Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Real-Life Effectiveness of Budesonide/Formoterol as Maintenance and Reliever Treatment via the Elpenhaler® Device in Patients with Asthma: The NOTOS Observational Study

Athena Gogali[1], Nikoletta Rovina[2], Konstantinos Samitas[3], Paschalis Steiropoulos[4], Dimitrios Potonos[3], Maria Bertoli[5], Polyanthi Papanastasiou[5], Alexandros Ginis[5], Konstantinos Kostikas[1]

[1]Respiratory Medicine Department, University of Ioannina, Ioannina, Greece; [2]1st Department of Respiratory Medicine, Medical School, National and Kapodistrian University of Athens and "Sotiria" Chest Hospital, Athens, Greece; [3]7th Respiratory Medicine Department, "Sotiria" Chest Hospital, Athens, Greece; [4]Department of Pulmonology, University General Hospital of Alexandroupolis, Alexandroupoli, Greece; [5]Medical Department, ELPEN Pharmaceutical Co. Inc., Attica, Greece

Correspondence: Konstantinos Kostikas, Respiratory Medicine Department, University of Ioannina, Ioannina, Greece, Email ktkostikas@gmail.com

Aim: Inhaled corticosteroid (ICS)/long-acting β2-agonist combinations are crucial for the effective treatment of asthma. ICS/formoterol regimens serve both as controller and reliever medications, as recommended by GINA 2019 onwards. In the six-month real-life NOTOS study, we aimed to evaluate the real-life effectiveness of budesonide/formoterol (BUD/FOR) administered with the Elpenhaler® device as controller and/or reliever medication on asthma control, quality of life, and lung function in patients with asthma.

Methods: We performed a multicenter open-label observational prospective study of adult asthma patients receiving BUD/FOR via Elpenhaler. Assessments were performed with Asthma Control Questionnaire (ACQ-6), Mini Asthma Quality of Life Questionnaire (MiniAQLQ), and spirometry. The incidence of exacerbations, frequency of rescue therapy use, and safety data were also recorded.

Results: In the 1107 patients recruited, we observed statistical and clinically relevant improvements at 6 months from baseline, in ACQ-6 [mean change (95% CI) −1.55 (−1.61, −1.4) points, p<0.001], MiniAQLQ [1.76 (1.68, 1.82) points, p<0.001], and FEV_1 [0.35 (0.31,0.38) L, p<0.001]. Subgroup analyses, according to the maintenance (A: BUD/FOR 200/6 μg "as needed", B: BUD/FOR 200/6 maintenance, or C: BUD/FOR 400/12 μg maintenance) and the reliever treatments (none, BUD/FOR or short-acting β2-agonists), showed significant improvements across all groups, with greater improvements observed in the higher maintenance dose of BUD/FOR group. The frequency of rescue therapy use was overall markedly reduced, and we observed no safety issues.

Conclusion: In this real-life study, treatment with BUD/FOR, as controller and/or reliever via the Elpenhaler device, was associated with significant improvement in patients' asthma control, quality of life, and lung function, over 6 months.

Keywords: asthma control, quality of life, budesonide, formoterol, maintenance and reliever treatment, Elpenhaler, real-life study

Introduction

Asthma is affecting more than 300 million people and is a leading cause of morbidity and economic burden worldwide.[1] Epidemiological data in Greece provided by a national survey conducted from the Asthma Working Group of the Hellenic Thoracic Society have shown that the prevalence of asthma in Greece is approximately 9% with 16 new cases per thousand.[2] Asthma management should be personalized and continually assessed and reviewed with goals to achieve elimination of symptoms and minimization of exacerbation risk, as well as avoidance of persistent airflow limitation and side effects of treatment.[1] Real-world evidence has shown that poor asthma control exists despite the availability of

Received: 19 February 2025
Accepted: 8 April 2025
Published: 21 April 2025

effective treatments. Reasons for that include poor adherence, lack of efficacy, inadequate treatment, or inhalation technique, resulting in worse quality of life (QoL), decreased productivity, and increased healthcare resource utilization.[3]

The pharmacological treatment of asthma consists of daily used maintenance controllers treatments, including inhaled corticosteroids (ICS), with or without long-acting β2-agonists (LABA), and "as needed" reliever treatments that contain rapid-onset bronchodilators, including low dose ICS/formoterol or short-acting β2-agonists (SABA).[4,5] Regimens containing ICS/formoterol serve both as controller and reliever medication, as well as "as-needed" anti-inflammatory reliever medication in milder asthma, as recommended by GINA 2019/2020.[6] GINA 2019 report made the most fundamental change in asthma management in the last 30 years stating that asthma in adults and adolescents should not be managed solely with SABAs, even in mild disease, based on evidence for the risks of SABA-only treatment and overuse, as well as evidence for benefit of inhaled corticosteroids use.[6] Anti-inflammatory reliever ICS/formoterol reduced severe exacerbations by ≥60% in mild asthma compared with SABA, with similar inflammatory outcomes as daily ICS, with nearly half the ICS cumulative dose.[7,8] GINA 2020 recommendations highlighted the ability of symptom driven use of ICS/formoterol, alone or on top of maintenance treatment, introducing a self-guided personalized approach.[9]

