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Original Research

Real-world use of beclometasone dipropionate and formoterol fumarate NEXThaler® and asthma control among adult asthmatic patients in Europe: The results of the Newton study

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ABSTRACT

Purpose: The NEWTON study aims to describe clinical characteristics and evolution of asthma control of adult asthmatic patients treated with extrafine beclometasone dipropionate and formoterol fumarate (BDP/FF) NEXThaler® 100/6 μg.

Subjects and methods: NEWTON (NCT05168995) is a European multinational, multicentre, observational, prospective cohort study that included adults with uncontrolled or poorly controlled asthma, starting BDP/FF NEXThaler® 100/6 μg treatment within 14 days of enrolment and with no use of extrafine formulations in the previous 6 months. Improvement of asthma control, lung function, quality of life (QoL), treatment adherence, and satisfaction with the device were assessed after 3 and 6 months from the enrolment visit. In addition, safety events were monitored.

Results: 620 subjects were enrolled in the study. 423 completed the ACQ-5 questionnaire at enrolment and at least once during the following 6 months. 69.3 % of patients were initiated on maintenance and reliever treatment. At baseline, the median ACQ-5 score was 2.0. After 6 months the median ACQ-5 score had decreased significantly to 0.6 ($p < 0.0001$). Similarly, after 6 months 66.1 % of patients showed improved asthma control. The proportion of subjects with poorly controlled asthma fell from 65.1 % to 17.5 %. These improvements were consistent with the 3-month follow-up results and improved lung function, QoL, treatment adherence and device satisfaction. No new safety concerns were reported.

Conclusion: Results of the NEWTON study confirm the effectiveness and safety of the extrafine fixed combination of BDP/FF NEXThaler® 100/6 μg in adults with uncontrolled asthma in a real-world setting.

1. Introduction

Asthma is a heterogeneous disease characterised by chronic inflammation of the airways, affecting around 300 million people worldwide, with increasing prevalence and significant costs to society and the healthcare system [1–3]. According to the Global Initiative for Asthma (GINA), the goal of asthma treatment is to achieve the best possible long-term outcome for the subject, i.e., that symptoms remain under

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[1] sorted by descending frequency of evaluable patients.

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control in the long term and that the risk of exacerbations, a deterioration in lung function and the occurrence of adverse drug effects is minimized. The treatment of asthma should also aim to control the disease with the minimum amount of medication over a prolonged period, taking into account the tolerability of treatment, the potential for adverse effects and the cost [1,3].

In recent years, effective new pharmacological options or new combinations of existing drug therapies have become available [4]. In particular, real-world studies have shown better asthma control and better quality of life (QoL) may be achieved with extrafine beclometasone dipropionate (BDP)/formoterol fumarate (FF) compared to the fixed combinations budesonide/formoterol or fluticasone/salmeterol [5,6]. The fixed BDP/FF NEXThaler® 100/6 μg combination can be used as both maintenance and reliever treatment (MART), allowing patients to manage their asthma with a single inhaler and potentially improving adherence [7].

Advancements in pharmaceutical research have led to the development of fixed-dose combinations of BDP/FF 100/6 μg resulting in extrafine powder formulations also available in an innovative delivery device, the NEXThaler®. The extrafine formulation improves the deposition into the peripheral airways so that a larger proportion of the inhaled compound reaches the pharmacological target in the small airways while maintaining consistent efficacy and safety [8–10]. The NEXThaler® proved to be an effective, well-tolerated and easy-to-use delivery device for the administration of maintenance and reliever therapy [11–15].

Despite favourable results in clinical trials, there is a significant discrepancy between the GINA treatment goals and the actual level of asthma control achieved, as many patients still have poorly controlled asthma. Large-scale population studies are essential to understand asthma characteristics and treatment outcomes better. The NEWTON study, a multinational, real-world study, aimed to obtain a better understanding of asthma characteristics and to assess asthma control during treatment with BDP/FF NEXThaler® 100/6 μg in a European patient population over a follow-up period up to 6 months.

2. Material and methods

2.1. Study design and participants

NEWTON (NCT05168995) is a multinational, multicentre, observational, prospective cohort study to evaluate the effects of BDP/FF 100/6 μg fixed combination administered via a DPI (NEXThaler®) in a real-world context. Details of inclusion and exclusion criteria, study treatments, study objectives have been reported previously (https://doi.org/10.2147/JAA.S422832) [16]. The study was performed according to the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements and was approved by the ethics committees of all participating institutions before the start of enrolment and data collection [17]. The study involved 52 respiratory medicine centres in six European countries, of which 47 enrolled at least one patient (6 sites in France, 7 in Germany, 4 in Hungary, 19 in Italy, 5 in Romania, and 6 in Spain).

The study included adult subjects with not-well-controlled or poorly controlled asthma, according to the clinical assessment, who started treatment with BDP/FF NEXThaler® 100/6 μg at enrolment or no longer than 14 days before and who had not been treated with extrafine formulations in the 6 months before enrolment. Two study populations were defined: the Safety Analysis Set (SAF) and Full Analysis Set (FAS) (see details in Fig. 1).

2.2. Endpoints

The primary endpoint was the probability of improvement in asthma control status using the ACQ-5 score, 6 months after starting treatment with BDP/FF NEXThaler® 100/6 μg. The proportion of subjects whose ACQ-5 score had improved after 6 months compared to baseline was measured.

The secondary endpoints included other BDP/FF NEXThaler® 100/6 μg treatment effectiveness measures such as asthma control, quality of life, treatment adherence, lung function, patient satisfaction with the inhaler and asthma exacerbations after 3 and 6 months.

