Izabela Kupryś-Lipińska[1], Damian Tworek[1], Francis Vanderbist[2], Małgorzata Bocheńska-Marciniak[3], Piotr Kuna[1]

[1]Department of Internal Diseases, Asthma and Allergy, Medical University of Łódź, Poland
Head: Prof. P. Kuna, MD, PhD
[2]Laboratoires SMB, Brussels, Belgium
[3]Department of Pulmonology and Allergology, Medical University of Łódź, Poland
Head: Prof. P. Górski, MD, PhD

Efficacy and safety of a 12-week therapy with a new formulation of fluticasone propionate at doses of 125 and 250 μg administered through a new generation cyclohaler twice daily, in comparison to fluticasone propionate 500 μg dry powder inhaler twice daily in patients with moderate asthma

Skuteczność i bezpieczeństwo terapii nowej formulacji flutykazonu w dawkach 125 i 250 μg z inhalatora cyclohaler nowej generacji w porównaniu z lekiem referencyjnym w dawce 500 μg z inhalatora suchego proszku u chorych na przewlekłą umiarkowaną astmę

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Abstract

Introduction: Inhaled fluticasone is used in the treatment of chronic bronchial asthma. Its high efficacy and good safety profile have been proven by clinical trials and observations. Its unique pharmacokinetic properties make it distinguishable from other drugs from this group. *In vitro* tests run on an artificial model of the airways and pharmacokinetic studies conducted on healthy volunteers have shown that the new formulation of this drug is outstanding due a twofold better lung deposition, compared to the reference medicine. The aim of this study was to evaluate the efficacy and safety of the new formulation of fluticasone propionate administered through new generation cyclohaler (CNG), compared to original fluticasone administered through dry powder inhaler (DPI) in patients with chronic moderate asthma.

Material end methods: The study included 457 patients. 376 subjects were randomized to one out of the three groups: 127 subjects — to the group treated with the new formulation of fluticasone at a dose of 125 μg BID, 125 subjects — to the group treated with new formulation of fluticasone at a dose of 250 μg BID, and 124 subjects — to the group treated with the reference drug — fluticasone DPI 500 μg BID. At the beginning of the study, the groups did not differ in demographical or clinical aspects. Active therapy lasted 12 weeks. The primary endpoint was a mean change in morning PEF during a 12-week course of therapy (ΔmPEF of 15 L/min was considered as statistically significant). Additionally, other functional parameters of the respiratory system — clinical symptoms and the use of rescue drugs were studied. During the whole study the safety of patients was monitored by recording adverse events; in addition, a systemic exposure to fluticasone was evaluated by testing the changes of cortisol in serum and in a 24-hour collection of urine in a subgroup consisting of 45 patients. Statistical analysis was conducted on both groups: intention-to-treat (ITT) and per protocol (PP).

Results: In PP as well as in ITT analysis, a mean change in morning PEF at the end of the therapy from the beginning of the active treatment was statistically significant in all therapeutic groups. The efficacy of the treatment with fluticasone at doses of 125 μg BID and 250 μg and the reference medicines did not differ statistically significantly after a 12-week course of therapy or during the whole period of treatment. During the study, significant improvement in the range of other functional parameters such as evening PEF, FEV_1, clinical symptoms and the use of rescue drugs was observed in all therapeutic groups, without significant differences

Adres do korespondencji: dr n. med. Izabela Kupryś-Lipińska, Klinika Chorób Wewnętrznych, Astmy i Alergii Uniwersytetu Medycznego w Łodzi, ul. Kopcińskiego 22, 90–153 Łódź, e-mail izabela.kuprys-lipinska@umed.lodz.pl

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in efficacy between the study groups. The comparison of efficacy of fluticasone at a dose of 125 μg BID with the generic product at a dose of 250 μg BID showed a weak dose-response relationship concerning the change in morning PEF, which arises from the almost flat dose-response curve in the range of medium and high doses for this drug. No significant quantitative or qualitative differences were shown between the groups in the recorded adverse events, qualified as related to treatment with fluticasone. There were no significant changes revealed in cortisol concentration in serum or in a 24-hour collection of urine between the initial level and the final visit in any of the groups.

Conclusions: Fluticasone administered through the new generation cyclohaler, compared to original fluticasone DPI, allows a twofold reduction in drug dose, retaining in new formulation clinical efficacy that corresponds to the reference drug at twice the dose. New formulation of fluticasone administered through the new generation cyclohaler has a safety profile clinically comparable to the reference drug.

Key words: bronchial asthma, fluticasone, new generation cyclohaler, non-inferiority study

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Streszczenie

Wstęp: Flutykazon w postaci wziewnej stosowany jest w leczeniu przewlekłej astmy oskrzelowej. Ma udowodnioną w badaniach klinicznych i obserwacyjnych wysoką skuteczność i dobry profil bezpieczeństwa. Wyróżnia się spośród innych leków należących do tej grupy unikatowymi właściwościami farmakokinetycznymi. Badania *in vitro* na sztucznym modelu dróg oddechowych jak i badania farmakokinetyczne przeprowadzane na zdrowych ochotnikach wykazały, że w nowej formulacji lek ten cechuje się dwukrotnie lepszą depozycją płucną w porównaniu z preparatem referencyjnym.