Fixed-dose combination products merging corticosteroids with long-acting β2 agonists administered in a single inhaler maintenance and/or reliever therapy is a safe, effective, and simplified approach to asthma treatment.[10,11] There is limited published data of the real-life effectiveness of the fixed-dose combination budesonide/formoterol (BUD/FOR) administered via the Elpenhaler® device prescribed as maintenance treatment by pulmonologists[12,13] or primary care physicians,[14] while no information exists regarding its use as reliever (with or without maintenance) treatment.[15]

In the six-month real-life NOTOS study, we aimed to evaluate the real-life effectiveness of the fixed BUD/FOR combination in the Elpenhaler® device, prescribed as maintenance and/or "as needed" treatment in asthmatic patients according to usual clinical practice, as assessed by asthma control, quality of life, lung function, incident severe asthma exacerbations, as well as the frequency of rescue therapy use.

Materials and Methods

Study Design

NOTOS (EvaluationN of Fixed Dose budesOnide/formoterol via Elpenhaler in asThma patients according to Standard clinical practice) is a multicenter, prospective, observational study (NCT04835961) in adults with asthma, enrolled and followed up in 100 sites (6 hospitals/institutions and 94 private practices) throughout Greece. Patients were treated per routine clinical care and data were collected in 3 visits: V0 (baseline), V1 (at 3 months ± 2 weeks), and V2 (at 6 months ± 2 weeks). The first patient enrolled in May 2021 and the last patient was followed up in May 2022. The diagnosis and management of the study population were based on the GINA 2020 recommendations.[16]

Study medication was BUD/FOR fixed-dose combination (FDC, Pulmoton Elpenhaler), in 200/6 μg and 400/12 μg dosing, administered through inhalation, as either maintenance treatment (dose 200/6 μg or 400/12 μg) and/ or a reliever (dose 200/6 μg). The study was performed in accordance with the recommendations of the Declaration of Helsinki, the International Conference of Harmonization – Good Clinical Practice (ICH-GCP) Guidelines, the EU-Directive 2001/20 as applicable and all national requirements, and was approved by an Institutional Review Board (IRB) and/or Ethics Committee (EC) or Scientific Council of the major institutions that participated in the study (University General Hospital of Ioannina, General Hospital of Chest Diseases of Athens "SOTIRIA", University General Hospital of Heraklion, University General Hospital of Patra, University General Hospital of Alexandroupolis, Interbalkan Medical Centre of Thessaloniki). Written informed consent was obtained from all participants.

Study Population

Eligible patients were adult patients with asthma, willing to provide a written informed consent prior to inclusion, and able to comply with treatments and study procedures. Patients with asthma on the following treatments could be included in the study: treatment naive patients; patients on prior treatment with low dose ICS/formoterol "as needed"; patients not adequately controlled with low dose (LD) ICS as maintenance treatment and required ICS/formoterol either as

maintenance treatment or as maintenance treatment and "as needed"; patients not adequately controlled with LD or medium dose (MD) ICS and LABA and required ICS/formoterol "as needed". Key exclusion criteria were: age under 18, diagnosis of Chronic Obstructive Pulmonary Disease (COPD) and/or diagnosis of Asthma-COPD overlap syndrome (ACO).

Study Assessments

At the baseline visit, informed consent was obtained, patient's demographics and medical history were recorded, and patients were treated according to the physician's judgment with FDC of BUD/FOR (Pulmoton®) with the dry powder inhaler (DPI) Elpenhaler device as a maintenance therapy at doses 200/6 μg or 400/12 μg and/or "as needed" therapy at 200/6 μg, as per standard clinical practice. Study assessments at baseline (V0), V1 and V2, included the Asthma Control Questionnaire 6-item (ACQ-6), the Mini Asthma Quality of Life Questionnaire (MiniAQLQ), and spirometry. Severe asthma-related exacerbations, need for rescue therapy throughout the study, and safety were assessed at V1 and V2.

