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Real-life effectiveness of extrafine beclometasone dipropionate/formoterol in adults with persistent asthma according to smoking status

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KEYWORDS
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Fixed combination;
Real-life effectiveness;
Smoking asthmatics

Summary
Background: The efficacy and safety of extrafine beclomethasone dipropionate 100 μg/formoterol 6 μg (BDP/F HFA) pressurized metered dose inhaler (pMDI) in patients with moderate-to-severe persistent asthma, has been demonstrated in randomised controlled trials (RCTs). The aim of this prospective observational study was to assess real-life effectiveness in terms of asthma control in smoking (most of the time excluded from RCTs) and non-smoking asthmatics.
Methods: Adult patients with persistent asthma, in whom treatment with an inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) combination is indicated, were included. Pulmonary function (FEV1%pred or PEF absolute value), Asthma Control Questionnaire (ACQ) and asthma control according to GINA criteria were measured at baseline as well as 2–8 months and >8–14 months after treatment initiation with BDP/F HFA.
Results: Overall, 619 patients were enrolled by 97 investigators. In the effectiveness cohort ($N = 568$), at baseline, smoking asthmatics ($N = 123$) had higher ACQ6 ($p < 0.0001$) and lower asthma control ($p = 0.021$) than non-smoking asthmatics. Treatment with BDP/F HFA pMDI was associated with significant ($p < 0.0001$) improvements in pulmonary function (+7.1% in FEV1% pred), ACQ6 (−1.32) and GINA asthma control (improvement of control in 49.8% of patients). Importantly, the same treatment benefits were observed in former or current smokers

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compared with non-smoking asthmatics. There was a reduction in the dose of ICS from 489 ± 192 μg BDP extrafine equivalents at baseline to 265 ± 125 μg after one year. The drug was well-tolerated.
Conclusion: This prospective cohort study demonstrates the real-life effectiveness and safety of BDP/F HFA in adult asthma patients, including smokers, in normal clinical practice.

Introduction

Asthma represents a global public health issue due to the high prevalence rates in the general population (ranging from 1% to 18% in the different European countries and 300 million people worldwide) and the impact and burden of asthma is even more pronounced due to the difficulty in achieving full disease control.[1,2] According to the Global Initiative for Asthma (GINA), achieving and maintaining asthma control should be the major goal of asthma care and there is now good evidence that the clinical manifestations of asthma, such as symptoms, sleep disturbances, limitations of daily activity, impairment of lung function and use of rescue medications, can be controlled with appropriate treatment.[3,4] The combination of a long-acting beta$_2$-agonist (LABA) and an inhaled corticosteroid (ICS) is currently the preferred treatment when a medium dose of ICS alone fails to achieve control of asthma in moderate to severe asthmatic patients. The addition of a LABA to an ICS in adult asthmatics indeed improves symptom scores and lung function compared to monotherapy with ICS, whereas it decreases nocturnal awakenings and the need for rescue treatment with short-acting beta$_2$-agonists (SABA).[3] In addition, combination therapy of LABA and ICS reduces the number of exacerbations and achieves asthma control more rapidly and with a lower dose of ICS than if ICS is given alone.[3]

The formulation of beclometasone dipropionate/formoterol (BDP/F; 100/6 μg) hydrofluoroalkane (HFA) in pressurized metered dose inhaler (pMDI) is characterized by extrafine particle size, which results in improved lung deposition and allows for uniform treatment of inflammation and bronchoconstriction throughout the entire bronchial tree.[5–8] The efficacy and safety of extrafine BDP/F HFA (100/6 μg), 1 to 2 puffs twice daily, in patients with moderate-to-severe persistent asthma, has been demonstrated in double-blind randomised controlled clinical trials (RCTs), versus placebo,[9–11] versus fluticasone/salmeterol 125/25 μg pMDI[12] and versus budesonide/formoterol 400/12 μg dry powder inhaler (DPI).[13]

Results of RCTs, ensuring high adherence to treatment and applying very selective inclusion/exclusion criteria, provide currently the cornerstone of clinical evidence in determining the efficacy of therapeutic interventions. They, however, do not guarantee that a particular therapy will be effective in the different patient populations seen in daily clinical practice on a long-term basis.[14] In the case of asthma, the eligibility criteria in most RCTs eliminate an estimated 95% of patients with a current diagnosis of asthma, since they exclude smoking asthmatics and patients who have co-morbidities, incomplete bronchodilator reversibility or impaired pulmonary function. Moreover, the design of such RCTs rarely accounts for the long-term factors that clinicians must consider, such as adherence, inhaler technique, tolerability, and physician and patient preferences. Observational studies can complement the findings from RCTs by assessing treatment effectiveness in real life and safety, in particular long-term safety and rare adverse events, in patients encountered in day-to-day clinical practice.[4,15–18]