Celem tego badania była ocena skuteczności i bezpieczeństwa nowej formulacji propionianu flutykazonu podawanego z inhalatora nowej generacji typu cyklohaler (CNG) w porównaniu z oryginalnym produktem flutykazonu w inhalatorze proszkowym DPI u chorych na przewlekłą umiarkowaną astmę.

Materiał i metody: Do badania włączono 457 pacjentów, 376 osób zrandomizowano przydzielając losowo do jednej z trzech badanych grup: 127 osób do grupy leczonej flutykazonem w nowej formulacji w dawce 125 μg BID, 125 osób do grupy leczonej flutykazonem w nowej formulacji 250 μg BID i 124 osoby do grupy z lekiem referencyjnym — flutykazon DPI 500 μg BID. Badane grupy nie różniły się na początku badania pod względem demograficznym ani klinicznym. Aktywna terapia trwała 12 tygodni. Pierwszorzędowym punktem końcowym była średnia zmiana porannego PEF podczas 12-tygodniowego okresu leczenia (za znamienną statystycznie różnicę uznano ΔmPEF o 15 l/min). Badano ponadto inne parametry czynnościowe układu oddechowego, objawy kliniczne i zużycie leków ratunkowych. W czasie trwania całego badania monitorowano bezpieczeństwo pacjentów rejestrując zdarzenia niepożądane, dodatkowo oceniano ekspozycję systemową na flutykazon, badając w 45-osobowej podgrupie zmiany kortyzolu w surowicy i dobowej zbiórce moczu. Analizę statystyczną przeprowadzono zarówno na grupie *intention-to-treat* jak i *per protocol.*

Wyniki: Zarówno w analizie PP, jak i ITT średnia zmiana porannego PEF na koniec okresu leczenia od początku aktywnej terapii była istotna statystycznie we wszystkich grupach terapeutycznych. Efektywność terapii flutykazonem zarówno w dawce 125 μg BID, jak i 250 μg BID oraz preparatem referencyjnym nie różniła się istotnie statystycznie po 12 tygodni terapii, jak również w całym okresie leczenia. Również w zakresie innych parametrów czynnościowych jak wieczorny PEF, FEV_1, objawy kliniczne i zużycie leków ratunkowych obserwowano istotną poprawę we wszystkich grupach terapeutycznych w czasie trwania badania, bez istotnej różnicy w efektywności pomiędzy badanymi grupami. Porównując efektywność dawki flutykazonu 125 μg BID z 250 μg BID produktu odtwórczego wykazano słabą zależność dawka–odpowiedź w zakresie zmiany parametru porannego PEF, co wynika z niemal płaskiej krzywej dawka–odpowiedź w zakresie dawek średnich i wysokich dla tego leku. Nie wykazano też istotnych różnic ilościowych i jakościowych między grupami w rejestrowanych zdarzeniach niepożądanych zakwalifikowanych jako związane z leczeniem flutykazonem. W żadnej z grup nie odnotowano istotnych zmian w stężeniu kortyzolu w surowicy i dobowej zbiórce moczu między poziomem wyjściowym i wizytą końcową.

Wnioski: Flutykazon CNG w porównaniu z oryginalnym produktem flutykazonu DPI, pozwala na dwukrotne obniżenie dawki tego leku przy zachowaniu efektywności klinicznej odpowiadającej lekowi referencyjnemu w dwukrotnie wyższej dawce. Flutykazon w nowej formulacji podawany z inhalatora typu CNG ma porównywalny klinicznie profil bezpieczeństwa do leku referencyjnego.

Słowa kluczowe: astma oskrzelowa, flutykazon, inhalator nowej generacji typu cyklohaler, badanie równoważności

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Introduction

Bronchial asthma is currently one of the most frequent chronic diseases of the respiratory system. There are nearly 4 million people with asthma in Poland [1]. The background of asthma is chronic inflammation of the airways, which causes bronchial hyperreactivity and clinical symptoms. Therefore, the basis for therapy are inhaled glycocorticosteroids, which are considered to be the strongest anti-inflammatory drugs, and which are recommended for all types of chronic asthma, irrespective of aetiology, severity and control [2].

Fluticasone distinguishes itself from other inhaled glycocorticosteroids by its high affinity to intracellular glycocorticosteroid receptor (18

times higher than dexamethasone), and its high lipophilic nature, which results in strong and long-lasting activity of the drug in the bronchi. Simultaneously, fluticasone demonstrates a very poor bioavailability from the oral cavity and alimentary tract (< 1%), it binds rapidly and in large proportion with plasma protein, and it comes under first-pass effect in the liver, which significantly reduces the risk of systemic side-effects [3].