The Greek version of ACQ-6 that was used to assess asthma control, consists of 6 items, 5 items on symptoms and 1 item on reliever use. The total score ranges from 0 (totally controlled asthma) to 6 (severely uncontrolled asthma), and a change ≥0.5 units in the ACQ score is considered as the minimal clinically important difference (MCID).[17–19]

The Greek version of MiniAQLQ was used to evaluate asthma-related quality of life.[20] This 15-item questionnaire consists of 4 domains (symptoms, environment, emotions, and activities), and provides an overall score and four subscores ranging from 0 (severely impaired) to 7 (not impaired at all), representing a shorter version of the 32 initially self-reported items;[21] the MCID in MiniAQLQ is defined as a change of ≥0.5 units is considered as the minimal clinically important difference (MCID).

Spirometry was performed in all visits, according to the ERS/ATS guidelines,[22] and forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and their ratio (FEV_1/FVC) were measured. Severe asthma-related exacerbations (defined as events that require oral/systemic corticosteroids for at least 3 days or emergency room (ER) visit or hospitalization) were recorded at 3 (V1) and 6 months (V2) from treatment initiation. Safety was assessed by recording adverse events (incidence, severity, and causality to the study drug) throughout the study.

Study Objectives and Endpoints

The primary endpoint of the study was change in ACQ-6 score at 3 and 6 months of treatment, assessing the effectiveness of the FDC of BUD/FOR treatment via Elpenhaler, used as a controller and/or a reliever, on asthma control.

Secondary objectives were the assessment of lung function changes as evaluated by change in spirometric indices (FEV_1, FVC, FEV_1/FVC) at 3 and 6 months of treatment, the assessment of the impact on the QoL as evaluated by change in the MiniAQLQ total score after 3 and 6 months of treatment, the recording of the frequence of rescue medication use defined as the mean daily number of inhalations of rescue therapy either SABA or LD ICS/formoterol (regular maintenance treatment with ICS/formoterol is not included), the number of severe exacerbations after 3 and 6 months of treatment and safety as assessed by the incidence of adverse events throughout the study.

Statistical Analysis

Descriptive statistics are presented as frequencies (N) with proportions (%) for categorical variables and continuous variables are presented as mean ± standard deviation (SD). Pearson's chi-square and Fisher's exact test were used for categorical variables and Wilcoxon ranked sum test or Kruskal–Wallis rank sum tests were used for the evaluation of differences among groups of interest in parametric and non-parametric groups, respectively. Changes in variables between visits are presented as mean values with 95% confidence intervals (CI). Statistical analysis was performed with SPSS (version 21.0) R version 4.3.1 (2023–06-16 ucrt). P values <0.05 were considered as statistically significant.

Results

In total, 1107 asthmatic patients were enrolled by 100 sites across Greece (Figure 1). Most of them were women (60.6%), with a mean (SD) age of 50.4 (16.1) years, a BMI 28.2 (5.9) kg/m2, while at least 6 out of 10 patients were non-smokers (Table 1). Regarding previous asthma treatments before enrollment, 39.7% of the patients were treatment-naive, while

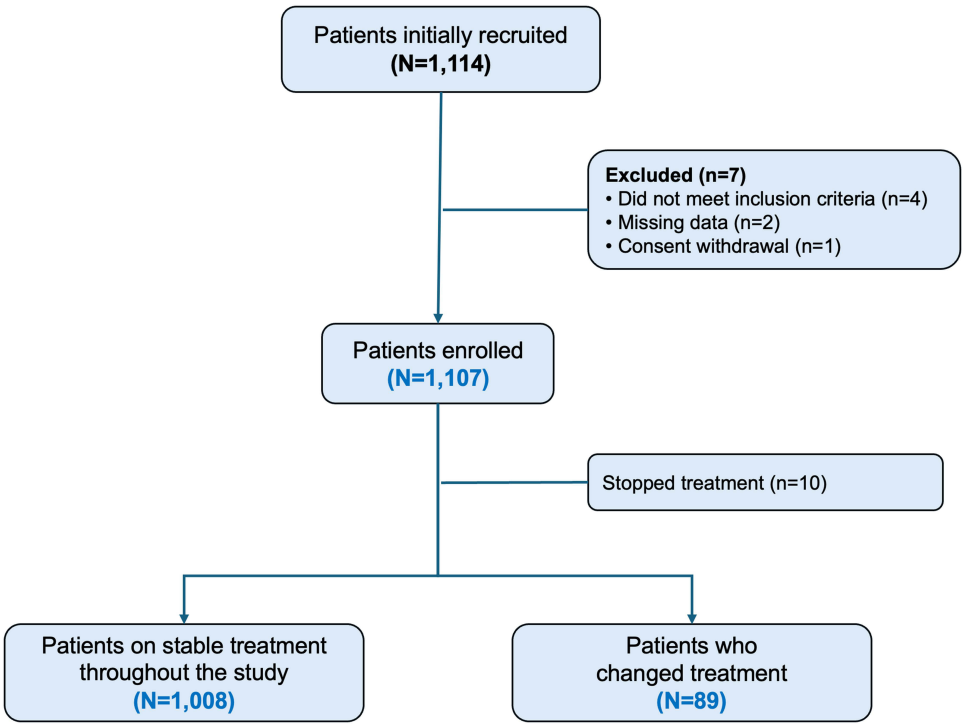

Figure 1 Flowchart of patients recruited in the study.