The objective of this prospective observational one-year cohort study was to evaluate the real-life effectiveness of the extrafine BDP/F (100/6 μg) HFA pMDI formulation (Inuvair® or Foster®, Chiesi Farmaceutica Spa, Parma, Italy) in adult patients with moderate-to-severe persistent asthma. Since conducting this study was a requirement of the health care reimbursement official body in Belgium (INAMI/RIZIV), the study was initiated shortly after the introduction of the drug on the Belgian market. In accordance with the updated GINA guidelines, we investigated whether patients with moderate-to-severe persistent asthma achieved or maintained good asthma control upon treatment with extrafine BDP/F HFA in real life. Since (current and former) smoking asthmatics are excluded from classical RCTs, we were particularly interested in the real-life effectiveness of extrafine BDP/F in adult asthmatics according to their smoking status.

Methods

Study objectives

This was a Phase IV, observational, non-interventional, prospective, open-label, multicentre study. Its primary objective was to describe the patients who were being treated with extrafine BDP/F in terms of demographics, diagnosis and clinical stage of asthma, level of asthma control, treatment history and concomitant asthma medications. The secondary objectives were to assess the effectiveness and safety of extrafine BDP/F over 12 months in terms of asthma control in patients with persistent asthma. Asthma control was assessed by using the GINA classification (investigator's perspective) and the Asthma Control Questionnaire (ACQ) (patient's perspective).[19,20] Pulmonary function was determined, as per routine practice, using the percentage of predicted forced expiratory volume in 1 s (FEV_1 % pred) or the peak expiratory flow (PEF) absolute value. All pulmonary function measurements were performed pre-bronchodilator. Spontaneously reported adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) were coded using the Medical Dictionary for Regulatory Affairs (MedDRA). The reduction in ICS dose (expressed as extrafine BDP equivalents in accordance with

Paggiaro[21]: 100 μg of BDP in extrafine HFA formulation was equivalent to 250 μg of BDP in traditional chlorofluorocarbon [CFC] formulation) was calculated.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. It was approved by the Ethical Committee of the Ghent University Hospital, Ghent, Belgium, and by all local ethical committees of involved investigational centres. All patients participating in the study provided written informed consent.

Study design

The decision to prescribe BDP/F had been made by the physician (pneumologist or general practitioner [GP]) independently of his/her decision to include the patient in the study. The inclusion criteria were as follows: Man or woman aged at least 18 years with moderate-to-severe persistent asthma in which a combination of ICS and LABA was indicated. The diagnosis of asthma was confirmed according to the American Thoracic Society definition.[22] The exclusion criteria were as follows: Pregnant or lactating woman, hypersensitivity and/or allergy to BDP/F and/or any other ingredient of the drug, and contraindications to beta$_2$-agonists.

The patients were to be followed as per usual clinical practice. Three visits were proposed in accordance with real-life practice: an inclusion visit, a second visit after 2—8 months and a third visit after >8 up to 14 months. If additional visits were performed, data were only registered in case of change in asthma medication, drop-out, drug discontinuation or ADRs/SADRs.

Statistics

Due to the observational nature of this trial and the non-comparative design, there was no ethical or statistical concern linked to the sample size. It was thus preferable to include as many patients as possible in order to obtain the most representative and complete set of data.

A planned sample size of 660 patients was thus only based on the expected capacity to recruit patients in GPs and pneumologists (around 100 investigators in total) from Belgium within approximately 12 months.

Two groups were considered for the analyses: patients who were previously not well controlled on ICS only and who were stepped-up to BDP/F and patients who were already on ICS + LABA treatment. Predefined subgroup analyses separating current or former smokers, and non-smokers were also made.

The statistical analysis was essentially descriptive. Non-smokers and smokers (former or current) were compared using independent Student's *t* tests, Fisher's exact tests and chi-square tests. Inferential statistics were also used to compare the efficacy of extrafine BDP/F at the three time points. Paired Student's *t* test were used to assess the over-time modification of the pulmonary function, ACQ6 (6 questions) and ACQ7 (6 first questions plus FEV$_1$% pred or PEF absolute value) at the three time points. The modification of asthma control as a function of GINA criteria was compared between the three time points using chi-square tests. *p* values lower than 0.05 were considered statistically significant. Drop-outs or withdrawals were not replaced. Missing values were not replaced, nor extrapolated. IBM SPSS Statistics (Version 19.0, Chicago, Illinois, USA) was used throughout the statistical analyses.