2.3. The safety profile was also evaluated

All adverse events starting at or after the informed consent signature

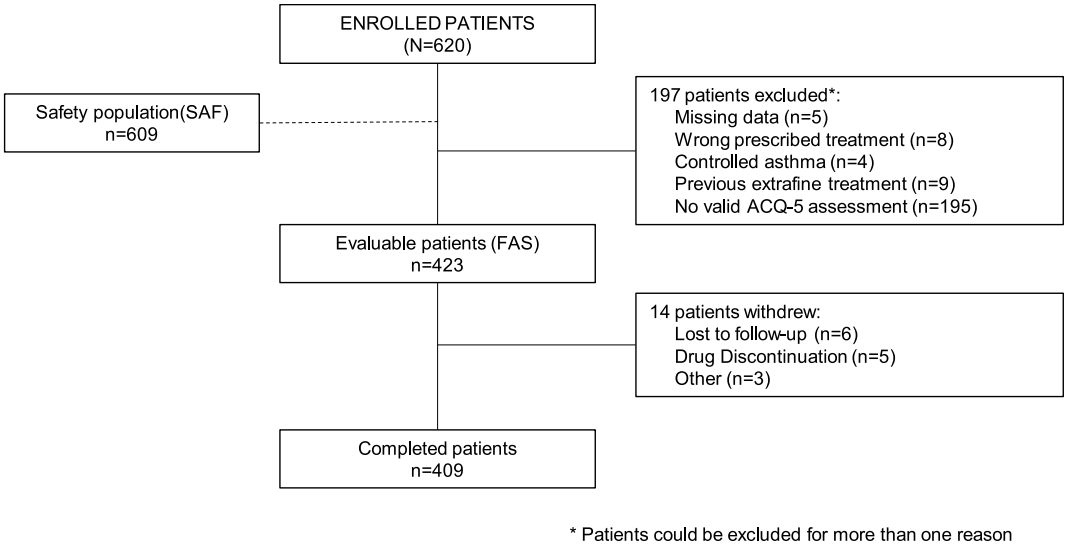

Fig. 1. Patient disposition
Safety Analysis Set (SAF): all enrolled subjects who signed informed consent form and received at least one administration of BDF/FF Nexthaler® 100/6 μg; Full Analysis Set (FAS): all eligible subjects who had a valid baseline assessment of ACQ-5 and at least one post-baseline assessment of ACQ-5 during the 6-month observation period (i.e. Evaluable Subjects);. The analysis of safety endpoints was performed in the SAF set. All other analyses (including primary and secondary endpoints) were performed in the FAS.

were classified as treatment emergent adverse events (TEAEs) and were included in the safety analysis.

2.4. Patient-reported outcomes (PRO) assessments

In the NEWTON study, the Bring Your Own Device approach was used, i.e. each participant completed the questionnaires/structured questions using their electronic device. The ePROs were completed at baseline and at the 3-month and 6-month during on site and/or remote visits (if foreseen by the clinical practice of the site). The study used the following questionnaires: (1) the ACQ-5 to assess asthma control, [18–20], (2) the EuroQol 5-dimension 5-level (EQ-5D-5L) to assess the health-related quality of life, [21,22], (3) the TAI-12 to assess treatment adherence and (4) a structured questionnaire consisting of three questions to assess satisfaction with the device (Fig. A1) [16,23]. ACQ-5 scores were classified into three groups ('grouped scores'): well-controlled asthma (ACQ-5 score ≤0.75); not well-controlled nor poorly controlled asthma (ACQ-5 score 0.75–1.5), or poorly controlled asthma (ACQ-5 score ≥1.5) [1,18–20]. EQ-5D-5L index scores can range from less than 0 to 1, with 0 being the value of a health state equivalent to death, negative values (<0) representing a health state worse than death, and 1 being the value of full health [21,22]. TAI scores in the range from 10 to 45 indicate 'poor adherence', between 46 and 49 indicate "intermediate adherence", and equal to 50 indicate 'good adherence') [23].

2.5. Statistical analyses

Continuous variables were described with the number of observations, median and interquartile range (IQR), while categorical variables were characterised by the number of subjects, percentages and 95 % confidence intervals (95 % CI), when applicable. Statistical tests to determine the significance of changes of primary and secondary endpoints over time and of group differences were performed at a 0.05 significance level (two-sided). The safety endpoints were analysed by counting the number of subjects (with calculated proportions) with TEAEs, TEAEs related to BDP/FF NEXThaler® 100/6 μg, serious adverse events (SAEs), SAEs related to BDP/FF NEXThaler® 100/6 μg, TEAEs leading to treatment discontinuation, TEAEs leading to death and specific special situations, if any. Missing data were not imputed, hence patients with missing data were excluded from the analyses of that variable(s), unless differently specified.

Analyses were performed using SAS Enterprise Guide v. 8.2 and SAS 9.4 (SAS Institute, Cary, NC, USA). Study design and conduct, data monitoring, eCRF set-up, and statistical analyses were performed by IQVIA Solutions Italy srl on behalf of Chiesi Italia S.p.A.

3. Results

3.1. Patient disposition and demographics

The study began in April 2022 (first patient, first visit) and was completed in February 2024 (last patient, last visit). The database was locked for analyses in April 2024.

A total of 620 subjects were enrolled in the study. Of those, 609 subjects started the treatment with BDP/FF NEXThaler® 100/6 μg at baseline or in the 14 days before baseline and were included in the SAF; 423 participants completed the ACQ-5 at baseline and at least once during the 6-month observation period (FAS population) (Fig. 1). The median observation period (IQR) in the FAS population was 6.2 months (6.0–6.5), which was in line with expectations.

The demographic and clinical characteristics of the FAS population are shown in Table 1 and Table A1: 67.8 % (n = 287) of subjects were female, 74.7 % (n = 316) were ≥35 years old, 65.0 % (n = 275) were non-smokers and 61.8 % (n = 254) were overweight or obese. The median time since diagnosis of asthma was 8.7 (IQR: 1.8–19.9) years.

Table 1
Demographic and clinical Characteristics at baseline.

