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ORIGINAL RESEARCH

Evaluation of the Efficiency of Single-Inhaler Combination Therapy with Budesonide/Formoterol Fumarate in Patients with Bronchial Asthma in Daily Clinical Practice

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ABSTRACT

Introduction: The effectiveness of single-inhaler budesonide/formoterol fumarate combination therapy for asthma has been previously shown for the original product. The aim of this nonrandomized, open-label, postauthorization efficacy study (PAES) real-life clinical assessment was to evaluate the clinical effectiveness of a second product (Bufomix Easyhaler®) in the daily clinical practice of asthma therapy.

Methods: This multicenter PAES was conducted by 220 unselected allergologists and pulmonologists who enrolled 2200 adult outpatients (age 49.8 ± 17.9 years) with asthma treated with Bufomix Easyhaler® for at least 14 days before enrolment. Asthma control was assessed during three subsequent visits with 8–12-week intervals on the basis of the Asthma Control Test (ACT). Adherence was assessed with the Medication Adherence Questionnaire. In addition, patient satisfaction with Bufomix Easyhaler® was scored, and adverse drug reactions were recorded.

Results: The percentage of patients with well-controlled asthma or total control of asthma (ACT score 20-25 points) increased from 46.6% at the first visit to 90.8% at the third visit ($p < 0.001$). In addition, the percentage of patients with poor control of asthma (ACT score less than 15 points) decreased from 14.9% to 1.2% ($p < 0.001$). The adherence rate increased from 88% at the first visit to 95.3% at the third visit. Patient satisfaction with the use of this dry powder inhaler increased with the duration of its use. Only one adverse drug reaction was reported.

Conclusion: The results obtained confirm the effectiveness of Bufomix Easyhaler® in the treatment of asthma in outpatient adults in daily clinical practice.

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Keywords: Bronchial asthma; Budesonide; Combination therapy; Dry powder inhaler;

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Inhaled corticosteroids; Formoterol fumarate; Postauthorization efficacy study; Respiratory

INTRODUCTION

Bufomix Easyhaler®, a second dry powder inhaler budesonide/formoterol fumarate combination product [1], was registered in Poland by Orion Pharma Poland in May 2014 via the European Medicines Agency's decentralized procedure on the basis of therapeutic equivalence with the originator product Symbicort Turbuhaler® (AstraZeneca) [2].

Better lung deposition of budesonide was shown for the Easyhaler® dry powder inhaler in comparison with most pressurized metered-dose inhalers [3]. In vitro performance of Bufomix Easyhaler® demonstrated its superiority over Symbicort Turbuhaler® in reliability of dosing across a wide range of inspiratory flow rates, and its performance was not affected by environmental moisture, dropping, vibration, and freezing/thawing [4].

Formoterol, a long-acting β_2-agonist (LABA), and budesonide, an inhaled corticosteroid (ICS), in combination demonstrate an additive effect in alleviating asthma symptoms [5]. Their fixed-dose combination in one inhaler simplifies the administration regimen, improves adherence, and ensures that a LABA will not be used as monotherapy. This combination product suppresses chronic inflammation seen in asthma and reduces airway hyperresponsiveness, which is important for the control of asthma [6, 7].

Clinical studies in adults showed that the addition of formoterol to budesonide alleviated asthma symptoms and reduced exacerbations [8]. In two 12-week studies, the effect on lung function of budesonide/formoterol was equal to that of the free combination of budesonide and formoterol and exceeded that of budesonide alone [9, 10]. All treatment arms used a short-acting β_2-adrenoceptor agonist as needed. There was no sign of attenuation of the antiasthmatic effect over time. The efficacy and safety of budesonide/formoterol maintenance and reliever therapy were demonstrated previously but limited data are available for the real-life setting [11]. Incorrect inhaler use remains common in real life and is associated with reduced disease control [12]. Errors in inhaler handling, not taken into account in clinical trials, could impact drug delivery and minimize treatment benefit [13].