Results

Number of patients enrolled and attrition from the study

Overall, 619 patients (Safety cohort) with persistent asthma were included by 97 investigators in Belgium: 291 patients were recruited by 34 pneumologists and 328 patients were recruited by 63 GPs. A total of 568 patients (Effectiveness cohort) had ACQ6 data at baseline and were available for the effectiveness analyses: 370 patients participated in Visit 2 (61—240 days after inclusion; mean = 168 days) and 340 patients completed the study (Visit 3; >240 days after inclusion; mean = 358 days). A total of 143 patients were lost to follow-up and 52 patients prematurely discontinued the study (Fig. 1): 18 patients (3.17%) prematurely discontinued the study for Adverse Events (AEs) or Adverse Drug Reactions (ADRs), encompassing palpitations (5 patients), oral candidiasis (3 patients), cough (1 patient), dyspepsia (1 patient) and other reasons (7 patients). One patient, a 75 year-old male smoker with diabetes, suffered from a cerebrovascular accident leading to aspiration pneumonia and death; this serious adverse event (SAE) was considered to be not related to the study drug.

Demographics and baseline characteristics

Demographics and baseline characteristics of the patient population (effectiveness cohort, non-smokers and smokers) are described in Table 1. The majority of patients were Caucasian (97.7%). The smoking status was as follows: 445 non-smokers and 123 smokers (current smokers + patients having stopped smoking for less than 1 year).

ACQ7 score was 2.23 ± 1.13 and ACQ6 score was 2.19 ± 1.17. Considering the fact that the majority of patients (79.8%) were already on maintenance treatment

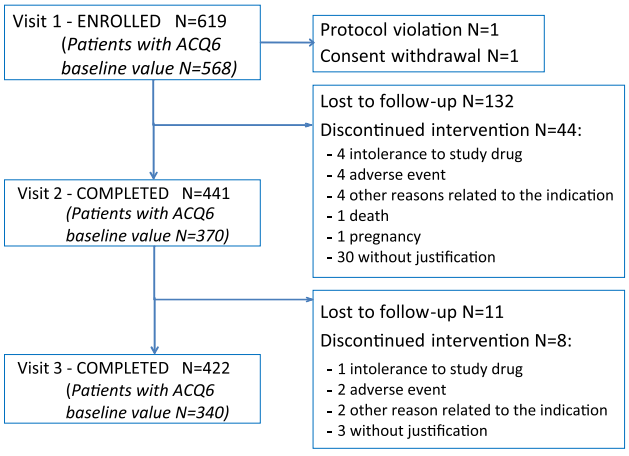

Figure 1 Patient flow chart.

Table 1 Demographics and baseline characteristics of the patient population (patients with ACQ6 measured at baseline [$N = 568$], non-smokers and smokers [former or current]).

	Total cohort with ACQ6 at baseline			Non-smokers ($N = 445$)			Smokers ($N = 123$)			p-value
	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Age (year)	568	48.6	16.9	445	50.2	17.0	123	42.7	15.6	<0.0001
Asthma duration (year)	461	11.9	15.6	362	12.1	15.8	96	10.9	15.0	0.511
Age at onset of asthma (year)	461	36.4	20.1	362	37.8	20.6	96	31.2	17.4	0.002
FEV_1 % pred	368	78.6	19.7	277	79.4	19.9	86	76.4	19.6	0.225
PEF absolute value (l/min)	89	269	189	70	276	192	19	243	180	0.502
ACQ7	395	2.23	1.13	300	2.14	1.17	92	2.51	0.96	0.002
ACQ6	568	2.19	1.17	445	2.11	1.19	123	2.50	1.03	<0.0001
	N	%		N	%		N	%		
Gender	568			445			123			
Female	305	53.7		231	51.9		74	60.2		0.126
Male	263	46.3		214	48.1		49	39.8		
Control of asthma[a]	568			445			123			
Controlled	33	5.8		32	7.2		1	0.8		
Partially controlled	419	73.8		319	71.7		100	81.3		
Uncontrolled	80	14.1		62	13.9		18	14.6		0.021
Missing information	36	6.3		32	7.2		4	3.3		

FEV1% pred = Predicted percentage of forced expiratory volume in 1 s; PEF = Peak Expiratory Flow; ACQ = Asthma Control Questionnaire.
Statistical comparisons between non-smokers and smokers (p values): Independent Student's t tests for continuous variables, Fisher's exact test for gender and chi-square test for control of asthma according to GINA.
[a] According to GINA = Global Initiative for Asthma.

for asthma, the pulmonary function measurements and ACQ scores were indicative of a population with moderate-to-severe asthma.