Characteristics	Evaluable subjects (N = 423)
Gender (n, %)	
Male	136 (32.2 %)
Female	287 (67.8 %)
Age, years	
Median (IQR)	49.0 (34.0–61.0)
Mean (SD)	48.1 (17.2)
Age classes, n (%)	
18–34 years old	107 (25.3 %)
35–59 years old	194 (45.9 %)
≥60 years old	122 (28.8 %)
Smoking status, n (%)	
Non-smoker	275 (65.0 %)
Current smoker	67 (15.8 %)
Ex-smoker	81 (19.1 %)
Body Mass Index (BMI) classes, n (%)	**N = 411**
Underweight	7 (1.7 %)
Normal weight	150 (36.5 %)
Overweight	131 (31.9 %)
Obese	123 (29.9 %)
Median time since first asthma diagnosis, years, (IQR)	**N = 413** 8.7 (1.8–19.9)
Moderate or severe exacerbation in the previous 12 months, n (%)	**N = 419**
Yes	60 (14.3 %)
No	359 (85.7 %)
ACQ-5 score	
Median (IQR)	2.0 (1.2–3.0)

The percentages were calculated excluding the missing/unknown (unk) data for each considered variable (see the number of available observations, when reported [N =]).
ACQ-5: Asthma Control Questionnaire-5 items; IQR: interquartile range.

14.3 % (n = 60) of subjects had moderate or severe exacerbations in the previous 12 months. The median ACQ-5 score at baseline was 2.0 (IQR: 1.2–3.0). The majority (87.5 %, n = 370) reported not well or poorly controlled asthma. As the ACQ-5 score was not an eligibility criterion, there were also participants (12.5 %, n = 53) who reported a well-controlled level of asthma, according to the ACQ score.

92.0 % (n = 389) of subjects had been previously treated with inhaled asthma medications; among them, 74.8 % (n = 291) had used inhaled corticosteroids (ICS) (Table A2).

The physicians decided in favour of treatment with BDP/FF NEXThaler® 100/6 μg primarily for reasons including poor symptom control (93.9 %, n = 397, physicians' statements) and for reasons including the type of device and its formulation (38.3 %, n = 162). 69.3 % (n = 293) of subjects used BDP/FF NEXThaler® 100/6 μg as MART while 30.7 % received the treatment as maintenance only (Table A3).

3.2. Improvements in asthma control (ACQ-5 score) and treatment changes at the end of observation

Among the subjects who completed ACQ-5 at baseline and 6-months (n = 395), 66.1 % (n = 261, 95 % CI: 61.2–70.7) had improved their level of asthma control. In this subset of population, the median [IQR] ACQ-5 score significantly decreased (0.6 [0.0–1.2] vs. 2.0 [1.2–3.0], p < 0.0001, n = 395), which corresponded to a decrease of the proportion of subjects with poorly controlled asthma from 65.1 % (n = 257) to 17.5 % (n = 69). Taking together the proportion of subjects with not-well-controlled asthma and poorly controlled asthma, the proportion decreased from 87.6 % (n = 346) at baseline to 43.3 % (n = 171) at the 6-month follow-up (Fig. 2A). The median [IQR] ACQ-5 score significantly decreased also at the 3-month visit in comparison to baseline (0.8 [0.2–1.4] vs 2.2 [1.2–3.0], p < 0.0001, n = 359), which corresponded to a decrease of the proportion of subjects with poorly controlled asthma from 67.4 % (n = 242) to 19.2 % (n = 69). Fig. 2B displays the change in ACQ-5 in the subset of the FAS population with the ACQ-5 score data at