The aim of this nonrandomized, open-label, postauthorization efficacy study (PAES) was to evaluate the clinical effectiveness of Bufomix Easyhaler® in therapy for asthma in daily clinical practice (real-life setting).

METHODS

This postmarketing, multicenter, open-label, nonrandomized noninterventional study was conducted by 220 unselected allergologists and pulmonologists with the participation of 2200 combination-naive adult outpatients with a diagnosis of asthma on the basis of the reversible (spontaneously or with treatment) clinical symptoms of airflow obstruction who had recently started combination therapy. Physicians were recruited via the Internet and medical representatives throughout Poland.

The inclusion criterion was recently started combination therapy with budesonide/formoterol fumarate (Bufomix Easyhaler® 160/4.5 μg or 320/9.0 μg) continued before enrolment for at least 14 days by an adult patient (age 18 years or older) with asthma without assistance. Inhaler use training was performed at the discretion of the center. The severity of the asthma clinical course was assessed according to the Global Initiative for Asthma (GINA) 2015 classification [14].

The exclusion criteria (in line with the summary product characteristics) were hypersensitivity to budesonide, formoterol, or lactose, pregnancy, breastfeeding, unstable asthma defined as the use of oral steroid cycles three times during the last year or hospitalization due to asthma in the last 6 months, and participation in another study.

The study was designed as a PAES, in line with Article 1(15) of Directive 2014/357/EC as a study related to an authorized medicinal product conducted within an authorized therapeutic indication aim of complementing

available efficacy data, which can be addressed only after authorization. According to Polish law, PAESs are not medical experiments and as such do not require either bioethics committee approval or informed consent from patients for their inclusion. Thus this study did not require ethics approval and it was not necessary to obtain informed consent from patients for their inclusion in this study.

The evaluation of therapy effectiveness and monitoring of adverse drug reactions was an element of routine patient management by the allergologists and pulmonologists. The study method included the collection of effectiveness and safety data during all three visits: on enrollment and during two control visits (the routine clinical checkups during therapy) with 8–12-week intervals. The doses of Bufomix Easyhaler® prescribed during each visit were recorded in the study questionnaire. The data were recorded in a study questionnaire completed at three subsequent control visits between May and November 2016.

Monitoring of Therapy and Its Effectiveness

Asthma control was assessed during each visit on the basis of the Asthma Control Test (ACT) [15]. The Medication Adherence Questionnaire (MAQ) was used for the assessment of adherence [16]. Patient satisfaction with the use of Bufomix Easyhaler® was analyzed on the basis of closed questions scored on a five-point scale (very easy/quite easy/not so easy/not easy/hard); see Table 1. In addition, overall self-assessment of the inhaler and the complexity of the instructions for use of the inhaler (on a six-point scale) was done by the patient during the three visits.

Adverse drug reactions were recorded during all three visits.

Data Analysis

The primary end point was the percentage of patients with well-controlled asthma or total control of asthma (ACT score 20–25 points) and the percentage of patients with poor control of asthma (ACT score less than 15 points).

Adherence to Bufomix Easyhaler® treatment was scored on the basis of the MAQ as follows: adherent (2 points or less) or nonadherent (more than 2 points).

Sixty-four patients (3% of the study population) were excluded from the analysis of Bufomix Easyhaler® efficacy. Twenty-nine patients were lost to follow-up during the observation period (for 11 patients the first visit was the last attended, and for 18 patients the second visit was the last attended). Thirty-five patients stopped the treatment (1.6% of the study population)—25 patients before the first visit and 10 before the second visit. Therefore efficacy data were calculated for 2136 patients (safety data were calculated for the whole group of patients enrolled; $N = 2200$).