668 of the patients (60.3%) were receiving at least one prior asthma treatment (ICS, ICS/SABA, ICS/LABA, ± leukotriene receptor antagonists-LTRA) and 37.7% of the treated patients were on a maintenance treatment for asthma. Overall, 43.3% of the patients were receiving "as needed" treatment, either with SABA or LD ICS/formoterol, of which 22.6% had only treatment on demand.

Table 1 Patient Demographics

	All n=1107	**Stable Treatment n=1008**				**Changed Treatment n=89**
		All (n=1008)	**A (n=79)**	**B (n=458)**	**C (n=471)**	
Sex						
Male	435 (39.3%)	392 (38.9%)	24 (30.4%)	185 (40.4%)	183 (38.6%)	40 (44.9%)
Female	672 (60.7%)	616 (61.1%)	55 (69.6%)	273 (59.6%)	288 (61.1%)	49 (55.1%)
Race						
Caucasian	1100 (99.4%)	1001 (99.3%)	78 (98.7%)	454 (99.1%)	469 (99.6%)	89 (100.0%)
Asian	7 (0.6%)	7 (0.7%)	1 (1.3%)	4 (0.9%)	2 (0.4%)	0 (0.0%)
Age (years)	50.4 (16.13)	50.6 (16.3)	46.4 (17.2)	50.0 (16.6)	51.9 (15.7)	49. (14.2)
BMI (kg/m^2)	28.2 (5.9)	28.16 (5.8)	27.3 (5.9)	27.8 (5.7)	28.7 (5.8)	28.0 (6.4)
Smoking						
Never smokers	665 (60.1%)	609 (60.4%)	60 (75.9%)	266 (58.1%)	283 (60.1%)	49 (55.1%)

(*Continued*)

 https://doi.org/10.2147/JAA.S517932

Table 1 (Continued).

	All n=1107	Stable Treatment n=1008				Changed Treatment n=89
		All (n=1008)	A (n=79)	B (n=458)	C (n=471)	
Ex smokers	229 (20.7%)	208 (20.6%)	10 (12.7%)	104 (22.7%)	94 (19.9%)	20 (22.5%)
Pack years	20.4 (23.3)	20.5 (24.0)	19.2 (20.3)	20.6 (26.3)	20.4 (21.9)	18.7 (13.7)
Current smokers	213 (19.2%)	191 (18.9%)	9 (11.4%)	88 (19.2%)	94 (19.9%)	20 (22.5%)
Pack years	19.3 (15.8)	19.59 (16.0)	8.7 (8.7)	17.9 (14.0)	22.2 (17.7)	19.0 (15.1)
Asthma diagnosis (years)	11.5 (10.9)	11.5 (10.8)	9.7 (10.7)	11.1 (10.9)	12.0 (10.8)	11.8 (11.7)

Notes: Data are presented as N (%) or mean (standard deviation, SD).
Abbreviation: BMI, body mass index.

From the 1107 patients included in the study, 10 stopped treatment for various reasons, while 89 required modifications in their initial asthma treatment provided according to the treating physicians' judgment and changed groups within visits, from which the majority (80.9%) had treatment reduction. Demographics of the whole cohort (N=1107), the patients with stable treatment (N=1008) and those with treatment change (N=89) are presented in Table 1.

The patients were divided according to asthma controller treatment at baseline into three groups: A ("as-needed" anti-inflammatory reliever treatment with LD BUD/FOR), B (maintenance treatment with FDC BUD/FOR 200/6μg), and C (maintenance treatment with FDC BUD/FOR 400/12μg). Groups B and C were further sub-categorized according to the reliever/rescue treatment used by patients during the study: no reliever (B1, C1), LD BUD/FOR (groups B2, C2), or SABA (B3, C3) (Table 2).

We initially present the overall results of the whole study cohort (N=1107). Subsequently, in the 1008 patients that received consistent treatment throughout the study, we present the aforementioned subgroup analyses, according to the maintenance (A, B, or C) and also the reliever treatments (1, 2, or 3). In the latter well-defined population we were able to demonstrate more accurately the effectiveness of the treatment with BUD/FOR via Elpenhaler.