The aim of the present study was to evaluate the efficacy and safety of a new formulation of fluticasone propionate at a dose of 125 and 250 μg administered twice a day (BID) for 12 weeks, compared to the original fluticasone DPI 500 μg in patients with moderate asthma.

Material and methods

It was a Phase III trial and was designed as a multicentre (23 centres: 16 in Poland and 7 in Ukraine), randomized, open-label, parallel-group and positive control study. The centres received consent to the study from local Bioethics Commissions. The scheme of the study is presented in Figure 1.

The study groups

The following criteria for participation in the study were applied.

Inclusion criteria

1. Patients of both sexes, from 18 to 70 years of age.
2. Moderate bronchial asthma diagnosed at least 3 months prior to the first visit.
3. Reversibility of airway obstruction (increase in FEV_1 of at least 12% after administration of 400 μg of salbutamol) shown during the first visit.
4. Predicted FEV_1 value in the range 50 to 85% on screening and randomization visits.
5. Ability to follow the procedures of the study, including the use of inhalators, peak expiratory flow meter and spirometry.
6. Non-use of short-acting β2-agonist at least 6 hours before visits at the centre.
7. Informed consent to participation in the study.
8. The use of an efficient contraceptive method by women of reproductive age and negative serum pregnancy test on the first visit, and negative urine pregnancy test on the randomization visit.

Exclusion criteria

1. Severe, life-threatening bronchial asthma or hospitalization due to exacerbation of asthma for 3 months prior to the first visit.
2. Uncontrolled or untreated clinically significant immunological, hormonal, haematological, psychiatric or neurological disorders, hepatopathy, nephropathy, diseases of the alimentary system or neoplasms.
3. The presence or history of cardiac dysrhythmia and diagnosed diseases of cardiovascular system, including coronary heart disease, circulatory failure and uncontrolled arterial hypertension (diastolic pressure ≥ 95 mm Hg).
4. Infection of the respiratory system requiring antibiotic therapy 8 weeks before the first visit.
5. Significant diseases of the respiratory system other than asthma.
6. Smoking more than 10 cigarettes/per day or more than 10 pack-years in their history.
7. Seasonal asthma or history of seasonal exacerbations of asthma.
8. The use of prohibited drugs.
9. Participation in another clinical trial 3 months prior to the first visit.

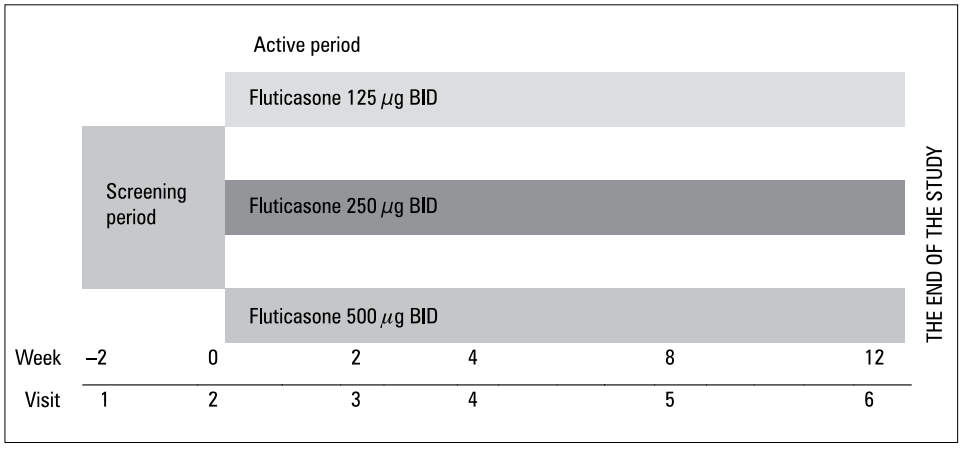

Figure 1. The scheme of the study

Rycina 1. Schemat badania

10. Other diseases or factors that, in the opinion of the researcher, may disrupt participation in the study.
11. Hypersensitivity or allergy to the drugs used in the study.
12. Diabetes.
13. Irregular PEF measurements and taking of the studied drugs (more than 20% of measurements omitted or doses of the studied drug not taken).
14. The use of systemic steroids 8 weeks prior to the first visit.

The scheme of the study

The active period of the study lasted 12 weeks and was preceded by a 2-week screening period, during which patients were given placebo (single-blind study). On the first day of the active period participants were randomly assigned to one of the three therapeutic arms. In the first arm patients were administered fluticasone 125 μg BID through new generation cyclohaler, in the second one — fluticasone 250 μg BID also through new generation cyclohaler, in the third one — fluticasone DPI 500 μg BID. Only doses administered through new generation cyclohaler were double-blinded. Each patient had 6 planned visits during the study.

The drugs used in the study

During the initial period, patients inhaled capsules with placebo through a metered-dose, new generation cyclohaler, Fantasmino®.