The total exposure to Bufomix Easyhaler® was calculated from the first visit while receiving therapy to the day of therapy cessation

Table 1 Closed questions used to score patient satisfaction with the use of Bufomix Easyhaler®

How does the patient assess the degree of difficulty in learning how to use the inhaler?
How does the patient assess the degree of difficulty in preparing the inhaler for use?
How does the patient assess the degree of difficulty of handling the inhaler in everyday life?
How does the patient assess the degree of difficulty in performing inhalation in everyday life?
How does the patient assess the degree of difficulty to keep the inhaler clean and ready for use?
How does the patient assess the degree of difficulty for performing activities of daily living (e.g., sports) with the inhaler with him/her?
How does the patient assess the degree of difficulty in handling the inhaler in terms of weight, size, and portability?

Scored on a five-point scale (very easy/quite easy/not so easy/not easy/hard)

reported by the patient, or the day of the last visit.

Statistical Analysis

Analyses were performed with STATISTICA 10.0 PL (StatSoft). All data are expressed as percentages or means with standard deviations. The χ^2 test, χ^2 for trend, and analysis of variance were used to compare variables within the group. A p value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The characteristics of the study patients are given in Table 2. According to the Global Initiative for Asthma 2015 classification [8], most patients had mild chronic asthma (32.6%) or moderate persistent asthma (59.8%). More than half of the patients had been treated for asthma for more than 5 years. Before the initiation of therapy with Bufomix Easyhaler®, 54.6% of them were using an ICS and 33.4% were using a LABA with an ICS separately.

In all patients, therapy included Bufomix Easyhaler®, usually used twice daily (93.8%) (Table 2) for at least 2 weeks. Some of the patients continued the therapy for 12 weeks. In addition, 13.9% were advised to continue using another ICS or 0.9% oral corticosteroid at the time of the first control visit after prescription of Bufomix Easyhaler®. Short-acting β_2-agonists were used by 43.3% of patients. Concomitant diseases and their medication were reported in 1058 patients (48.1%).

Patients prescribed the higher Bufomix Easyhaler® doses were significantly older, had more concomitant medication, a longer history of asthma, and its more severe clinical presentation (greater prevalence of moderate and severe persistent disease), and were more frequently receiving a LABA with an ICS separately before starting combination therapy (Table 2).

Efficacy Data for Bufomix Easyhaler®

The mean period of exposure to Bufomix Easyhaler® covered by this analysis of efficacy was 142 ± 27 days, from the first visit to the third visit. There was a small insignificant shift in the number of patients from the use of 320/9 μg per inhalation strength toward the use of 160/4.5 μg per inhalation strength during the observation (Table 3). The drop-out of patients from the study groups could impact this observation.

At the first visit, 46.6% of patients had well-controlled or total control of asthma (ACT score 20–25 points) (Table 3). The percentage of patients with well-controlled or total control of asthma increased to 90.8% at the third visit ($p < 0.001$). The increase was observed for patients treated with 320/9 μg per inhalation strength (from 41.1% to 87.7%; $p < 0.001$) and for patients treated with 160/4.5 μg per inhalation strength (from 55.0% to 95.5%; $p < 0.001$). In addition, the percentage of patients with poor control of asthma (ACT score less than 15 points) decreased from 14.9% at the first visit to 1.2% at the third visit ($p < 0.001$); see Fig. 1.

The mean ACT score increased by 4.3 points in the whole group, and by 4.5 and 4.2 points in the subgroups receiving higher and lower drug doses, respectively (Table 4).

All patients discontinued therapy with oral steroids during the study period.

The adherence to the use of Bufomix Easyhaler® increased from 88.0% at the first visit to 95.3% at the third visit (Table 3).