Overall, smokers tended to have lower pulmonary function (FEV_1 % pred [$p > 0.05$] and PEF [$p > 0.05$]) and worse asthma control (ACQ6 [$p < 0.0001$], ACQ7 [$p = 0.002$] and GINA classification [$p = 0.021$]) at baseline compared to non-smokers (Table 1).

Overall, 453 (79.8%) patients were reported to be already on asthma treatment. In 23.2% of patients it corresponded to a step-up treatment (replacement of ICS) and in 72.2% of patients BDP/F replaced another combination of ICS + LABA.

Other pathologies in relation with asthma were recorded in 172 patients (30.3%). The predominant co-morbidities were allergy (64.5%) and chronic bronchitis, chronic obstructive pulmonary disease or emphysema (6.3%).

Real-life effectiveness of extrafine BDP/F HFA

In the effectiveness cohort, extrafine BDP/F induced a significant improvement of the pulmonary function measured as FEV_1 % pred (increase of 8.1% and 7.1% at Visits 2 and 3, respectively [$p < 0.0001$]) (Fig. 2) or as PEF absolute value (increase of 90.7 l/min at Visit 2 [$p = 0.067$] and 113.2 l/min at Visit 3 [$p = 0.002$]) (Fig. 3), during the entire period of observation. The ACQ7 (Fig. 4) and ACQ6 (Fig. 5) scores, completed by the patients, significantly improved by 1.16 and 1.22 unit ($p < 0.0001$) at Visit 2 and by 1.17 and 1.32 unit ($p < 0.0001$) at Visit 3, respectively. The minimum clinically important difference (MCID) in the ACQ scores is considered to be 0.5 unit.[20] The control of asthma as judged by the treating physicians according to the GINA criteria, also improved significantly: 92.0% of patients maintained (42.2%) or improved (49.8%) asthma

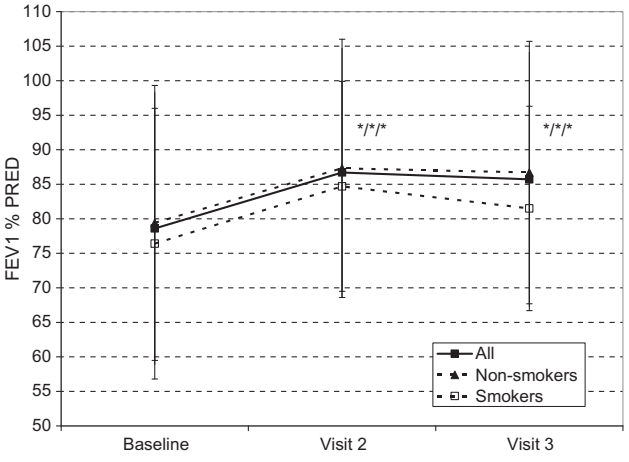

Figure 2 Pulmonary function measured by spirometry: percentage of predicted forced expiratory volume in 1 s (FEV1% pred) at baseline, visit 2 (after ±6 months of treatment) and visit 3 (after ±12 months of treatment) (mean ± standard deviation; paired Student's t tests; */*/*$p < 0.0001$ versus baseline for all patients, non-smokers and active/former smokers, respectively).

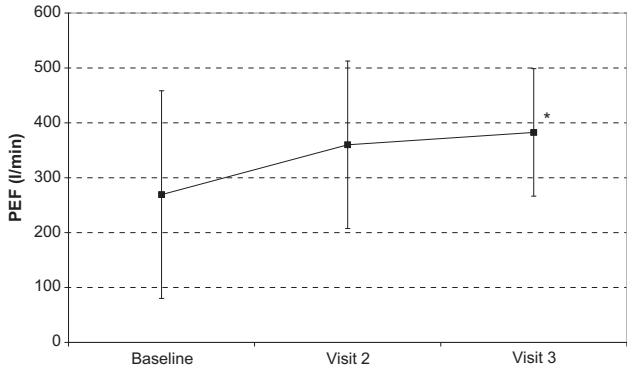

Figure 3 Pulmonary function measured by peak flow: peak expiratory flow (l/min) at baseline, visit 2 (after ±6 months of treatment) and visit 3 (after ±12 months of treatment) (mean ± standard deviation; paired Student's *t* tests; *$p = 0.002$ versus baseline).