During the active period the studied drug, fluticasone, was administered through a new generation cyclohaler, Fantasmino®, at doses of 125 μg (Flutixon® 125 μg) or 250 μg (Flutixon® 250 μg).

The reference drug was fluticasone 500 μg (Flixotide Disc® 500).

The rescue medication was Ventolin® 100 μg (GlaxoSmithKline).

Administration of the investigational drug

Each drug was administered twice a day (in the morning and in the evening). The number of used capsules of the studied fluticasone and the doses of original fluticasone DPI was registered in the documentation during each visit. A criterion for continuation in the study was administration of ≥ 80% of the doses of the drug.

Efficacy evaluation

The aim of the study was to evaluate the clinical efficacy of a new formulation of fluticasone at doses of 125 and 250 μg BID in comparison to the reference drug, fluticasone DPI 500 μg BID. We intended to demonstrate that the new formulation of the drug at the studied doses is as effective as the reference drug.

The primary endpoint was a mean change in morning PEF during 12 weeks of therapy (from the initial value — T0, to the value in the 12th week — T12). The initial value was the mean of 14 days of the screening period. A mean PEF was calculated during the 6th visit, from all data collected between the 5th and 6th visit.

Secondary endpoints were:

A. mean change in evening PEF (T0:T12),
B. mean change in FEV_1 (T0:T12),
C. mean change in overall severity of asthma symptoms (T0:T12). The following asthma symptoms were assessed: wheezing, cough and dyspnoea on a scale from 0 — lack of symptoms up to 3 — serious symptoms,
D. sleep disturbances due to asthma (T0:T12),
E. use of the rescue medication (T0:T12).

Safety evaluation

The secondary aim of the study was to evaluate the safety of new formulation of fluticasone at doses used in the study and to compare it with the safety profile of the reference drug.

The safety of the drugs was evaluated through the analysis of the occurrence and nature of adverse events, the frequency and reasons for withdrawal from the study, vital parameters, deviations from physical examination and laboratory investigation results. In the subgroup consisting of 45 subjects (15 subjects from each therapeutic arm) morning cortisol concentration in serum and in a 24-hour urine collection was determined.

Statistical analysis

Values of $p < 0.05$ were assumed as statistically significant. Clinical efficacy measured in a primary variable was compared between the groups by using the ANOVA model. The lower limit of a bilateral 95% confidence interval for the difference of a mean change in morning PEF between the studied therapies above -15 L/min in both intention-to-treat and per protocol analyses was considered as a criterion for non-inferior efficacy of the two doses of fluticasone.

Secondary endpoints — change in evening PEF was analysed similarly to morning PEF, whereas the remaining parameters were analysed by using ANOVA: changes of a given parameter between initial data and endpoint were compared.

The frequency of patients' withdrawal from the study in different groups was compared with the use of Kaplan-Meier analysis.

The analysis of adverse events was carried out using of descriptive statistics and tests for qualitative data analysis.

Additional analysis was made in the subgroup, where the cortisol levels in serum and urine were assessed. The change was assessed with the ANOVA method.

The size of the study group

It was calculated that the availability of complete data from 100 patients per each therapeutic group, with standard deviation from morning PEF 50 L/min, will allow to find a statistically significant difference by 15 L/min of morning PEF change, with 80% force and 5% level of significance for paired comparisons.

Results

Characteristics of the study groups

A total of 457 patients were included in the study. Of these, 356 patients made the study group in accordance with the protocol (per protocol group, PP). Intention-to-treat analysis (ITT group) included 376 patients who were all randomized and treated with at least one dose of the studied drug. A description of patients in the separate therapeutic groups is presented in Table 1. Randomization of patients is presented in Figure 2. In all patients the use of the studied drug and the number of PEF measurements were more than 80%.

Efficacy evaluation

Primary endpoint — a mean change in morning PEF after 12 weeks of therapy

In PP and ITT analyses, a mean change in morning PEF at the end of the treatment period, compared to the initial period, was statistically significant in all therapeutic groups. No significant differences concerning the mean change in morning PEF between the groups were observed during the 12th week of the therapy, or during the