Patient Satisfaction with the Use of Bufomix Easyhaler®

Patient satisfaction with the use of the inhaler increased with the duration of use. The percentage of patients who rated the learning to use, using, and handling the inhaler in everyday life as “not so easy,” “not easy,” or “hard” was about 10% at the first visit. The number of patients reporting problems in their use decreased throughout the study, reaching only 3% of the population at the end of study (Table 4). The overall assessment of the inhaler

Table 2 Characteristics of the study patients

	All patients ($N = 2200$)	BUFOMIX Easyhaler® dose		p
		160 µg budesonide + 4.5 µg formoterol fumarate ($N = 873$)	320 µg budesonide + 9 µg formoterol fumarate ($N = 1327$)	
Age (years)	49.8 ± 17.9	46.3 ± 16.4	54.4 ± 15.3	< 0.001
Sex				
Male	984 (44.7%)	371 (42.5%)	613 (46.2%)	NS
Female	1216 (55.3%)	502 (57.5%)	714 (53.8%)	
Duration of asthma therapy				
<3 months	77 (3.5%)	36 (4.1%)	41 (3.1%)	< 0.001[a]
3–6 months	81 (3.7%)	44 (5.0%)	37 (2.8%)	
6–12 months	147 (6.7%)	83 (9.5%)	64 (4.8%)	
2–3 years	368 (16.7%)	178 (20.4%)	190 (14.3%)	
4–5 years	347 (15.8%)	126 (14.4%)	221 (16.7%)	
>5 years	1180 (53.6%)	406 (46.5%)	774 (58.3%)	
Severity of asthma according to the GINA 2015 classification				
Intermittent asthma	52 (2.4%)	33 (3.8%)	19 (1.4%)	< 0.001[a]
Mild chronic asthma	718 (32.6%)	422 (48.3%)	296 (22.3%)	
Moderate persistent asthma	1316 (59.8%)	406 (46.5%)	910 (68.8%)	
Severe persistent asthma	114 (5.2%)	12 (1.4%)	102 (7.7%)	
Concomitant medication for asthma before introduction of BUFOMIX Easyhaler®				
Short-acting β_2-agonist	1601 (72.8%)	605 (69.3%)	996 (75.1%)	0.01
Inhaled corticosteroid	1202 (54.6%)	497 (56.9%)	705 (53.1%)	NS
Long-acting β_2-agonist	36 (1.6%)	0	36 (2.7%)	< 0.001
Inhaled corticosteroid + long-acting β_2-agonist separately	734 (33.4%)	254 (29.1%)	480 (36.2%)	0.003
Antileukotriene drug	536 (24.4%)	214 (24.5%)	322 (24.3%)	NS
Short-acting anticholinergic drug	162 (7.4%)	56 (6.4%)	106 (8.0%)	NS

Table 2 continued

	All patients ($N = 2200$)	BUFOMIX Easyhaler® dose		p
		160 µg budesonide + 4.5 µg formoterol fumarate ($N = 873$)	320 µg budesonide + 9 µg formoterol fumarate ($N = 1327$)	
Tiotropium	44 (2.0%)	5 (0.6%)	39 (2.9%)	0.001
Theophylline	234 (10.6%)	52 (6.0%)	182 (13.7%)	< 0.001
Oral corticosteroid	54 (2.5%)	11 (1.3%)	43 (3.2%)	0.01
BUFOMIX Easyhaler® daily schedule				
Once daily	77 (3.5%)	38 (4.4%)	39 (2.9%)	NS
Once daily and as needed	55 (2.5%)	55 (6.3%)	0	–
Twice daily	1735 (79.0%)	447 (51.4%)	1288 (97.1%)	< 0.001
Twice daily and as needed	329 (15.0%)	329 (37.9%)	0	–
Concomitant medication for asthma				
Short-acting β_2-agonist	952 (43.3%)	295 (33.8%)	657 (49.5%)	< 0.001
Inhaled corticosteroid	305 (13.9%)	93 (10.6%)	212 (16.0%)	< 0.001
Antileukotriene drug	178 (8.1%)	68 (7.8%)	110 (8.3%)	NS
Short-acting anticholinergic drug	97 (4.4%)	97 (11.1%)	0	–
Tiotropium	28 (1.3%)	19 (2.1%)	9 (0.7%)	0.002
Theophylline	139 (6.3%)	36 (4.1%)	103 (7.8%)	< 0.001
Oral corticosteroid	20 (0.9%)	8 (0.9%)	12 (0.9%)	NS
Coexisting chronic diseases	1058 (48.1%)	324 (37.1%)	734 (55.3%)	< 0.001
Hypertension	705 (32.0%)	194 (22.2%)	511 (38.5%)	< 0.001
Lipid disorders	251 (11.4%)	70 (8.0%)	181 (13.6%)	< 0.001
Coronary artery disease	50 (2.3%)	10 (1.1%)	40 (3.2%)	0.004
Past myocardial infarction	34 (1.5%)	7 (0.8%)	27 (2.0%)	0.02
Stable coronary artery disease	87 (4.0%)	20 (2.3%)	67 (5.2%)	0.001
History of stroke	34 (1.5%)	7 (0.8%)	27 (2.0%)	0.02
Heart failure	47 (2.1%)	6 (0.7%)	41 (3.1%)	< 0.001
Heart arrhythmia	41 (1.9%)	9 (1.0%)	32 (2.4%)	0.02
Chronic kidney disease	8 (0.4%)	3 (0.3%)	5 (0.4%)	NS
Type 2 diabetes	155 (7.0%)	35 (4.0%)	120 (9.1%)	< 0.001