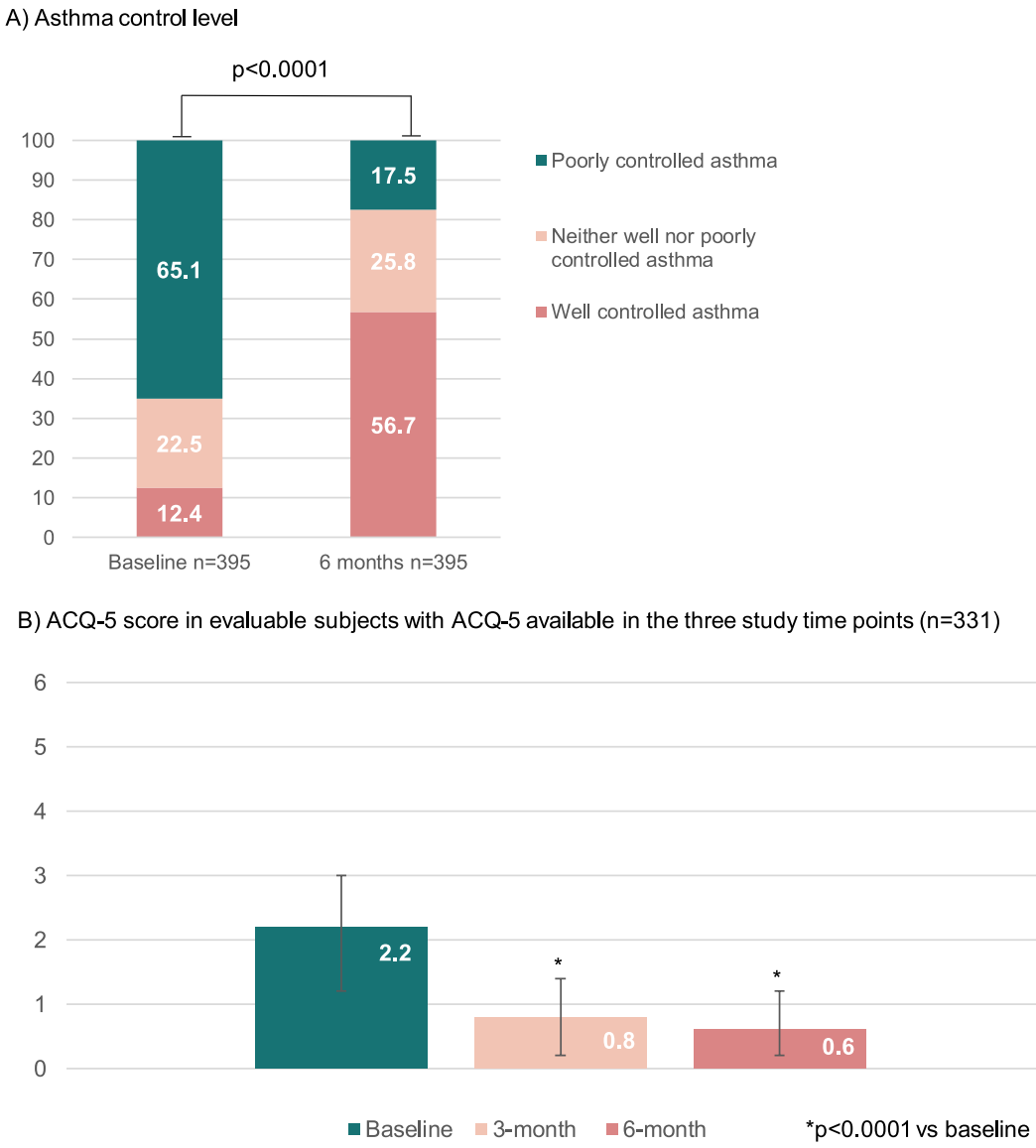

Fig. 2. Improvements in asthma according to ACQ-5 score. Baseline vs 3-month and vs 6-month follow-ups.
ACQ-5: Asthma Control Questionnaire-5 items; A) The McNemar-Bowker test was used to compare the distribution of asthma control categories at baseline and 6-month follow-up. B) The ACQ-5 score ranges between 0 (totally controlled) and 6 (extremely poorly controlled). The Wilcoxon Signed Rank test for paired samples was used to test median differences in ACQ-5 score between baseline and 3-month follow-up and between baseline and 6-month follow-up.

all time points (n = 331), which shows a significant change in asthma control after 3 and 6 months from baseline (0.8 and 0.6 at 3 months and 6 months, respectively; $p < 0.0001$).

Since the study included also subjects who self-reported well-controlled asthma (according to ACQ-5), a sensitivity analysis was performed to evaluate asthma control including only the subset of the FAS population with an ACQ-5 score >0.75 (that is, not-well-controlled or poorly controlled according to ACQ-5 score) at baseline (n = 346). The median (IQR) ACQ-5 score at the end of the 6-month observation period was 0.6 (0.2–1.2) with a median (IQR) change from baseline to this time point of −1.4 (−2.2 to −0.6). The percentage of patients with poorly controlled asthma decreased from 74.3 % (n = 257) to 18.5 % (n = 64) (Table A4). These results were consistent with the results of the whole FAS population.

59.8 % of subjects was treated with BDP/FF NEXThaler® 100/6 μg alone. Among subjects on MART, 30.4 % (n = 89) had at least one concomitant medication for asthma, while among subjects on maintenance only, 62.3 % (n = 81) had at least one concomitant medication for asthma. When considering the frequency of treatment combinations in MART group vs maintenance only, there was a significant difference in the concomitant use of SABA, which was equal to 4.1 % in patients treated with MART compared to 50 % in the maintenance-only group ($p < 0.0001$).

3.3. Improvements in lung function

The NEWTON study also collected information about lung function during the observation period. According to the measurements available in the clinical practice, not all subjects had FEV_1, $FEF_{25\ \%–75\ \%}$, and PEF recordings at baseline and 6-month follow-up. Among the subjects with available data about FEV_1 (% of predicted) (n = 150), the median change at 6 months in FEV_1 (% of predicted) pre-bronchodilator was 7.0 (IQR: -2.0 – 15.5) and was statistically significant ($p < 0.0001$). Among the subjects with available data about $FEF_{25\ \%–75\ \%}$, at baseline and 6-month follow-up (n = 100), the $FEF_{25\ \%–75\ \%}$ (% of predicted) pre-bronchodilator significantly improved ($p < 0.0001$). In addition, the median change of PEF (% of predicted) pre-bronchodilator at 6 months was 7.0 (IQR: -5.0 – 19.3) among subjects with available data (n = 125)

Table 2
Pulmonary Function pre-bronchodilator at baseline and 6-month follow-up.

	Baseline	6-month follow-up	Change at 6-month vs baseline
FEV_1 actual value (L) (n = 151) Median (IQR)	2.5 (1.9–3.0)	2.7 (2.2–3.3)	0.1 (−0.1–0.4)*
FEV_1 (% of predicted) (n = 150) Median (IQR)	86.0 (73.2–92.0)	93.0 (83.0–104.0)	7.0 (−2.0-15.5)*
FVC actual value (L) (n = 151) Median (IQR)	3.3 (2.5–3.9)	3.3 (2.8–4.1)	0.1 (−0.1–0.4)*
FVC (% of predicted) (n = 151) Median (IQR)	92.0 (80.0–101.0)	97.0 (88.0–106.0)	4.0 (−2.0-13.0)*
FEV_1/FVC ratio (n = 151) Median (IQR)	0.8 (0.7–0.8)	0.8 (0.7–0.9)	0.0 (−0.0-0.1)§
$FEF_{25\ \%-75\ \%}$ (L/s) (n = 102) Median (IQR)	2.3 (1.6–3.1)	3.0 (1.9–3.6)	0.3 (−0.2–1.0)^
$FEF_{25\ \%-75\ \%}$ (% of predicted) (n = 100) Median (IQR)	67.5 (53.0–85.5)	80.0 (60.0–99.5)	8.0 (−4.5-25.5)*
PEF (L/min) (n = 136) Median (IQR)	365.4 (234–471.0)	388.5 (316.7–512.8)	28.3 (−18.6–92.0)*
PEF (% of predicted) (n = 125) Median (IQR)	78.0 (61.0–97.0)	91.0 (74.0–102.0)	7.0 (−5.0-19.3)*

*$p < 0.0001$; §$p = 0.009$; ^ $p = 0.0002$. FEV_1: Forced expiratory volume in 1st second; FVC: Forced vital capacity; FEV_1/FVC: Forced expiratory volume in 1st second/forced vital capacity; $FEF_{25\ \%-75\ \%}$: Mean forced expiratory flow between 25 % and 75 % of FVC; PEF: Peak Expiratory Flow; IQR: interquartile range. The Wilcoxon Signed Rank test for paired samples was used to test median differences in lung function parameters between baseline and 6-month follow-up.

and it was statistically significant ($p < 0.0001$) (Table 2).

3.4. Improvements in QoL measured by the EQ-5D-5L index

Similarly to the asthma control levels also the QoL improved significantly. The EQ-5D-5L index increased in both subsets of subjects, who had available questionnaires at baseline and either 3-month follow-up (n = 354) or 6 month-follow-up (n = 391), from 0.881 to 0.970 and 0.887 to 1.000, respectively ($p < 0.0001$ for both) (Tables 3 and 4).

