF relative to placebo. There were no statistically significant changes in rescue treatment-free days during BF Spiromax, Symbicort Turbohaler, or placebo periods (data not shown).

A total of 38 adverse events (AEs) were reported by 20 children (26.0%) during the entire study period. During treatment with BF Spiromax, eight children experienced 13 AEs; during the Symbicort Turbohaler period, six children experienced 10; and during placebo, 11 children experienced 15 AEs. Two of the AEs were serious, the others were mild [cough ($n = 11$), oropharyngeal pain ($n = 3$), pyrexia ($n = 3$), gastroenteritis ($n = 2$), headache ($n = 2$), rash ($n = 2$), nasopharyngitis ($n = 2$); influenza, otitis media, pain in jaw, rhinorrhea, sneezing, ear pain, conjunctivitis, oral discomfort, vomiting, and chest pain ($n = 1$, respectively)]. One serious AE was an asthma exacerbation that occurred during treatment with placebo and led to withdrawal of the child. The asthma exacerbation was ongoing at the end of the study. The other was gastroenteritis that occurred during the washout period following treatment with BF Spiromax. The gastroenteritis resolved and the subject completed the study. There were no drug-related AEs reported during the

TABLE 3. AM AND PM PEF AND CHANGE FROM PERIOD SPECIFIC BASELINE IN CHILDREN WITH ASTHMA DURING PLACEBO AND BF SPIROMAX 160+9 µg AND SYMBICORT TURBOHALER 200+12 µg B.I.D. PERIODS

	BF Spiromax	Symbicort Turbohaler	Placebo
AM PEF			
<i>n</i>	68	69	69
Baseline:	225.2 (52.1)	228.7 (52.3)	228.9 (52.3)
Mean (SD)			
Change:	19.0 (21.0)*	16.0 (17.2)*	0.2 (13.6)
Mean (SD)			
PM PEF			
<i>n</i>	69	70	69
Baseline:	231 (52.3)	231.9 (52.7)	231.4 (50.7)
Mean (SD)			
Change:	16.3 (20.6)*	15.9 (18.8)*	0.9 (15.3)
Mean (SD)			

* $p < 0.001$ versus placebo.

AM, morning; BF, budesonide-formoterol, B.I.D., twice daily; PEF, peak expiratory flow; PM, afternoon; SD, standard deviation.

study. Vital signs (blood pressure and heart rate) showed no clinically meaningful changes during the study, and there were no appreciable differences among the treatment groups. Oropharyngeal examinations at each visit did not show any clinically abnormal findings. There was no evidence of oral candidiasis in any subject during the study. Physical examinations conducted at start and the end of the study did not show any clinically abnormal findings.

Discussion

The inhalation-driven, multi-dose, dry powder BF formulation Spiromax was designed to be comparable to the Symbicort Turbohaler. In accord with this, BF Spiromax was formulated similarly to Symbicort Turbohaler in three matching BF metered dosage strengths: 100/6 μg , 200/6 μg , and 400/12 μg , which deliver approximately 80/4.5 μg , 160/4.5 μg , and 320/9 μg ex-mouthpiece, respectively. In the present study, the dosage strength of BF Spiromax was expressed as delivered (ex-mouthpiece) dose (i.e., BF Spiromax 80/4.5 μg was formulated to deliver approximately the same dose as Symbicort Turbohaler in the labeled dosage of 100/6 μg). The doses of budesonide applied in the present study may be considered somewhat high in children 6–11 years of age. However, considering that intrapulmonary deposition rates of inhaled corticosteroids may be lower in younger children than in >12-year-olds in whom similar doses have been licensed, we felt that this was warranted.⁽¹⁾

Having said that, there are no available data to compare pharmacokinetics (PKs) of BF Spiromax with Symbicort Turbohaler in children. Four studies in healthy adult volunteers comparing BF Spiromax with Symbicort Turbohaler have been performed to evaluate PK profiles and bioequivalence of single dose treatments with and without charcoal blocking.⁽⁴⁾ Plasma concentrations of BF and bioequivalence analyses uniformly indicated that the systemic bioavailability of the treatments was similar. Accordingly, it was expected that the safety profile of BF Spiromax and Symbicort Turbohaler would be comparable.