Table 1. Characteristic of therapeutic groups

Tabela 1. Charakterystyka grup terapeutycznych

	Fluticasone CNG 125	Fluticasone CNG 250	Fluticasone DPI 500	P
Number of patients	127	125	124	-
Women/men	82/45	78/47	70/54	-
Age (years) mean ± SD	42.26 ± 12.9	42.57 ± 13.33	42.57 ± 13.80	0.2751
Height [cm] mean ± SD	167.53 ± 8.49	168.9 ± 10.18	168.9 ± 13.12	0.4923
Weight [kg] mean ± SD	74.18 ± 14.03	74.86 ± 14.69	74.86 ± 15.79	0.8544
Tobacco smokers	22	21	20	0.9683
Heart rate/min	71.99 ± 7.94	72 ± 7.5	72 ± 7.43	0.5694
Systolic pressure [mm Hg]	126 ± 44	122.58 ± 9.48	124.49 ± 10.08	0.3022
Diastolic pressure [mm Hg]	79.12	77.32 ± 7.09	78.15	0.531
Respiratory rate/min	16.76	17.07 ± 2.23	16.92	0.4917
FEV_1 [L] mean ± SD	2.2 ± 0.59	2.25 ± 0.63	2.26 ± 0.62	0.3342
FEV_1% PREDICTED mean ± SD	71.31 ± 9.35	70.16 ± 9.42	71.16 ± 8.37	0.491
ΔFEV_1% (reversibility test)	24.75 ± 13.13	25.3 ± 12.59	25.97 ± 12.97	-
FVC [L] mean ± SD	3.25 ± 0.88	3.37 ± 0.94	3.37 ± 0.92	0.4659
mPEF [L/min] mean ± SD	357 ± 94.03	360.56 ± 80.92	369.68 ± 109.96	0.5771
ePEF [L/min] mean ± SD	371.10 ± 93.13	378.62 ± 80.33	385.02 ± 108.56	0.5078
Wheezing mean points ± SD	1.18 ± 0.7	1.12 ± 0.73	1.07 ± 0.68	0.4704
Cough mean points ± SD	1.1 ± 0.68	1.0 ± 0.73	0.98 ± 0.65	0.3376
Dyspnea mean points ± SD	1.38 ± 0.65	1.37 ± 0.69	1.25 ± 0.69	0.2392
Sleep disorders mean points ± SD	1.84 ± 0.66	1.81 ± 0.66	1.76 ± 0.63	0.6068
Rescue medication mean N/d ± SD	3.88 ± 3.22	3.67 ± 3.44	3.83 ± 3.53	0.7546

All abbreviations in the text

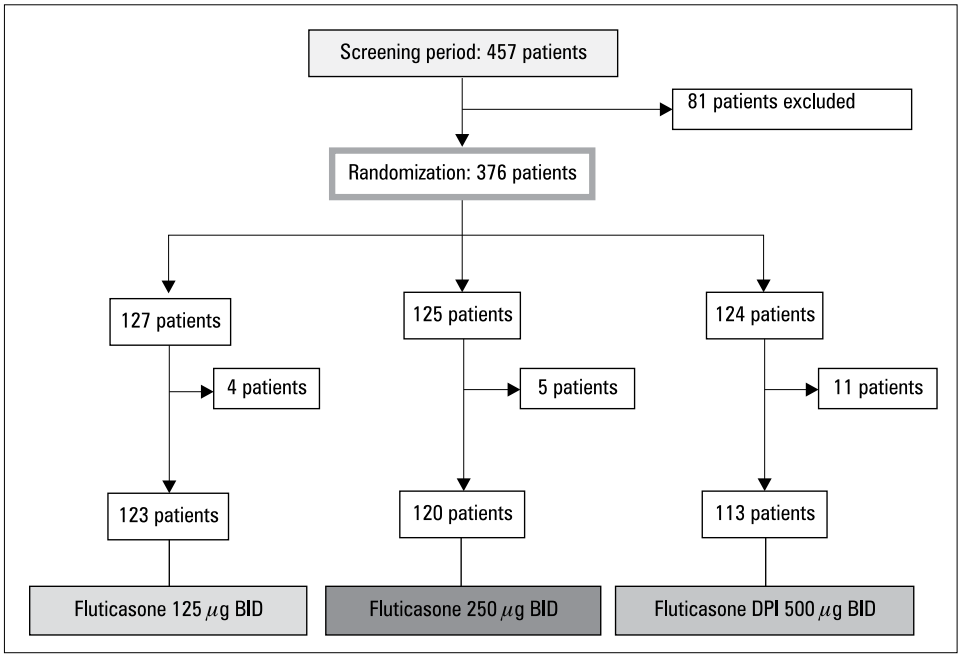

Figure 2. Randomization of patients in the study

Rycina 2. Losy pacjentów w badaniu

Table 2. The results of a mean change in morning PEF and standard deviations after 12 weeks of active treatment

Tabela 2. Wyniki średniej zmiany porannego PEF i odchyleń standardowych po 12 tygodniach aktywnego leczenia

	Fluticasone CNG 125		Fluticasone CNG 250		Fluticasone DPI 500		P*	
Analysis	PP	ITT	PP	ITT	PP	ITT	PP	ITT
Number of patients	123	127	120	125	113	124		
ΔmPEF L/min	25.9 ± 42.6	25.9 ± 42.6	31.9 ± 46.6	34 ± 47.9	24.3 ± 52.0	25.2 ± 51.8	0.4058	0.2571
P**	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001		

PP — *per protocol*; ITT — *intention-to-treat*; PEF — *peak respiratory flow*

P* analysis between the groups

P** analysis in the groups

whole period of treatment. A similar efficacy of fluticasone 125 and 250 μg BID, compared to the reference drug, was demonstrated after 12 weeks of the therapy as well as during the whole period of treatment (Table 2).