3.5. Treatment adherence and satisfaction with the device

In the two subgroups of subjects who compiled the TAI questionnaire at enrolment and either 3-month follow-up (n = 312) or 6-month follow-up (n = 345) adherence to therapy improved and the percentages of the subjects in the category "good adherence" at baseline rose from 31.7 % (n = 99) to 50.0 % (n = 156) at 3-month follow-up and from 30.4 % at baseline (n = 105) to 49.9 % (n = 172) at 6-month follow-up (Fig. 3). Adherence score increased from 46.0 at baseline to 49.5 at 3-month follow-up visit, and the improvement remained substantially maintained at the 6-month follow-up. The change was statistically significant ($p < 0.0001$).

The improvement in adherence was consistent with overall satisfaction with the device. Among subjects who completed the structured interview with the 3 questions about their satisfaction with the BDP/FF NEXThaler® 100/6 μg (n = 387), 79.3 % (n = 307) were completely or very satisfied with the device in general, 83.7 % (n = 324) were completely or very satisfied with the delivered dose check and 81.1 % (n = 314) were completely or very satisfied with the ease of use at the end of observation (Fig. A1), with similar results at 3-month follow-up visit.

Table 3
Improvements of QoL after 3-month according to EQ-5D-5L index.

EQ-5D-5L INDEX	Evaluable subjects (N = 354)		
	Baseline	3-month follow-up	p-value
Median (IQR)	0.881 (0.799–0.970)	0.970 (0.913–1.000)	<0.0001

EQ-5D-5L: EuroQol 5-dimension 5-level; IQR: interquartile range. The Wilcoxon Signed Rank test for paired samples was used to test median differences in EQ-5D INDEX value between 3-month follow-up and baseline. Median, IQR, and test were obtained on evaluable subjects with available information on EQ-5D-5L at baseline and at 3-month follow-up.

Table 4
Improvements of QoL after 6-month according to EQ-5D-5L index.

EQ-5D-5L INDEX	Evaluable subjects (N = 391)		
	Baseline	6-month follow-up	p-value
Median (IQR)	0.887 (0.801–0.907)	1.000 (0.913–1.000)	<0.0001

EQ-5D-5L: EuroQol 5-dimension 5-level; IQR: interquartile range. The Wilcoxon Signed Rank test for paired samples was used to test median differences in EQ-5D INDEX value between 6-month follow-up and baseline. Median, IQR, and test were obtained on evaluable subjects with available information on EQ-5D-5L at baseline and at 6-month follow-up.

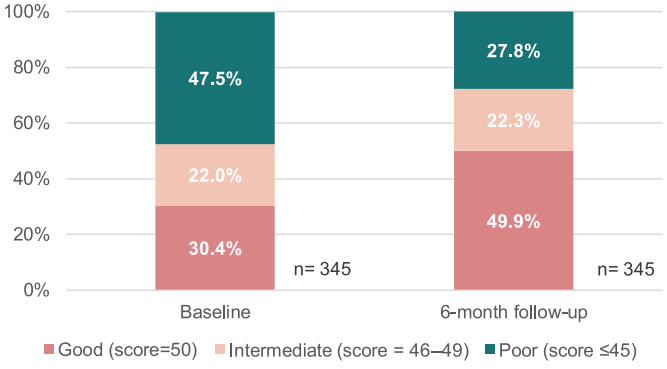

Fig. 3. Level of Adherence to therapy according to the TAI questionnaire.

3.6. Safety and exacerbations

In the SAF population (n = 609), 10.2 % (n = 62) of subjects experienced a TEAE and 4.3 % (n = 26) reported at least one TEAE related to BDP/FF NEXThaler® 100/6 μg. Overall, 2.1 % of subjects (n = 13) reported at least one TEAE that led to treatment discontinuation. No TEAE related to BDP/FF NEXThaler® 100/6 μg leading to death were observed during the study period (Table A5). The most frequent TEAEs (>2.0 %) were infections and infestations (3.3 %, n = 20), respiratory events (2.1 %, n = 13) and nervous system disorders (2.0 %, n = 12). As expected, the most frequent infections were COVID-19 and influenza (n = 6, 1.0 % and n = 5, 0.8 % respectively), while the most frequent respiratory events were asthma (n = 7, 1.1 %) and cough (n = 4, 0.7 %) (Table A6). Among the 421 special situations during the observation

period, the majority (n = 418) were caused by off-label use.

In the 12 months before the enrollment 79 subjects (13.0 %) of the SAF population experienced moderate-to-severe exacerbations. At the end of observation, 21 subjects (3.4 %) experienced moderate-to-severe exacerbations. 22 moderate-to-severe exacerbations occurred during the study period and resulted in either increase of the dosage (18.2 %, n = 4) or permanent withdrawal of the drug (13.6 %, n = 3). In most of the exacerbation cases (59.1 %, n = 13), however, the event did not affect the dosage. 2 out of 22 (9.1 %) required admission to the emergency room and most of them (n = 19, 86.4 %) were resolved during the observation period (Table A7).

4. Discussion

According to GINA 2024, asthma control is assessed by two domains: symptom control and risk of adverse outcomes, including exacerbations [1]. The MART approach is considered a better approach for reducing asthma exacerbations compared to maintenance therapy, and this has, among other things, also been demonstrated with BDP/FF 100/6 μg [24]. For this reason, the National Heart, Lung and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP), the GINA recommendations, and the National Institute for Health and Care Excellence (NICE) guidelines advocate using a MART approach as preferred treatment [25]. In addition to exacerbation risk, symptom control is also important [1,26]. In this context, BDP/FF NEXThaler® 100/6 μg, a patient-friendly and effective administration device, proved to be a reliable and well-tolerated tool for regular asthma treatment with a fixed dose combination of BDF/FF. The NEXThaler® was found to be non-inferior to extrafine BDP/FF treatments administered via pMDI in terms of lung function, asthma control and use of rescue medication [27]. The favourable outcomes with NEXThaler® can be attributed to its extrafine formulation. Most inhalers, such as pMDIs and other DPIs, do not consistently produce particles small enough to reach the distal airways, which are also involved in the inflammatory process that characterize asthma and that may lead to a small airways disease [28,29]. NEXThaler® produces aerosols with MMAD <2 μm, enhancing lung deposition and drug bioavailability [30]. This enables greater distal airway delivery and reduced oropharyngeal exposure, potentially limiting side effects and systemic absorption [31]. A pooled analysis from Austria confirmed the effectiveness and tolerability of extrafine BDP/FF in real-world settings, regardless of smoking status [32].