Table 2 continued

	All patients ($N = 2200$)	BUFOMIX Easyhaler® dose		p
		160 µg budesonide + 4.5 µg formoterol fumarate ($N = 873$)	320 µg budesonide + 9 µg formoterol fumarate ($N = 1327$)	
Type 1 diabetes	9 (0.4%)	3 (0.3%)	6 (0.5%)	NS
Obesity	120 (5.5%)	28 (3.2%)	92 (6.9%)	< 0.001
Allergic skin diseases	57 (2.6%)	22 (2.5%)	35 (2.6%)	NS
Psoriasis	9 (0.4%)	3 (0.3%)	6 (0.5%)	NS

GINA Global Initiative for Asthma, *NS* not significant
[a] χ^2 for trend.

(six-point scale) and assessment of the complexity of the instructions for use are shown in Table 5. Only a few patients assessed the inhaler as unsatisfactory or the inhaler instruction as "not easy" or "difficult" (Fig. 2).

Therapy Discontinuation and Adverse Drug Reactions

Therapy was discontinued in 35 patients (1.6% of the study population), including three patients with reported adverse events (xerostomia, cough, hoarseness after application), three patients in whom Bufomix Easyhaler® was considered ineffective, 12 patients who obtained alleviation of their asthma with time, nine patients in whom the therapy was modified by another physician, three patients for economic reasons, and single individuals because of difficulties in drug application and because of a pregnancy. In three patients the cause of discontinuation was not reported.

The single adverse drug reaction reported by a physician (a cough after application) was probably related to the use of Bufomix Easyhaler®.

DISCUSSION

This real-life nonrandomized, open-label PAES involved 2200 adult patients with asthma treated with two fix doses of budesonide/formoterol fumarate (Bufomix Easyhaler®). There were very limited exclusion criteria (known hypersensitivity to inhaler compounds) that differentiate this study from randomized clinical trials. According to clinical judgment, patients with a more severe presentation of asthma more frequently received higher doses. The results obtained demonstrate that most patients treated with budesonide/formoterol fumarate combination therapy (Bufomix Easyhaler®) may obtain good or complete control of asthma (ACT score 20–25 points). During the study (mean duration 142 days), the proportion of patients with well-controlled asthma or total control of asthma increased from 46.6% to 90.8%. The increase was observed regardless of the prescribed dose; however, because of inclusion of a large number of patients with moderate or severe asthma in the group receiving the higher dose (320/9 µg) compared with the lower dose (160/4.5 µg), a smaller proportion of those with well-controlled asthma or total control of asthma was observed in higher-dose group, both at the first visit (18.5% vs 9.4%) and at the third visit (87.7% vs 95.5%). The results of our study may be compared with real-life data reported from an Italian cohort [17]. A fixed combination therapy with an ICS and a LABA was used by 77.0% of patients, resulting in full or good control of asthma in 80.9% after 12 months.