However, in both PP and ITT analyses, a tendency towards improvement in mPEF was observed in the group treated with fluticasone 250 μg BID, compared to patients treated with fluticasone 125 μg BID (Table 3).

Secondary endpoints

In PP analysis, in all therapeutic groups, a significant improvement was observed in all secondary endpoints after 12 weeks of the therapy, compared to the initial period (Table 4). No significant differences were found between the groups in the mean change of secondary endpoints after 12 weeks of the therapy. Similar results were obtained in ITT analysis (Table 4).

Compliance — evaluation of the use of the studied drugs and PEF measurements during the study

During the whole study, patients from all study groups were administered more than 98% of the planned doses of the studied drugs. Only one randomized patient omitted more than 20% of the drug doses between the 3rd and 4th visit; in the remaining period of treatment he met the criteria of the drug administration by more than 80%. The mean number of PEF measurements also exceeded 98% of the planned measurements for all therapeutic groups. None of the patients

Table 3. Non-inferiority analysis for ΔmPEF

Tabela 3. Analiza typu *non-inferiority* dla ΔmPEF

	95% confidence interval			
ΔmPEF analysis	**PP**		**ITT**	
limit of the interval	Lower	Upper	Lower	Upper
ΔmPEF fluticasone 125 vs. fluticasone 250	–18.26	4.66	–20.18	2.78
ΔmPEF fluticasone 125 vs. fluticasone DPI 500	–11.37	11.78	–12.22	10.96
ΔmPEF fluticasone 250 vs. fluticasone DPI 500	–4.72	18.74	–3.61	19.75

PP — *per protocol*; ITT — *intention-to-treat*; PEF — *peak respiratory flow*

Table 4. The results for secondary variables after 12 weeks of the therapy compared to the initial data in PP and ITT analysis

Tabela 4. Wyniki dla zmiennych drugorzędowych po 12 tygodniach terapii w porównaniu z danymi wyjściowymi w analizie PP i ITT

	Fluticasone CNG 125		**Fluticasone CNG 250**		**Fluticasone DPI 500**		**P***	
Analysis	PP	ITT	PP	ITT	PP	ITT	PP	ITT
Number of patients	123	127	120	125	113	124		
Δ ePEF (L/min) mean ± SD, *P***	21.2 ± 42.4 *0.0001*	21.2 ± 42.4 *0.0001*	24.6 ± 42.1 *0.0001*	25.9 ± 42.8 *0.0001*	19.7 ± 46.9 *0.0001*	20.6 ± 47.1 *0.0001*	0.6802	0.5401
Δ FEV_1 (L) mean ± SD, *P***	0.28 ± 0.40 *0.0001*	0.29 ± 0.40 *0.0001*	0.32 ± 0.43 *0.0001*	0.31 ± 0.43 *0.0001*	0.30 ± 0.42 *0.0001*	0.31 ± 0.42 *0.0001*	0.8801	0.8212
Δ FEV_1 %N mean ± SD, *P***	9.43 ± 13.38 *0.0001*	9.79 ± 13.4 *0.0001*	10.30 ± 14.5 *0.0001*	10.20 ± 14.4 *0.0001*	9.65 ± 13.12 *0.0001*	10.1 ± 13.03 *0.0001*	0.8564	0.9384
Δ FVC (L) mean ± SD, *P***	0.27 ± 0.50 *0.0001*	0.28 ± 0.49 *0.0001*	0.25 ± 0.56 *0.0001*	0.25 ± 0.55 *0.0001*	0.33 ± 0.49 *0.0001*	0.33 ± 0.48 *0.0001*	0.5259	0.4145
Δ pkt of symptoms mean ± SD, *P***	–0.29 ± 0.48 *0.0001*	–0.29 ± 0.48 *0.0001*	–0.34 ± 0.57 *0.0001*	–0.34 ± 0.56 *0.0001*	–0.29 ± 0.55 *0.0001*	–0.31 ± 0.56 *0.0001*	0.4807	0.4971
Δ pkt of sleep disorders mean ± SD, *P***	–0.32 ± 0.55 *0.0001*	–0.32 ± 0.55 *0.0001*	–0.30 ± 0.63 *0.0001*	–0.31 ± 0.62 *0.0001*	–0.24 ± 0.59 *0.0001*	–0.25 ± 0.59 *0.0001*	0.7673	0.7937
Δ use of SABA mean ± SD, *P***	–1.73 ± 2.61 *< 0.0001*	–1.73 ± 2.61 *< 0.0001*	1.36 ± 2.81 *< 0.0001*	1.37 ± 2.8 *<0.0001*	–1.62 ± 2.72 *< 0.0001*	–1.7 ± 2.81 *< 0.0001*	0.7026	0.6046

PP — *per protocol*; ITT — *intention-to-treat*; PEF — *peak respiratory flow*; other abbreviations in the text

P* analysis between the groups

P** analysis in the groups

omitted 20% of the planned measurements, and so nobody was excluded from the study for this reason.