control at Visit 3 ($p < 0.0001$) (Fig. 6). Importantly, there was a reduction in the dose of ICS from 489 ± 192 μg BDP extrafine equivalents at baseline to 273 ± 122 μg at Visit 2 and 265 ± 125 μg at Visit 3 under treatment with extrafine BDP/F (Fig. 7). In Figs. 8 and 9, the effectiveness of extrafine BDP/F HFA on pulmonary function (FEV1 %pred) and on asthma control (ACQ6) is shown according to the maintenance treatment at baseline: either ICS monotherapy or another combination of ICS + LABA.

Effectiveness of extrafine BDP/F HFA in smoking asthmatics

In the cohort of smokers (former or current), FEV_1 % pred increased significantly by 8.3% ($p < 0.0001$) and 5.1% ($p < 0.0001$) at Visit 2 and Visit 3, respectively (Fig. 2). PEF was measured in a too small number of patients to stratify the analysis by smoking status. ACQ7 and ACQ6 decreased

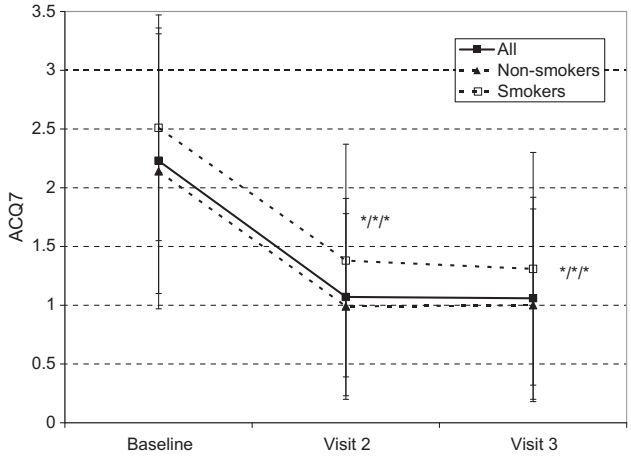

Figure 4 Asthma Control Questionnaire (ACQ7; 6 questions + FEV1% pred or PEF % pred) at baseline, visit 2 (after ±6 months of treatment) and visit 3 (after ±12 months of treatment) (mean ± standard deviation; paired Student's *t* tests; */*/*$p < 0.0001$ versus baseline for all patients, non-smokers and active/former smokers, respectively).

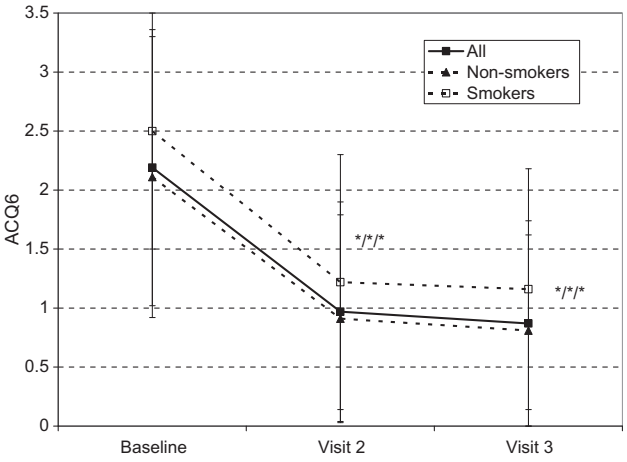

Figure 5 Asthma Control Questionnaire (ACQ6; 6 first questions) at baseline, visit 2 (after ±6 months of treatment) and visit 3 (after ±12 months of treatment) (mean ± standard deviation; paired Student's *t* tests; */*/*$p < 0.0001$ versus baseline for all patients, non-smokers and active/former smokers, respectively).

significantly by 1.1 and 1.3 unit at Visit 2 ($p < 0.0001$), and by 1.2 and 1.3 unit at Visit 3 ($p < 0.0001$), respectively (Figs. 4 and 5). Approximately 91% of patients maintained (44.4% and 42.6%) or improved (45.8% and 47.5%) asthma control according to GINA criteria at Visit 2 ($p = 0.127$) and Visit 3 ($p = 0.016$), respectively. All comparisons between smokers and non-smokers in terms of outcome measures of effectiveness (pulmonary function, patient-completed ACQ and physician-judged control of asthma according to GINA criteria) did not reveal any significant differences in therapeutic response to BDP/F HFA pMDI ($p > 0.05$).