The methodology of our study differs from those of previous studies usually assessing asthma exacerbation during ongoing therapy. Recently, Peters et al. [18] reported asthma

Table 3 The assessment of fixed-dose budesonide/formoterol fumarate combination therapy (Bufomix Easyhaler®) efficacy and changes in Asthma Control Test (ACT) score

	1st visit ($N = 2200$)	2nd visit ($N = 2168$)	3rd visit ($N = 2136$)	ANOVA, χ^2 for trend
Bufomix Easyhaler® 160/4.5 μg (%)	39.5	39.1	40.6	NS
Bufomix Easyhaler® 320/9.0 μg (%)	60.5	60.9	59.4	
Number of daily doses applied	1.96 ± 0.03	1.97 ± 0.03	1.95 ± 0.03	NS
Adherence (%)	88.0	96.2	95.3	$p < 0.001$
All patients				
ACT score (points)	18.6 ± 4.2	21.6 ± 3.1	22.9 ± 2.5	$p < 0.001$
ACT score <15 points	328 (14.9%)	56 (2.6%)	26 (1.2%)	1st visit vs 2nd visit $p < 0.001$
ACT score 15–19 points	847 (38.5%)	399 (18.4%)	171 (8.0%)	
ACT score ≥20 points	1025 (46.6%)	1713 (79.0%)	1939 (90.8%)	1st visit vs 3rd visit $p < 0.001$
				2nd visit vs 3rd visit $p < 0.001$
Initial dose of Bufomix Easyhaler® 160/4.5 μg				
ACT score (points)	19.5 ± 3.9	22.5 ± 2.6	23.7 ± 1.9	$p < 0.001$
ACT score <15 points [*N*; %]	82 (9.4%)	8 (0.9%)	2 (0.2%)	1st visit vs 2nd visit $p < 0.001$
ACT score 15-19 points	309 (35.6%)	105 (12.3%)	36 (4.3%)	1st visit vs 3rd visit
ACT score ≥20 points	478 (55.0%)	742 (86.8%)	806 (95.5%)	$p < 0.001$
				2nd visit vs 3rd visit $p < 0.001$
Initial dose of Bufomix Easyhaler® 320/9.0 μg				
ACT score (points)	18.0 ± 4.3	21.0 ± 3.3	22.5 ± 2.7	$p < 0.001$
ACT score <15 points	246 (18.5%)	48 (3.7%)	24 (1.9%)	1st visit vs 2nd visit
ACT score 15–19 points	538 (40.4%)	294 (22.4%)	135 (10.4%)	$p < 0.001$
ACT score ≥20 points	547 (41.1%)	971 (73.9%)	1133 (87.7%)	1st visit vs 3rd visit $p < 0.001$
				2nd visit vs 3rd visit $p < 0.001$

ANOVA applies for ACT scores expressed in points with standard deviation. The others are chi square
ANOVA analysis of variance, *NS* not significant

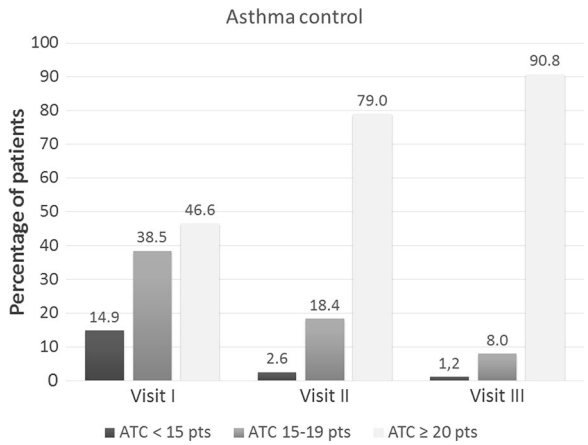

Fig. 1 Asthma control obtained with fix-dosed budesonide/formoterol fumarate combination therapy (Bufomix Easyhaler®) during three visits ($p < 0.001$; χ^2 for trend). ATC Asthma Control Test, pts points