In the NEWTON study, up to 66.1 % of subjects significantly improved their level of asthma control score 6 months after starting treatment with BDP/FF NEXThaler® 100/6 μg. The proportion of subjects with not-well-controlled or poorly controlled asthma decreased from 87.6 % to 43.3 % at the 6-month follow-up. The improvements in ACQ-5 score were found even after those who had already reported well-controlled asthma at baseline were excluded from the analysis, with patients with poorly controlled asthma decreasing from 74.3 % to 18.5 %. This finding is not unexpected, given that the ACQ score is a patient-reported outcome (PRO), and therefore, discrepancies between the patients' perception and clinical evaluation may exist. The sensitivity analysis (excluding the well-controlled subgroup according to ACQ-score) confirmed that the improvement in ACQ-5 was consistent with that observed in the FAS population.

These changes were already visible to a similar extent at the 3-month visit indicating that asthma control had already improved quickly after the start of the treatment and then remained stable until the end of the study period. These observations are also consistent with other recent national studies: Bakakos and colleagues showed that more than 70 % of subjects had well-controlled asthma 6 months after the start of BDP/FF NEXThaler® 100/6 μg treatment (based on ACQ-6 score). Similarly, in a study by Ulmenau and colleagues ACQ-7 in subjects treated with BDF/FF 100/6 μg pMDI scores changed significantly from baseline to the 6-month visit (1.05 ± 0.78 vs 3.05 ± 0.80 at baseline) [2,33]. It is noteworthy that NEWTON reported consistent results in a European population. About 70 % of patients underwent MART during observation and 30 % maintenance only. Of note, the concomitant use of SABA in patients treated with MART was 4.1 % compared to 50 % in the maintenance only group ($p < 0.0001$). This is more aligned with current recommendations and in contrast to what emerged in a recent international survey, which reported that most patients using MART were also prescribed a rescue inhaler [34]. This may indicate a general proper knowledge and use of MART in the considered European countries.

The study found that the use of the extrafine BDP/FF NEXThaler® 100/6 μg led to improvements in pulmonary function, e.g. FEV_1 and $FEF^{25\ \%-75\ \%}$, during the observational period. These findings are consistent with other clinical trials, in which lung function and asthma control improved with the BDP/FF combination using pressurized metered-dose inhalers (pMDIs) or BDP/FF NEXThaler® 100/6 μg [1,27,35].

Although 60 % of the subjects were overweight or obese, the treatment demonstrated significant effectiveness. This observation is of utmost importance considering that change in BMI is found to be an independent factor in the improvement of asthma control and a significant relation between the higher BMI (overweight or obese) and the worse ACQ-score [36,37].

Better asthma control, expressed by lower ACQ-5 scores, was found to be the most important predictor of better asthma-related QoL [36]. Similar to other studies, the NEWTON study showed that quality of life, captured by the EQ-5D-5L index, improved significantly from baseline to 3-month and the median EQ-5D-5L index score at 6-month follow-up was equal to 1, corresponding to the maximum value for the scale [2,4].

Among subjects who completed the structured interview about their satisfaction with the device, most of them were satisfied in terms of ease of use and ability to check dose intake, with a general satisfaction equal to 79.3 %.

The safety profile was in line with the summary of product characteristics.

As widely recognised, observational studies offer the opportunity to assess treatment effectiveness and safety in routine clinical practice, complementing evidence from randomized clinical trials (RCTs) [38]. While RCTs focus on restricted populations under controlled experimental conditions, using specifically designed data collection tools, observational studies aim to gather information on broader populations and real-world scenarios that reflect routine clinical practice, using data from everyday clinical settings. However, some limitations of the study should be considered: 1) the study centres were not randomly selected, potentially limiting the representativeness of the final sample. To enhance generalizability, sites were chosen from different countries. 2) Only subjects who were able to understand and independently complete the questionnaires were eligible according to exclusion criteria. This may have introduced a selection bias towards younger and healthier participants. 3) Subjects could initiate treatment no more than 14 days before enrolment, leading to the exclusion of those who had discontinued BDP/FF NEXThaler® 100/6 μg before. However, the risk of immortal-time bias should be limited considering the shortness of the period. In addition, study drug's effect during this short window is thought to be limited, according to clinical judgment. 4) Some clinical outcomes (i.e. lung functions) and PROs were affected by missing information, as is common in observational data collection. This may further limit the generalizability of the results. Nonetheless, the available data reflect the actual clinical practice in the participating centres and indicate a lower frequency of such clinical outcomes during the study visits. Importantly, sample size simulations accounted for these scenarios and the precision of the resulting estimates was deemed acceptable; 5) since only 67 subjects were current smokers, no specific analysis was performed to describe asthma control within this subgroup. However, an explorative analysis on asthma control improvement (not shown) indicated that the proportion of patients who improved was similar among current or former smokers and non-smokers. Finally, the focus of the study was to describe the response to the extrafine

fixed-dose formulation of BDP/FF 100/6 μg delivered via the NEXThaler® in adults in a real-life context; therefore, the comparison with other products was out of scope.

5. Conclusion

The results of the NEWTON observational study confirm the effectiveness and safety of extrafine fixed combination of BDP/FF NEXThaler® 100/6 μg in European adults with uncontrolled moderate-to severe asthma in a real-world setting, leading to clinically relevant improvements in asthma control, QoL and pulmonary function. During the observation period the subjects reported high adherence to the treatment and satisfaction with the device.