Safety

In the safety cohort ($N = 619$), 16 ADRs were reported by 15 patients (2.42%). The majority of these ADRs were in line with the Summary of Product Characteristics of BDP/F HFA pMDI. In particular, palpitations ($N = 5$) and headache ($N = 1$) are well-known side effects of LABA and oral/oesophageal candidiasis ($N = 5$) are well-known side effects of ICS. Serious adverse events were reported in 3 patients, but none was considered related to the investigational drug. All together, 22 patients (3.55%) prematurely discontinued the study for adverse events or ADRs.

Discussion

This prospective one-year observational cohort study in adult asthmatics clearly demonstrates the real-life effectiveness of extrafine BDP/F (100/6 μg) HFA pMDI, leading to clinically and statistically significant improvements in pulmonary function (+7 to +8%) and asthma control, as evaluated by the patient (ACQ6: −1.2 to −1.3) or rated by the treating physician (according to the GINA criteria) (improvement in asthma control in 49.8% of patients).

However, since spirometry was measured during the follow-up in only a part of the subjects, the observation of

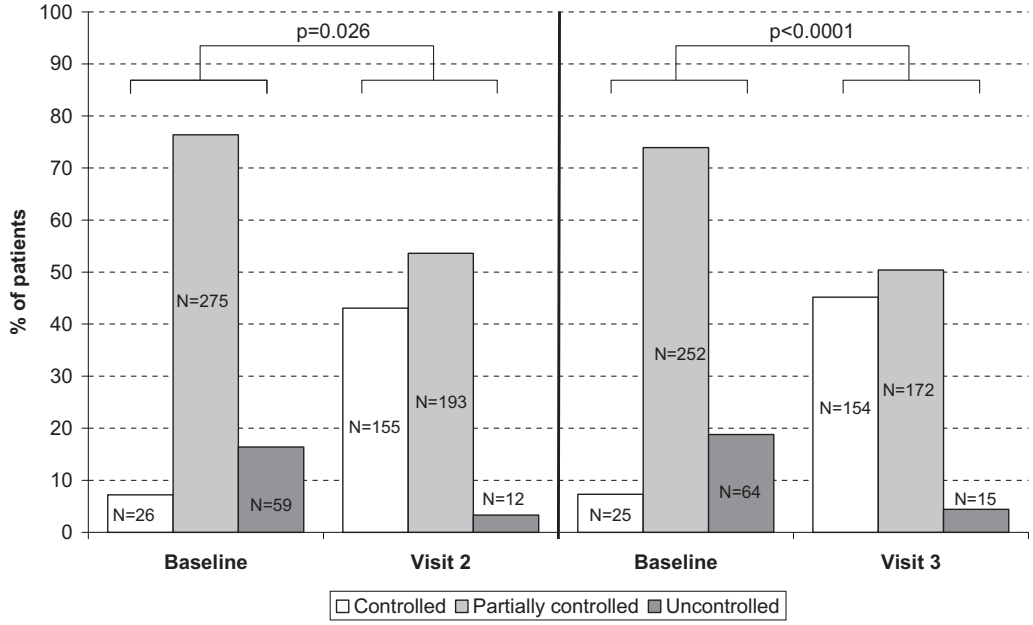

Figure 6 Comparison of the control of asthma according to the Global Initiative for Asthma (GINA) criteria between baseline and visit 2 (after ±6 months of treatment) as well as between baseline and visit 3 (after ±12 months of treatment) (number of patients at each visit; % of patients; Chi-square tests).

the improvement in FEV_1 should be interpreted with caution.

Importantly, smoking asthmatics had lower pulmonary function and worse asthma control at baseline compared to non-smoking asthmatics, which corroborates the observations made in other studies.[3,23,24] However, our study clearly demonstrates that the absolute improvements in lung function and asthma control upon treatment with extrafine BDP/F HFA are similar in magnitude in both smoking and non-smoking asthmatics.