Table 2 Distribution of the Patients According to Asthma Treatment at Baseline and the Need for Rescue Treatment

Maintenance and "as needed" Reliever Treatment Used	Patients
A. Anti-inflammatory reliever treatment with BUD/FOR (200/6 μg)	79 (7.8%)
B. Maintenance treatment with BUD/FOR (200/6 μg)	458 (45.4%)
Maintenance treatment with BUD/FOR (200/6 μg) and no reliever treatment used	213
Maintenance treatment with BUD/FOR (200/6 μg) and reliever BUD/FOR (200/6μg)	213
Maintenance treatment with BUD/FOR (200/6 μg) and reliever SABA	32
C. Maintenance treatment with BUD/FOR (400/12 μg)	471 (46.7%)
Maintenance treatment with BUD/FOR (400/12 μg) and no reliever treatment used	337
Maintenance treatment with BUD/FOR (400/12 μg) and reliever BUD/FOR (200/6μg)	49
Maintenance treatment with BUD/FOR (400/12 μg) and reliever SABA	85

Note: Data are presented as N or N (%).
Abbreviations: BUD/FOR, budesonide/formoterol; SABA, short-acting β_2-agonist.

https://doi.org/10.2147/JAA.S517932

Table 3 Asthma Control, QoL, and Lung Function in the Whole Cohort

Asthma Control, QoL, and Lung Function in the Whole Cohort					
N=1107	**V0 mean (SD)**	**V1 mean (SD)**	**V2 mean (SD)**	**Δ V1-V0 mean (95% CI)**	**Δ V2-V0 mean (95% CI)**
ACQ-6	2.16 (0.99)	0.97 (0.69)	0.62 (0.59)	−1.21 (−1.2 to −1.1)	−1.55 (−1.61 to −1.4)
miniAQLQ	4.54 (1.12)	5.89 (0.79)	6.29 (0.66)	+1.38 (1.31 to 1.43)	+1.76 (1.68 to 1.82)
FEV_1 (L)	2.45 (0.90)	2.67 (0.89)	2.72 (0.92)	+0.27 (0.24 to 0.30)	+0.35 (0.31 to 0.38)

Abbreviations: ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; FEV_1, forced expiratory volume in 1 second.

Outcomes in the Whole Cohort and in Subgroups with Stable Treatment

Asthma Control

The mean (SD) score of ACQ-6 in the whole cohort of 1107 patients at baseline, was 2.16 (0.99). After 6 months of treatment, ACQ-6 score was reduced by a mean of 1.55 points ($p<0.001$) (Table 3).

Significant improvements in ACQ-6 were also observed across all groups (A, B, C) after 3 and 6 months, in the 1008 patients on consistent treatment, with the mean difference exceeding the MCID of 0.5 points. Greater improvement was observed in group C patients who received high dose maintenance treatment with BUD/FOR 400/12μg. The mean change (Δ) (95% CI) in ACQ-6 score from baseline after 3 months was −0.96 (−1.13,−0.79) points in group A, −1.09 (−1.17,−1.02) in group B, and −1.24 (−1.32,−1.17) in group C, and improved further after 6 months −0.98 (−1.19,−0.77) points in group A, −1.36 (−1.44,−1.27) in group B, and −1.65 (−1.73,−1.56) in group C ($p<0.001$ for all comparisons) (Figure 2).

The mean (95% CI) changes from baseline in ACQ-6 across subgroups according to the use of rescue therapy were also significant at 3 months [B1=−1.03 (−1.14,−0.92), B2=−1.13 (−1.25,−1.01), B3=−1.26 (−1.56,−0.95), C1=−1.18 (−1.27,−1.1), C2=−1.54 (−1.82,−1.25), C3=−1.31 (−1.49,−1.13)], and 6 months [B1=−1.32 (−1.45,−1.18), B2=−1.40 (−1.53,−1.27), B3=−1.32 (−1.6,−1.04), C1=−1.58 (−1.67,−1.48), C2=−1.85 (−2.26,−1.44), and C3=−1.81 (−2.02,−1.61)] ($p<0.001$ for all comparisons) (Figure 2).