CRediT authorship contribution statement

Fulvio Braido: Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Kai-Michael Beeh:** Writing – review & editing, Investigation, Data curation. **Carolina Cisneros Serrano:** Writing – review & editing, Investigation, Data curation. **Anh Tuan Dinh-Xuan:** Writing – review & editing, Investigation, Data curation. **Lilla Tamási:** Writing – review & editing, Investigation, Data curation. **Antigona Trofor:** Writing – review & editing, Investigation, Data curation. **Eleonora Ingrassia:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Alessio Piraino:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Cristiano Caruso:** Writing – review & editing, Supervision, Investigation, Data curation.

Ethics Approval and informed consent

The Ethics Committee of each participating centre approved the study protocol before the study started. The informed consent for participation in the study and use of personal data were obtained from all subjects before any study-related procedures were performed.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alessio Piraino reports article publishing charges and writing assistance were provided by Chiesi Italia S.p.A. Fulvio Braido reports financial support was provided by Chiesi Farmaceutici SpA. Carolina Cisneros Serrano reports financial support was provided by Chiesi España SA. Fulvio Braido reports a relationship with GSK that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Chiesi that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Menarini group that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Astra Zeneca that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Sanofi that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Regeneron that includes: board membership and speaking and lecture fees. Kai-Michael Beeh reports a relationship with Astra Zeneca that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with Chiesi Farmaceutici SpA that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with Bosch Healthcare Solutions GmbH that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with Berlin-Chemie AG that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with Sanofi-Aventis Deutschland GmbH that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with GlaxoSmithKline Inc that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Carolina Cisneros Serrano reports a relationship with Sanofi SA that includes: consulting or advisory, funding grants, non-financial support, speaking and lecture fees, and travel reimbursement. Carolina Cisneros Serrano reports a relationship with GlaxoSmithKline SpA that includes: consulting or advisory and speaking and lecture fees. Carolina Cisneros Serrano reports a relationship with AstraZeneca that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Anh Tuan Dinh-Xuan reports a relationship with Boehringer Ingelheim that includes: speaking and lecture fees. Anh Tuan Dinh-Xuan reports a relationship with GSK that includes: speaking and lecture fees. Anh Tuan Dinh-Xuan reports a relationship with Menarini that includes: speaking and lecture fees. Anh Tuan Dinh-Xuan reports a relationship with Sanofi that includes: speaking and lecture fees. Eleonora Ingrassia reports a relationship with Chiesi Italia that includes: employment. Alessio Piraino reports a relationship with Chiesi Farmaceutici SpA that includes: employment. Kai-Michael Beeh declares that, in the past five years, the institution has received compensation for the conduct of clinical trials by the following corporations: AstraZeneca, Bosch Healthcare Solutions GmbH, Chiesi, GSK, Novartis, Sterna. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2025.108224.

Abbreviations

ACQ-5: Asthma Control Questionnaire-5 items; BDP/FF: Beclometasone dipropionate/formoterol fumarate; BMI: Body mass index; CRF: Case report form; FEF25 %-75 %: Mean forced expiratory flow between 25 % and 75 % of FVC; FEV1: Forced expiratory volume in 1st second; FEV1/FVC: Forced expiratory volume in 1st second/forced vital capacity; FVC: Forced vital capacity; GINA: Global initiative for asthma; ICS: Inhaled corticosteroid; LABA: Long-acting beta-2-agonist; MART: Maintenance and reliever therapy; PEF: Peak Expiratory Flow; pMDI: Pressurized metered-dose inhaler; SAE: Serious adverse event; SABA: Short-acting beta-2-agonist; SD: Standard deviation.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request and with prior permission of Chiesi.

References

[1] Global Initiative for Asthma, Global strategy for asthma management and prevention, 2024. Update may 2024, Available from: www.ginasthma.org. June 2024.

[2] P. Bakakos, P. Chatziapostolou, P. Katerelos, et al., Extrafine beclometasone dipropionate/formoterol NEXThaler on device usability, adherence, asthma control, and quality of life: a Panhellenic prospective, non-interventional observational study in patients with asthma—the NEXT-Step Study, J. Personalized Med. 12 (2022) 146.

[3] F. Braido, G. Brusselle, D. Guastalla, et al., Determinants and impact of suboptimal asthma control in Europe: the international cross-sectional and longitudinal assessment on asthma control (LIAISON) study, Respir. Res. 17 (2016) 51.

[4] E.D. Bateman, H.A. Boushey, J. Bousquet, et al., Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study, Am. J. Respir. Crit. Care Med. 170 (2004) 836–844.

[5] L. Allegra, G. Cremonesi, G. Girbino, et al., PRISMA (PRospectIve Study on asthMA control) Study Group. Real-life prospective study on asthma control in Italy: cross-sectional phase results, Respir. Med. 106 (2012) 205–214.

[6] V. Müller, G. Gálffy, N. Eszes, et al., Asthma control in patients receiving inhaled corticosteroid and long-acting beta2-agonist fixed combinations: a real-life study comparing dry powder inhalers and a pressurized metered dose inhaler extrafine formulation, BMC Pulm. Med. 11 (2011) 40.

[7] F. Di Marco, Today's improvement in asthma treatment: role of MART and Easyhaler, Multidiscip Respir Med. 15 (2020) 649.

[8] J.C. Virchow, G. Poli, C. Herpich, et al., Lung deposition of the dry powder fixed combination beclometasone dipropionate plus formoterol fumarate using NEXThaler® device in healthy subjects, asthmatic patients, and COPD patients, J. Aerosol Med. Pulm. Drug Deliv. 31 (2018) 269–280.

[9] H. Watz, S. Barile, D. Guastalla, E. Topole, et al., Targeting the small airways with inhaled corticosteroid/long-acting beta agonist dry powder inhalers: a functional respiratory imaging study, J. Aerosol Med. Pulm. Drug Deliv. 34 (2021) 280–292.

[10] A. Papi, Inhaled BDP/formoterol extra-fine combination: evidence and future perspectives, Pneumologie 63 (Suppl 2) (2009) S102–S106.

[11] T. Voshaar, M. Spinola, P. Linnane, et al., Comparing usability of NEXThaler® with other inhaled corticosteroid/long-acting β2-agonist fixed combination dry powder inhalers in asthma patients, J. Aerosol Med. Pulm. Drug Deliv. 27 (2014) 363–370.