The majority of patients suffering from moderate-to-severe asthma, were partially controlled (73.8%), and were already treated with a fixed combination of ICS and LABA for most cases (72.2%). The patient population included in this study is representative of the asthmatic population in Belgium in terms of age (±48 years), gender (slight predominance of women), age at onset of asthma (±36 years), asthma duration (±12 years) and smoking status (22% former or current smokers).[23,25]

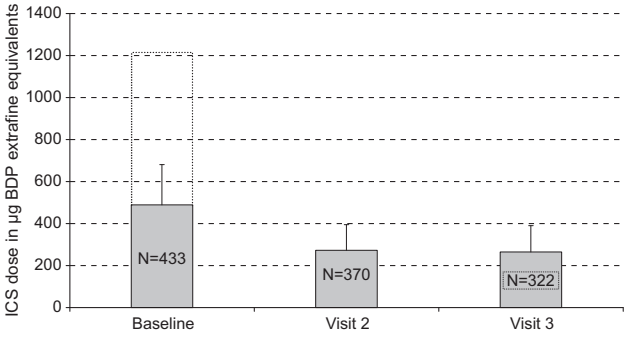

Figure 7 Over-time modification of the ICS dose (in µg beclometasone dipropionate [BDP] extrafine equivalents) between baseline (before starting the treatment with extrafine BDP/formoterol 100/6 µg) and visit 2 (after ±6 months of treatment), and visit 3 (after ±12 months of treatment) (number of patients at each visit; mean ± standard deviation). The surface delimited with dotted lines at baseline represents the ICS dose of chlorofluorocarbon-BDP non-extrafine equivalent (2.5 times the BDP extrafine dose).

ICS are known to be less effective in smokers than in non-smokers.[26,27] Interestingly, in the current study, the same benefits, in improving pulmonary function and asthma control, were also demonstrated in smokers (former or current), who are mostly excluded from RCTs. This improvement could be related to the drug particle size, which results in improved lung deposition and allows for uniform treatment of inflammation and bronchoconstriction throughout the entire bronchial tree,[5–8] without increasing systemic load.[21,28] In the START study, an improvement has also been observed in a subset of smoking patients with mild persistent asthma, in whom the benefits of therapy with budesonide in preventing lung function decline were similar in smokers and non-smokers.[29] The results of our study extend this observation to extrafine BDP/F used to treat smoking patients with moderate-to-severe persistent asthma.

Pharmacokinetic and pharmacodynamic characteristics that can enhance the efficacy of ICS include small particle size, high glucocorticoid receptor binding affinity, long-lasting pulmonary residence time and lipid conjugation.[30] During the course of this study, the BDP extrafine equivalent dose (calculated in accordance with Paggiaro[21]: 100 µg of BDP in extrafine HFA formulation is equivalent to 250 µg of BDP in traditional CFC formulation) decreased by 45%. This is also an important objective to achieve in order to limit the burden of chronic treatment with ICS in asthma care.[3] Safety of ICS is further increased in case of on-site

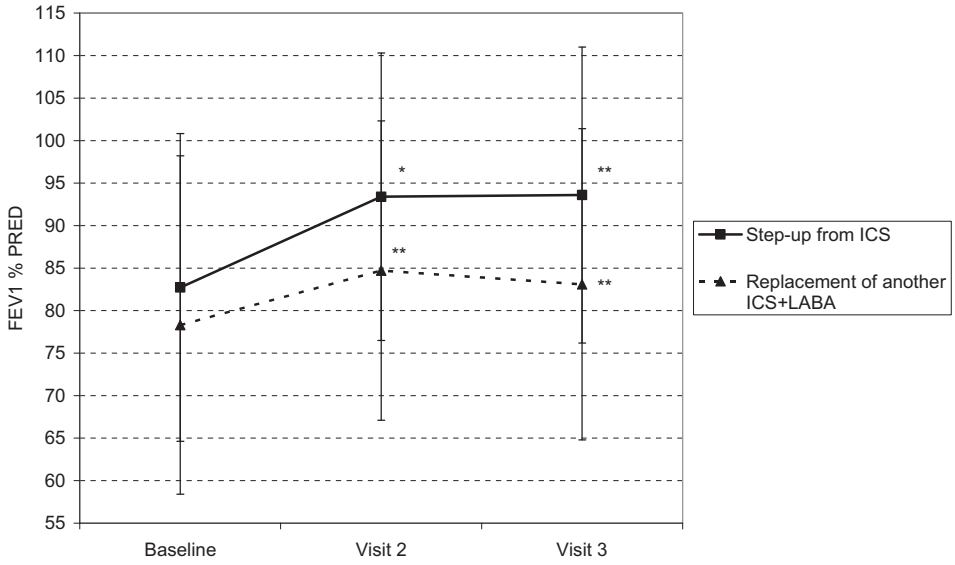

Figure 8 Pulmonary function measured by spirometry: percentage of predicted forced expiratory volume in 1 s (FEV1% pred) at baseline, visit 2 (after ±6 months of treatment) and visit 3 (after ±12 months of treatment) in patients who stepped-up from an ICS to extrafine BDP/F HFA or who received extrafine BDP/F HFA in replacement of another ICS + LABA (mean ± standard deviation; paired Student's *t* tests; **p* = 0.002 versus baseline and ***p* < 0.0001 versus baseline).

activation in the lung, low oropharyngeal exposure, negligible oral bioavailability and rapid systemic clearance.[30]

Extrafine BDP/F was well-tolerated in our cohort study. ADRs were in line with the well-known effects of formoterol and beclometasone.