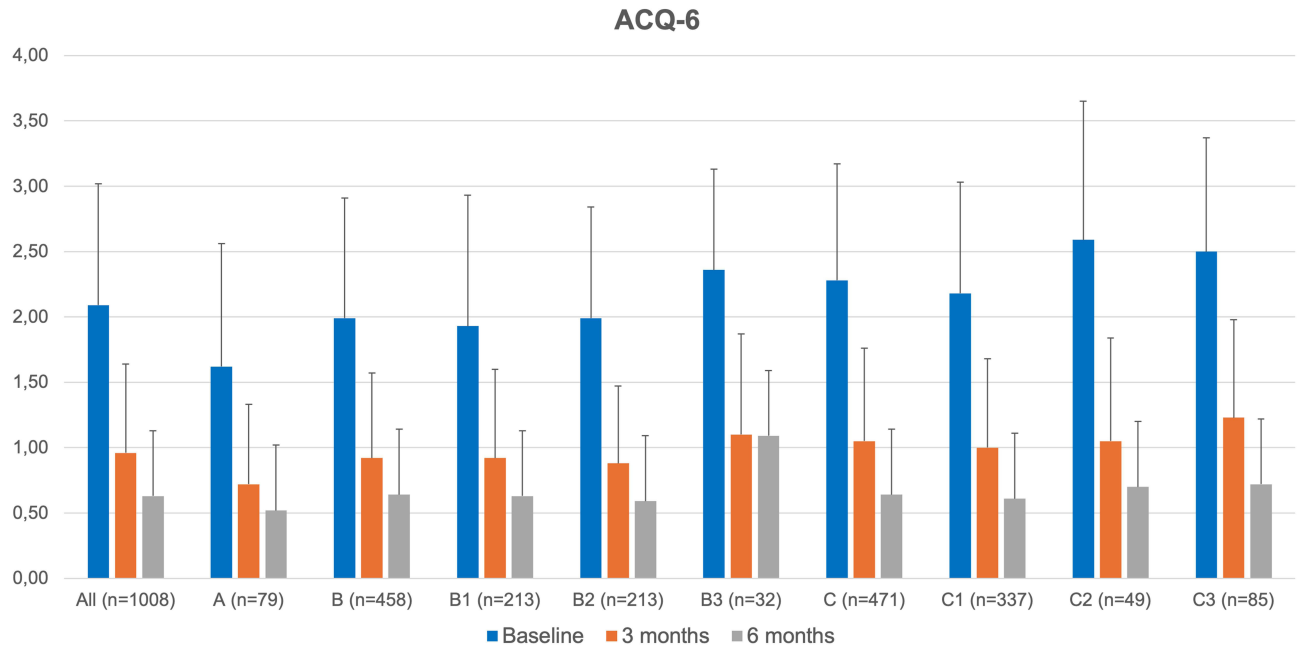

Figure 2 ACQ-6 scores across all subgroups at baseline, 3, and 6 months.

 https://doi.org/10.2147/JAA.S517932

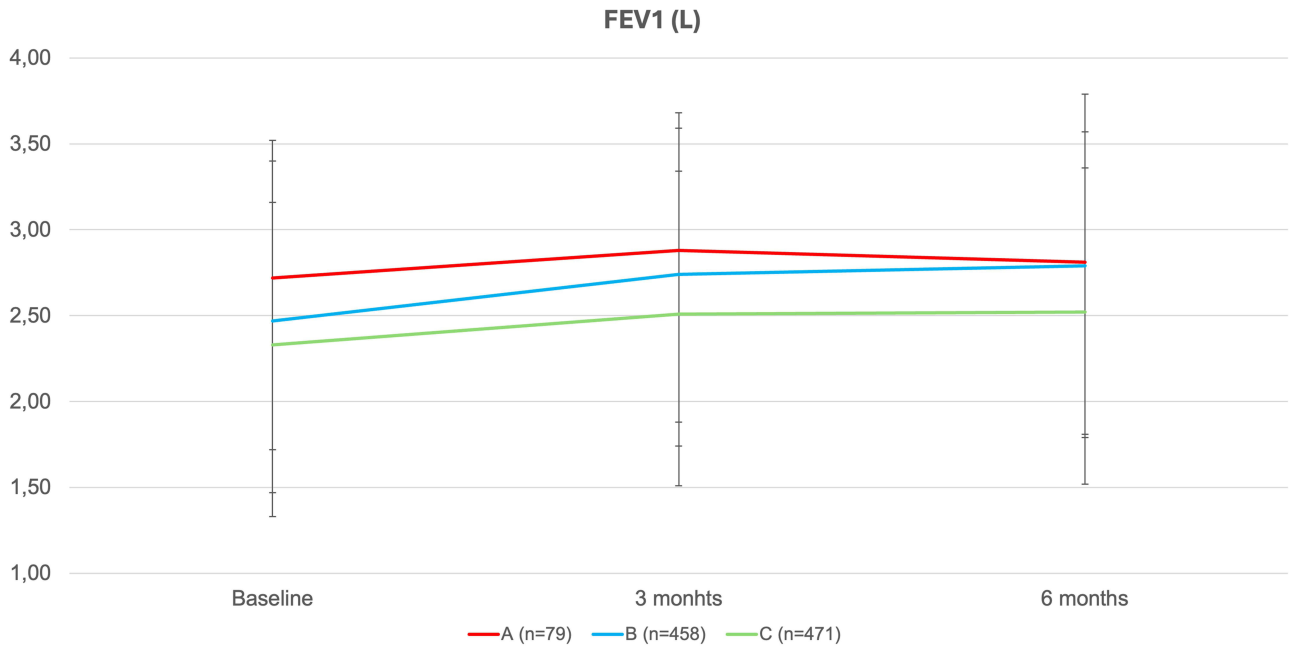

Figure 3 Change in forced expiratory volume in 1 second (FEV_1) measured (in L) across all visits.