Safety evaluation

Safety analysis was carried out on the ITT group.

Adverse events

Generally, 143 adverse events were noted (61 — in the group treated with fluticasone 125 μg, 30 — in the group treated with fluticasone 250 μg, and 52 — in the group treated with fluticasone DPI 500 μg) in 81 patients (29 patients from the group treated with fluticasone 125 μg, 23 — from the group treated with fluticasone 250 μg, and 29 — from the group treated with fluticasone DPI μg 500). The frequency of adverse events was significantly lower in the group treated with fluticasone 250 μg than in the remaining groups (p = 0.0005).

Of these, 48 cases of adverse events were expected and 95 were unexpected. 62.2% of all events were qualified as mild symptoms, 26.6% — as moderate, and 4.9% — as severe. In all study groups, treatment-related events with frequency exceeding 1% included: hoarseness, dry cough and sore throat. The frequency of treatment-related events did not exceed 5% in any gropus, therefore, a comparative analysis was not carried out.

During the active treatment three serious adverse events occurred (uterine bleeding, infective exacerbations of asthma and pregnancy), but they were recognized as not related to the studied drug.

Table 5. Cortisol level in serum and urine, and its changes during 12 weeks of therapy

Tabela 5. Stężenie kortyzolu w surowicy i moczu i jego zmiany w okresie 12 tygodni terapii

	Fluticasone CNG 125	Fluticasone CNG 250	Fluticasone DPI 500	P*
Number of patients	11	10	11	
Cortisol in serum (N 116-1060 nmoL/L)				
During the randomized visit	301.7 ± 117.7	304.8 ± 96.8	412.82 ± 354.86	0.4381
Δ during the final visit	–26.2 ± 126.4	–59.9 ± 95.9	–153 ± 398.4	0.6635
P**	0.8311	0.098	0.2324	
Cortisol in urine (N 88-671 nmoL/24h)				
During the randomized visit	281.27 ± 149.35	323.4 ± 196.05	232.91 ± 146.7	0.4604
Δ during the final visit	–44.5 ± 145.9	–81.2 ± 275.5	–33.2 ± 169.6	0.9879
*P***	*0.3352*	*0.4023*	*0.5513*	

P* analysis between the groups
P** analysis in the groups

Laboratory results, vital functions and physical examination

No differences were observed in quantity or quality of deviation from the norm in laboratory investigations between the study groups. No significant differences were discovered in measurements of vital functions or physical examination between the three therapeutic groups during the study.

Cortisol concentrations

No significant differences were observed in initial serum cortisol concentration in the morning, in cortisol concentration in a 24-hour collection of urine before the active therapy, or after 12-week treatment, between the three groups. Significant changes in cortisol concentration in serum or in a 24-hour collection of urine between the initial level and the final visit were not observed in any of the groups (Table 5).

The frequency of exclusions from treatment with the studied drug

In total, 20 subjects were withdrawn from the study after randomization: 4 subjects from the group treated with fluticasone 125 μg, 5 from the group treated with fluticasone 250 μg, and 11 from the group treated with fluticasone DPI 500 μg. Therapeutic groups were comperatable in respect of number ($p = 0.0716$) and reasons for exclusion of patients from the study.

Discussion

The studied drug — fluticasone propionate — administered through a new generation inhaler is a generic, new formulation drug. In comparison with the original drug, it is characterized by a twofold improved lung deposition, equal molecular weight and a smaller drug fraction remaining in the oral cavity after inhalation. This was proved by *in vitro* tests, run on an artificial model of the airways [4] and pharmacokinetic studies, conducted on healthy volunteers with single (paper in press) and multiple doses (paper in press).

Their results allowed the hypothesis to be proposed that a therapeutic effect equivalent to that of the original drug may be obtained by using half the dose of the new formulation of fluticasone. In order to confirm this hypothesis, a 12-week clinical trial was planned. It was carried out on patients with chronic moderate asthma in accordance with guidelines by the EMA (*European Medicines Agency*) [5] concerning requirements for bioequivalence studies of a generic and reference drug.

According to the characteristics of the reference drug, in moderate asthma it is recommended to use fluticasone DPI at doses from 250 μg twice a day (BID) to 500 μg BID. In the present clinical study equivalents of the lowest therapeutic dose used in moderate asthma — fluticasone 125 μg DPI BID (equivalent to fluticasone DPI 250 μg BID), and of the highest dose — fluticasone 250 μg (equivalent to fluticasone DPI 500 BID), were assumed. The lowest dose was assumed in order to show efficacy of the lowest dose used, whereas the highest dose was to prove the safety of the drug according to guidelines by the EMA [5].