Therefore, a non-inferiority study design was warranted for the present study of short-term growth, which is the first to compare measures of systemic activity of different fixed combination products in children. LLGR was chosen as the principal outcome measure because knemometry is the most sensitive noninvasive substitute marker of systemic activity of topical corticosteroids available in children.⁽⁷⁾ A measurement error in the detection of the changes in lower leg length of 0.09 mm to 0.13 mm provides a highly accurate and reproducible method for investigation of the influence of inhaled corticosteroids on short-term growth.^(7,14–16) A two-period crossover design with a treatment-free run-in has been found to be the most sensitive design,⁽⁷⁾ however, previous non-inferiority three-period crossover comparison designs similar to the present of various drugs and formulations of inhaled corticosteroids have found quite clear results.^(17–18) In one three-period study a statistically significant period effect was observed.⁽¹⁹⁾ Similarly, in the present trial consistently lower growth rates during all placebo and active treatments in the first treatment period were found that could not be explained by any methodological flaws. To some extent, the finding may explain why non-inferiority between BF Spiromax and Symbicort Turbohaler could not be statistically

significantly proven. As the lower limit of the CI was only marginally outside of the pre-specified non-inferiority margin, however, further studies may be needed for comparison of systemic activity of BF Spiromax and Symbicort Turbohaler before firm conclusions about their comparability may be drawn.

The observed reductions in LLGR were to be anticipated from previous knemometry assessments. Inhaled budesonide from a metered dose inhaler caused a dose-related suppression of short-term lower leg growth,⁽²⁰⁾ and dry powder formulations of budesonide 200 μg to 400 μg (labelled dosages) from the Turbohaler caused growth reductions in the same magnitude as observed with Symbicort Turbohaler in the present study.^(21,22) Combination treatment with BF has been assessed in one previous knemometry study.⁽²³⁾ In that study, the growth suppressive effect of dry powder budesonide 400 μg from the Turbohaler, which was also similar to the effect seen in the present study, was ameliorated during a comparative 4-week period of treatment with dry powder budesonide 200 μg from the Turbohaler plus dry powder formoterol 12 μg . Dry powder formulations of budesonide have been found to be associated with height growth suppression of around 1 cm to 2 cm during 12 months' treatment,^(21,23) and final height to be reduced to the same extent.⁽²⁵⁾ A recent analysis indicated that inhaled corticosteroid suppression of short-term LLGR of 25% or more implies a clinically relevant risk of long-term height growth suppression of 1 cm to 2 cm during the first year of continuous twice-daily treatment.⁽⁷⁾

Since mean LLGR during BF Spiromax 160+9 μg b.i.d. and Symbicort Turbohaler 200+12 μg b.i.d. corresponded with a relative suppression of 78.9% and 45.7%, respectively, both treatments should be anticipated to be associated with a significant risk of long-term growth suppression. That is further supported by a 12-month randomized, double-blind parallel group study in which treatment with Symbicort Turbohaler 85+4.5 μg once daily caused a mean height growth reduction of 1 cm.⁽⁵⁾ However, it is very unlikely that the observed small numerical differences in mean LLGR between BF Spiromax 160+9 μg b.i.d. and Symbicort Turbohaler 200+12 μg b.i.d. in the present study would translate into long-term differences in height growth suppression.⁽⁷⁾

Secondary analyses of 24-hr urinary cortisol excretion showed no treatment-related differences. This is in line with recent evaluations of equipotent drugs and devices.^(15–18) The overall effects of BF Spiromax and Symbicort Turbohaler on PEF were similar and both treatments resulted in statistically significant and clinically relevant improvements relative to placebo that exceeded 15 L/min for both morning and evening PEFs. Overall both treatments were well tolerated and the safety and tolerability was comparable. Though non-inferiority between BF Spiromax 160+9 μg b.i.d. and Symbicort Turbohaler 200+12 μg b.i.d. marginally could not be demonstrated, when all data are taken together, the present study suggests that variations in systemic effects between the treatments may be so small that clinical implications may not be detected.

Acknowledgments

Thanks to study nurse Charlotte Pedersen for taking the knemometry measurements and to nurse Anne Karina Kjaer for help with recruiting children.

Author Disclosure Statement

Dr Tushar Shah is from Global Respiratory Research and Development, Teva Pharmaceuticals, Horsham, PA, USA. The study was sponsored by Teva Branded Pharmaceutical Products R&D, Inc., 74 NW 176th Street, Miami, FL 33169, USA. The protocol was designed by Teva and Ole D. Wolthers. Ole D. Wolthers was responsible for and took part in the clinical conduct of the study. The data were processed by Teva and Ole D. Wolthers in collaboration. Ole D. Wolthers wrote the manuscript and Tushar Shah commented on it. The authors alone were responsible for the content of the article, and Ole D. Wolthers was responsible for publication of the article. Ole D. Wolthers has not been and is not employed by Teva, and he has no stock ownership or any compensation tied directly to the success of Teva products or their marketing approval.

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Received on May 15, 2014
in final form, June 27, 2014

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