Previously published RCTs found no differences between the effect of extrafine BDP/F and budesonide/formoterol or fluticasone/salmeterol on pulmonary function, use of rescue medications, exacerbations and safety.[12,13] In the real-life study of Muller et al.[1]patients treated with extrafine BDP/F achieved a greater level of asthma control as compared to patients treated with fluticasone/salmeterol and budesonide/formoterol larger particle size combinations. The results of the present study indirectly corroborate those of Muller et al.[1] and suggest that higher deposition of extrafine particles in the small airways might be contributing to these beneficial effects, particularly in smoking asthmatics.

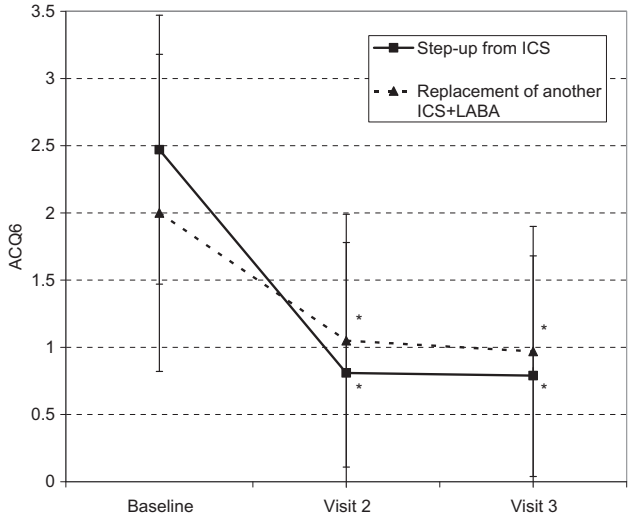

Figure 9 Asthma Control Questionnaire (ACQ6) as filled in by the patient at baseline, visit 2 (after ±6 months of treatment) and visit 3 (after ±12 months of treatment) in patients who stepped-up from an ICS to extrafine BDP/F HFA or who received extrafine BDP/F HFA in replacement of another ICS + LABA (mean ± standard deviation; paired Student's *t* tests; **p* < 0.0001 versus baseline).

Observational studies in large populations are useful to complement the findings from RCTs by assessing treatment effectiveness and safety in patients encountered in daily clinical practice.[4,15–18] Because observational studies do not exclude asthma patients who are smoking or who have co-morbidities, the present study contributes to a better assessment of the real-life effectiveness and safety of extrafine BDP/F (100/6 μg) in patients suffering from moderate-to-severe persistent asthma. However, the limitations of this observational study are also inherent to its design: no comparative data, no active patient follow-up, no data on treatment adherence, no measure of asthma exacerbations. In the present study, the drop-out rate is high (comparable in pneumologists and GPs), in particular between baseline and Visit 2 (30%), but much less between Visit 2 and Visit 3 (5%). The high rate of withdrawal may have selected more compliant patients with better outcomes from a more strict follow-up.

For a long time, observational studies were considered to overestimate the magnitude of treatment effects compared to RCTs. Literature reviews, covering 99 reports in 5 therapeutic areas on one hand and 136 reports for 19 diverse treatments on the other hand, among which asthma, tend to show that this is not the case.[31,32] However, we cannot make firm conclusions concerning a causal relationship of the observed associations in our study due to the observational study design.

In conclusion, the results of this large observational study demonstrate the real-life effectiveness and safety of extrafine fixed combination of BDP/F (100/6 μg) in adult patients with moderate-to-severe persistent asthma, encompassing statistically and clinically important improvements in pulmonary function and asthma control, despite a significant reduction in ICS dose. Interestingly, they also extend the same conclusions to smoking asthmatic patients.

Conflict of interest

Guy Brusselle has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pfizer and UCB Pharma. He is member of advisory boards for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline and Novartis.

Rudi Peché has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, Merck Sharp & Dohme, Novartis, Pfizer and UCB Pharma.

Paul Van den Brande has no particular conflict of interest.

Albert Verhulst is an employee of Chiesi SA/NV.

Wim Hollanders is an employee of UCB Pharma.

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