exacerbation in about 10% of patients treated with budesonide/formoterol for 180 days. However, it seems that changes in the ACT score better measure real-life day-to-day asthma control, especially in patients with mild to moderate asthma, in whom the risk of exacerbation is relatively low. Therefore, the ACT score is a much better primary end point in such a group of patients with asthma such as ours.

The effectiveness of therapy for chronic diseases such as asthma is limited by patient adherence [19], which in our study, self-assessed (MAQ), progressively increased from 88% to 95%. Patient adherence is bidirectionally affected by satisfaction with use of the drug and its tolerance. Our study showed that the proportion of satisfied patients was more than 90%. Overall, patients considered Bufomix Easyhaler® as portable, easy to use, and easy to keep clean during daily activities. This statement is supported by the very low number of patients who discontinued its use. Over the time of observation, only one patient stopped using Bufomix Easyhaler® because of difficulties in dosing.

Our data are in line with previous findings. Gálffy et al. [20] reported that 97% of patients with asthma were very satisfied or satisfied with the use of Bufomix Easyhaler®, 77% achieved its correct use with just one demonstration, and it was easy to teach 92% of patients how to handle the inhaler. In the other study comparing patient satisfaction with the use of Bufomix Easyhaler®, patients who had previously used another pressure inhaler appreciated its easy preparation before inhalation and the ease of keeping it clean [21]. Also other studies confirm easy handling of Bufomix Easyhaler® in the patients' everyday life [4, 11, 13, 22–24].

It should be stressed that the physicians participating in this study reported a single adverse event (a cough after application). This supports the safety profile of Bufomix Easyhaler® formulations, at least in patients with asthma. A potential reason for such a low number of adverse events in our study in relation to controlled randomized trials was the lack of on-site monitoring.

Another important aspect of Bufomix Easyhaler® covered by this analysis was treatment discontinuation related to drug ineffectiveness. According to the clinical judgment of the investigators, the proportion was very low—0.14% (three patients). However, ineffectiveness might be the cause of therapy modification by another physician in an additional nine patients. In this case we can conclude that the ineffectiveness was not greater than 0.55%.

The main limitation of the current study was the lack of on-site monitoring by a contract research organization and the lack of on-site verification of original medical documentation regarding efficacy data and adverse events by qualified staff. It is not known how many patients who started therapy with Bufomix Easyhaler® under the care of allergologists and pulmonologists participating in the study and discontinued therapy before the first (enrolment) visit were not observed during the study. Furthermore, the adherence was probably overestimated as it was assessed on the basis of self-reported data, with use of the MAQ.

CONCLUSION

The results obtained confirm the clinical effectiveness of Bufomix Easyhaler® in the treatment of asthma in adult outpatients in routine daily clinical practice.