In bioequivalence studies of inhaled anti-inflammatory drugs, in order to show comparable efficacy of both products, the EMA recommends

that the study lasts at least 6–8 weeks, to exclude the loss of asthma control [5]. To evaluate the safety of a generic product, it is recommended that the study lasts 12 weeks. The present study lasted 12 weeks; therefore, both conditions — efficacy and safety evaluation of the drug — were fulfilled. In order to confirm the systemic safety of the studied drug, a subgroup of patients was distinguished, in whom, additionally, the influence of the therapy on cortisol concentration in blood and in a 24-hour collection of urine, was evaluated, and thus the additional recommendations of the EMA were fulfilled [5].

The study results showed a significant improvement in morning PEF for the two evaluated doses of the studied drug. A beneficial change was also observed in secondary parameters of therapeutic efficacy: evening PEF, FEV_1 and FEV_1%, FVC, severity severity of asthma symptoms and the use of rescue medications. It proves the clinical efficacy of the two studied doses of the generic product.

The comparison of the efficacy of fluticasone at a dose of 125 μg BID with the generic product at a dose of 250 μg BID showed a weak dose--response relationship in the range of change in morning PEF.

The majority of benefits resulting from the use of inhaled glycocorticosteroids are achieved by the use of low doses (up to 250 μg/d expressed in fluticasone, which equals 90% of the efficacy obtained with a dose of 1000 μg/d). Holt et al. estimated that the maximal therapeutic effect measured in the change of functional pulmonary parameters is achieved by the use of fluticasone DPI 500 μg/d [6]. Due to the fact that for these drugs the dose-response curve in the range of medium and higher doses has an almost flat course, a further increase in the dose results in a small clinical effect in respect of asthma control and functional pulmonary parameters, yet it increases the risk of intolerance and adverse, particularly local, events. The use of higher doses in clinical practice is justified by patients who are resistant to low doses of inhaled glycocorticosteroids, but who respond to high doses.

The comparison of the results concerning the efficacy of treatment with the generic product to treatment with the reference drug, demonstrated that the efficacy of the new formulation of fluticasone 250 μg BID administered through new generation cyclohaler is equal to the efficacy of fluticasone DPI 500 μg BID in the range of primary and secondary variables. It confirms the previous observations made during *in vitro* tests and pharmacokinetic studies, that two times better pulmonary deposition and equal molecular weight for a new formulation of the drug administered through new generation cyclohaler, compared to fluticasone DPI, allow the dose of the drug to be halved, retaining the clinical efficacy corresponding to the reference drug at a twofold higher dose.

The present study has not shown a higher efficacy of fluticasone DPI 500 μg BID, compared to the efficacy of fluticasone 125 μg BID administered through new generation cyclohaler. This confimes the previously-described flat dose-response curve for fluticasone at doses higher than 250 μg/d for fluticasone DPI. The study by Wolf et al. [7] did not show a dose-response relationship for fluticasone in metered-dose inhaler (MDI) 100, 200 and 500 μg administered BID.

Therefore, the results of the present study confirm the efficacy of treatment with the new formulation of fluticasone at doses of 125 μg and 250 μg BID in patients with moderate asthma. The higher studied dose is recommended only for patients who cannot control the disease with a dose of 125 μg BID, which is equal to fluticasone DPI 250 μg BID.

During the study the tolerance and safety of the studied drug, in comparison to the reference drug, were also evaluated. A safety profile comparable to the original drug was proven for the two studied doses. The number, severity and type of reported adverse events did not differ between the studied products and the reference drug, except for local events, which were reported the most seldom for fluticasone administered through the new generation cyclohaler at a dose of 250 μg BID. The absence of significant changes in cortisol level in urine and in serum after 12 weeks of treatment confirm the lack of any influence of the used therapy on the hypothalamic hypophyseal adrenal axis, and prove the high safety profile of the studied drug at the two doses.

Concluding, it may be stated that:

Fluticasone administered through a new generation cyclohaler at doses of 125 and 250 μg BID is an efficient drug in the therapy of moderate bronchial asthma.

A dose of 250 μg BID of the new formulation of fluticasone administered through a new generation cyclohaler is clinically equivalent to a twofold higher dose of fluticasone DPI.

The clinical activity of fluticasone 125 μg BID is not weaker than the activity of fluticasone DPI at a dose of 500 μg BID. There is no clinically significant difference in efficacy between the dose of 250 μg of fluticasone BID and the dose of

125 μg administered through the new generation cyclohaler, which arises from a flat dose-response curve in the range of medium and high doses for this drug.

Fluticasone administered through the new generation cyclohaler has a safety profile clinically comparable to the reference drug.

Conflict of interest

Izabela Kupryś-Lipińska — lack of conflict.

Damian Tworek — lack of conflict.

Francis Vanderbist — R& D Manager of Laboratoires SMB S.A.

Małgorzata Bocheńska-Marciniak — lack of conflict.

Piotr Kuna — lectures sponsored by Adamed and GlaxoSmithKline.

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