[12] J. Schreiber, T. Sonnenburg, E. Luecke, Inhaler devices in asthma and COPD patients: a prospective cross-sectional study on inhaler preferences and error rates, BMC Pulm. Med. 20 (2020) 222.

[13] K. Ruessel, E. Luecke, J. Schreiber, Inhaler devices in a geriatric patient population: a prospective cross-sectional study on patient preferences, Patient Prefer. Adherence 14 (2020) 1811–1822.

[14] D. Singh, F. van den Berg, B. Leaker, et al., Comparison of the effect of beclometasone/formoterol in asthma patients after methacholine-induced bronchoconstriction: a noninferiority study using metered dose vs. dry powder inhaler, Br. J. Clin. Pharmacol. 85 (2019) 729–736.

[15] M. Corradi, H. Chrystyn, B.G. Cosio, et al., NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclometasone and formoterol to treat large and small airways in asthma, Expet Opin. Drug Deliv. 11 (2014) 1497–1506.

[16] F. Braido, E. Arnaboldi, S. Barile, et al., BDP/FF NEXThaler to improve asthma control status in the real world: the Newton study, J. Asthma Allergy 16 (2023) 1177–1186.

[17] Public Policy Committee, International Society of Pharmacoepidemiology, Guidelines for good Pharmacoepidemiology practices (GPP), Pharmacoepidemiol. Drug Saf. 25 (2016) 2–10.

[18] E.F. Juniper, P.M. O'Byrne, G.H. Guyatt, et al., Development and validation of a questionnaire to measure asthma control, Eur. Respir. J. 14 (1999) 902–907.

[19] E.F. Juniper, K. Svensson, A.C. Mörk, E. Ståhl, Measurement properties and interpretation of three shortened versions of the asthma control questionnaire, Respir. Med. 99 (2005) 553–558.

[20] E.F. Juniper, J. Bousquet, L. Abetz, E.D. Bateman, Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire, Respir. Med. 100 (2006) 616–621.

[21] M. Herdman, C. Gudex, A. Lloyd, et al., Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L), Qual. Life Res. 20 (2011) 1727–1736.

[22] M.F. Janssen, A.S. Pickard, D. Golicki, et al., Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study, Qual. Life Res. 22 (2013) 1717–1727.

[23] V. Plaza, C. Fernández-Rodríguez, C. Melero, et al., TAI Study Group, Validation of the 'test of the adherence to inhalers' (TAI) for asthma and COPD patients, J. Aerosol Med. Pulm. Drug Deliv. 29 (2016) 142–152.

[24] A. Papi, M. Corradi, C. Pigeon-Francisco, et al., Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial, Lancet Respir. Med. 1 (2013) 23–31.

[25] National Institute for Health and Care Excellence (NICE), Asthma: Diagnosis, Monitoring and Chronic Asthma Management, BTS, NICE, SIGN, 2024.

[26] M.M. Cloutier, A.P. Baptist, K.V. Blake, et al., 2020 focused updates to the asthma management guidelines: a report from the national asthma education and prevention Program coordinating committee expert panel working group, J. Allergy Clin. Immunol. 147 (2021) 1528–1530.

[27] F. Kanniess, M. Scuri, S. Vezzoli, et al., Extrafine beclomethasone/formoterol combination via a dry powder inhaler (NEXThaler®) or pMDI and beclomethasone monotherapy for maintenance of asthma control in adult patients: a randomised, double-blind trial, Pulm. Pharmacol. Ther. 30 (2015) 121–127.

[28] F. Lavorini, S. Pedersen, O.S. Usmani, , et al.Confusion Dilemmas, Misconceptions related to small airways directed therapy, Chest 151 (6) (2017 Jun) 1345–1355.

[29] M. Cottini, C. Lombard, C. Micheletto, Small airway dysfunction and bronchial asthma control: the state of the art, Asthma Res Pract 1 (2015) 13.

[30] M. Tamm, et al., Inhaled corticosteroid and long-acting β2-agonist pharmacological profiles: effective asthma therapy in practice, Respir. Med. 106 (2012) S9–S19. Suppl1.

[31] O.S. Usmami, N. Scichilone, B. Mignot, D. Belmans, et al., Airway deposition of extrafine inhaled triple therapy in patients with COPD: a model approach based on functional respiratory imaging computer simulations, Int. J. Chronic Obstr. Pulm. Dis. 15 (2020) 2433–2440.

[32] A. Renner, K. Marth, R. Breyer-Kohansal, et al., Combined analysis of five non-interventional studies of the effectiveness, tolerability, and safety of the extrafine fixed dose beclomethasone/formoterol combination in the treatment of asthma in Austria, Respir. Med. 207 (2023) 107097.

[33] R. Ulmenau, S. Boju, O. Vittos, Assessment of symptoms control, pulmonary function, and related quality of life in asthmatic patients treated with extrafine beclomethasone dipropionate/formoterol fumarate 100/6 μg pMDI: results of a multicenter observational study in Romania (ALFRESCO Study), J. Asthma Allergy 15 (2022) 919–933.

[34] K.R. Chapman, G.W. Canonica, K.L. Lavoie, et al., Patients' and physicians' perspectives on the burden and management of asthma: results from the APPaRENT 2 study, Respir. Med. 201 (2022) 106948, https://doi.org/10.1016/j.rmed.2022.106948.

[35] G. Huchon, H. Magnussen, A. Chuchalin, et al., Lung function and asthma control with beclometasone and formoterol in a single inhaler, Respir. Med. 103 (2009) 41–49.

[36] G. Luis, B. Pétré, F. Schieich, et al., Predictors of change in asthma-related quality of life: a longitudinal real-life study in adult asthmatics, Qual. Life Res. 32 (2023) 1507–1520.

[37] K.L. Lavoie, S.L. Bacon, M. Labrecque, et al., Higher BMI is associated with worse asthma control and quality of life but not asthma severity, Respir. Med. 100 (2006) 648–657.

[38] A.S. Gershon, S.R. Jafarzadeh, K.C. Wilson, A.J. Walkey, Clinical knowledge from observational studies: everything you wanted to know but were afraid to ask, Am. J. Respir. Crit. Care Med. 198 (2018) 859–867.