Lung Function

Improvement in lung function was observed after 3 and 6 months of maintenance and/or reliever treatment with BUD/FOR FDC. The mean (SD) FEV_1 value was 2.45 (0.90) L at baseline and 2.72 (0.92) L in 6 months (mean change 0.35 L, $p<0.001$) for the total study population (Table 3). Improvement in lung function assessed by FEV_1 was observed across all groups (A, B, C) after 3 and 6 months (Figure 3). Table 4 shows in detail the mean values (SD) and change (95% CI) of FEV_1 in all subgroups across visits.

There was also a small increase in FVC in the whole cohort between visits. Specifically, at V0 FVC was 3.26 (1.14) L and at V2 3.43 (1.13) L, with a mean (95% CI) change between V2-V0 of 0.24 (0.20, 0.28) L. The smallest increase between V2-V0 was observed in Group A: mean Δ (95% CI) for, A=0.09 (−0.01,0.19), B=0.21 (0.15,0.27), and C=0.24 (0.18,0.31).

Table 4 FEV_1 Values and Change in Subgroups Across Visits, in the 1008 Patients on Consistent Treatment

Visits Groups	V0 Mean (SD)	V1 Mean (SD)	V2 Mean (SD)	Δ V1-V0 Mean (95% CI)	Δ V2-V0 Mean (95% CI)
A (N = 79)	2.72 (0.80)	2.88 (0.71)	2.81 (0.76)	0.34 (0.20 to 0.48)	0.16 (0.09 to 0.23)
B (N = 458)	2.47 (0.93)	2.74 (0.94)	2.79 (1.00)	0.24 (0.19 to 0.29)	0.32 (0.26 to 0.37)
B1 (N=213)	2.46 (0.90)	2.70 (0.90)	2.88 (0.98)	0.22 (0.14 to 0.31)	0.35 (0.27 to 0.43)
B2 (N=213)	2.53 (0.93)	2.78 (0.98)	2.78 (1.04)	0.25 (0.18 to 0.31)	0.30 (0.22 to 0.38)
B3 (N=32)	2.16 (0.96)	2.72 (0.98)	2.37 (0.60)	0.34 (0.03 to 0.65)	0.22 (0.06 to 0.39)
C (N = 471)	2.33 (0.83)	2.51 (0.83)	2.52 (0.84)	0.28 (0.24 to 0.32)	0.36 (0.31 to 0.42)
C1 (N=337)	2.39 (0.82)	2.51 (0.85)	2.53 (0.85)	0.23 (0.18 to 0.27)	0.33 (0.26 to 0.39)
C2 (N=49)	2.24 (0.96)	2.66 (0.90)	2.67 (0.96)	0.48 (0.27 to 0.68)	0.58 (0.32 to 0.83)
C3 (N = 85)	2.15 (0.76)	2.42 (0.71)	2.38 (0.73)	0.32 (0.25 to 0.39	0.36 (0.26 to 0.45)

Abbreviations: CI, confidence intervals; FEV_1, Forced expiratory volume in 1 second.

https://doi.org/10.2147/JAA.S517932

We also observed a small increase in FEV_1/FVC between visits in the whole cohort: V0 0.76 (0.11) and V2 0.79 (0.09), with a mean (95% CI) change between V2-V0 of 0.04 (0.03,0.05).

Quality of Life

In the whole cohort, the mean (SD) score of MiniAQLQ was 4.54 (1.12) at baseline (V0). After 6 months of treatment (V2), MiniAQLQ score was increased by 1.76 points (p<0.001) (Table 3).

Significant improvement in MiniAQLQ was observed across all subgroups, in the 1008 patients on consistent treatment, regardless of the maintenance BUD/FOR 200/6, 400/12μg or "as-needed" BUD/FOR 200/6μg treatment. The mean (95% CI) change in MiniAQLQ score after 3 and 6 months of treatment demonstrated statistically significant (p<0.001) improvements in each group: at 3 months A=1.1 (0.92,1.27), B=1.21 (1.12,1.3), and C=1.41 (1.32,1.5) points; at 6 months A=1.27 (1.04,1.5), B=1.54 (1.44,1.64), and C=1.84 (1.73,1.94). Mean changes exceeded the MCID of 0.5 points for MiniAQLQ, indicating meaningful clinical improvements. Greater improvement in QoL was observed in patients that received 6-month maintenance treatment with higher dose of BUD/FOR (Figure 4).