Table 4 Patient satisfaction with the use of Bufomix Easyhaler®

	Visit	Very easy (%)	Quite easy (%)	Not so easy (%)	Not easy (%)	Hard (%)
Difficulty level of learning how to use the inhaler	1	45.1	43.5	10.1	1.1	0.1
	2	62.5	34.2	3.1	0.1	0
	3	69.7	28.5	1.8	0	0
χ^2 for trend		2nd visit vs 1st visit, $p < 0.001$; 3rd visit vs 1st visit, $p < 0.001$				
Difficulty level of preparation of the inhaler for use	1	48.9	41.4	9.1	0.6	0
	2	63.8	32.8	3.3	0.1	0
	3	71.5	26.9	1.5	0.1	0
χ^2 for trend		2nd visit vs 1st visit, $p < 0.001$; 3rd visit vs 1st visit, $p < 0.001$				
Difficulty level of daily use of the inhaler	1	50.3	40.9	8.0	0.8	0
	2	64.7	31.9	3.2	0.1	0
	3	71.8	26.6	1.6	0	0
χ^2 for trend		2nd visit vs 1st visit, $p < 0.001$; 3rd visit vs 1st visit, $p < 0.001$				
Difficulty level of inhalation in everyday life	1	51.0	41.1	7.0	0.9	0.1
	2	65.8	30.8	3.5	0	0
	3	71.4	26.0	1.6	0	0
χ^2 for trend		2nd visit vs 1st visit, $p < 0.001$; 3rd visit vs 1st visit, $p < 0.001$				
Difficulty level of keeping the inhaler clean and ready for use	1	48.1	41.9	9.2	0.8	0
	2	62.2	33.0	4.6	0.3	0
	3	69.2	27.9	2.7	0.2	0
χ^2 for trend		2nd visit vs 1st visit, $p < 0.001$; 3rd visit vs 1st visit, $p < 0.001$				
Difficulty level of performing activites of daily living (e.g., sports) with the inhaler with you	1	44.5	43.0	11.1	1.2	0.2
	2	59.4	35.0	5.1	0.5	0
	3	67.0	29.5	3.1	0.4	0
χ^2 for trend		2nd visit vs 1st visit, $p < 0.001$; 3rd visit vs 1st visit, $p < 0.001$				
Difficulty level of handling the inhaler in terms of weight, size, and portability	1	51.0	40.2	8.0	0.8	0.1
	2	64.3	32.0	3.5	0.2	0
	3	71.6	25.6	2.8	0	0
χ^2 for trend		2nd visit vs 1st visit, $p < 0.001$; 3rd visit vs 1st visit, $p < 0.001$				

Table 5 Overall assessment of the inhaler and complexity of the instructions for use of the inhaler (six-point scale)

	1st visit ($N = 2200$)	2nd visit ($N = 2168$)	3rd visit ($N = 2136$)	ANOVA
Overall assessment of the inhaler (points)	4.9 ± 1.9	5.2 ± 1.7	5.3 ± 1.6	< 0.01
Overall assessment of the complexity of the instructions for use of the inhaler (points)	4.2 ± 1.2	4.5 ± 1.2	4.6 ± 1.4	< 0.01

A score of 0 corresponds to complicated to use and a score of 6 corresponds to very easy to use.
ANOVA analysis of variance

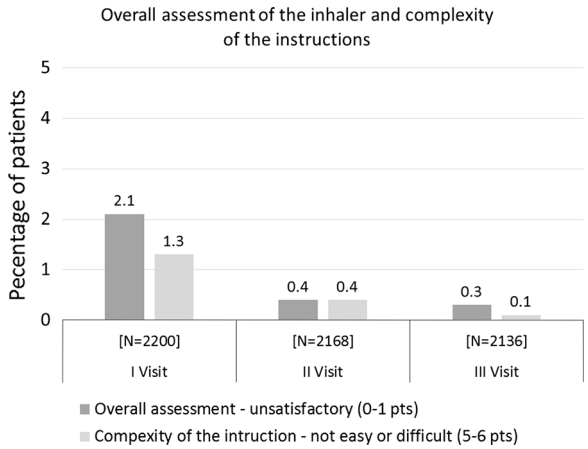

Fig. 2 The overall assessment of the inhaler and complexity of the instructions for use of the inhaler during three visits ($p < 0.001$; χ^2 for trend). pts points

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All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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Compliance with Ethics Guidelines. According to Polish law (Journal of Laws 2001, No 126. Pos. 1381), noninterventional studies are not medical experiments and as such do not require either bioethics committee approval or informed consent from the patients for their inclusion. To support compliance and ethics guidelines on postauthorization efficacy studies (Directive 2001/20/EC) that are conducted voluntarily, study information is available in the EU electronic register of postauthorization studies (EU PAS Register) maintained by the European Medicines Agency.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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