The mean (95% CI) changes from baseline in MiniAQLQ across subgroups according to the use of rescue therapy were also significant at 3 months [B1=1.16 (1.04,1.29), B2=1.2 (1.07,1.33), B3=1.55 (1.1,2), and C1=1.36 (1.26,1.47), C2=1.66 (1.38,1.94), C3=1.46 (1.25,1.67)], and at 6 months [B1=1.45 (1.31,1.59), B2=1.57 (1.43,1.72), B3=1.90 (1.46,2.33), and C1=1.77 (1.66,1.89), C2=1.99 (1.61,2.37), C3=2.00 (1.76,2.23)] (p<0.001 for all comparisons) (Figure 4).

More than 8 out of 10 patients were diagnosed with at least one comorbidity. Patients with comorbidities had worse QoL in V0: MiniAQLQ mean (SD) 4.43 (1.16) and showed higher improvement in V2 [mean change (95% CI) V2-V0: 1.82 (1.73, 1.92)], compared to patients without comorbidities (mean MiniAQLQ (SD) in V0: 4.70 (1.06) and V2: 6.36 (0.57), mean change (95% CI) V2-V0: 1.66 (1.56,1.76).

Use of Reliever Treatment

The frequency of rescue medication use was reduced during the study, on the whole cohort and across subgroups. In total, the mean (SD) number of inhalations "as needed" was reduced from 9.29 (16.10) for Elpenhaler and 13.62 (19.53) for SABA in the 1st month, to 6.03 (12.80) and 7.54 (15.06) in the 3rd month, and 3.64 (9.20) and 2.13 (3.21) in the 6th

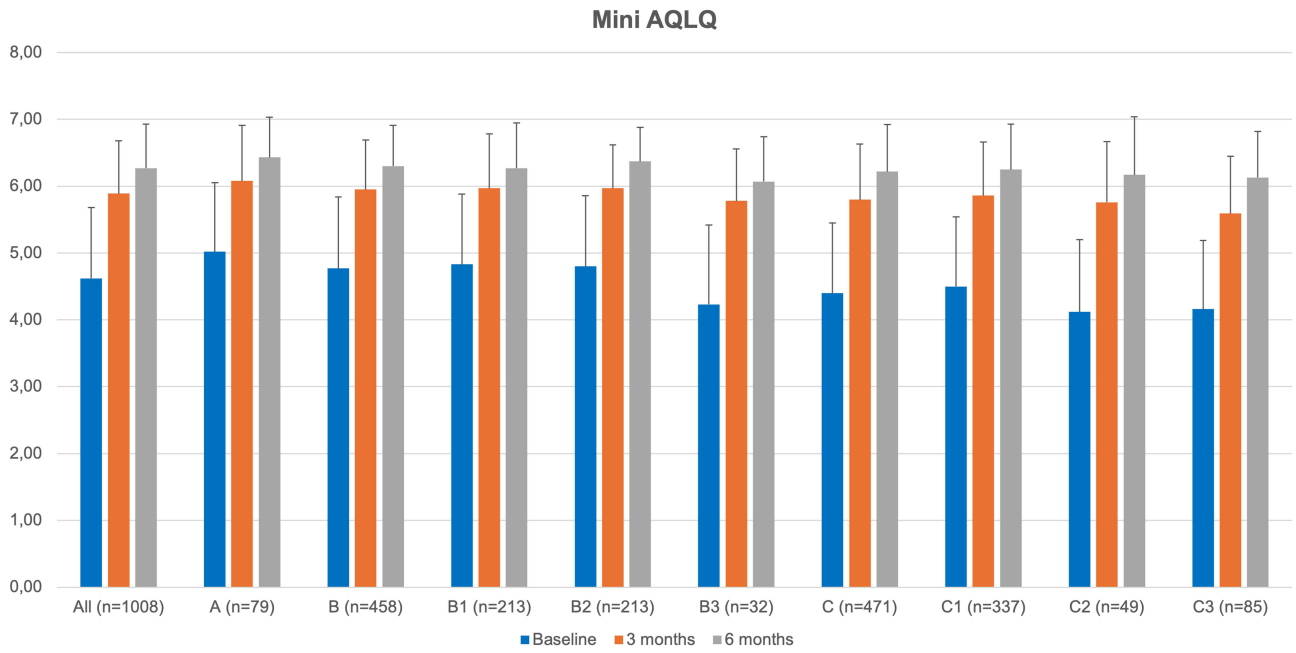

Figure 4 Mini asthma quality of life questionnaire (miniAQLQ) scores across all subgroups at baseline, 3, and 6 months.

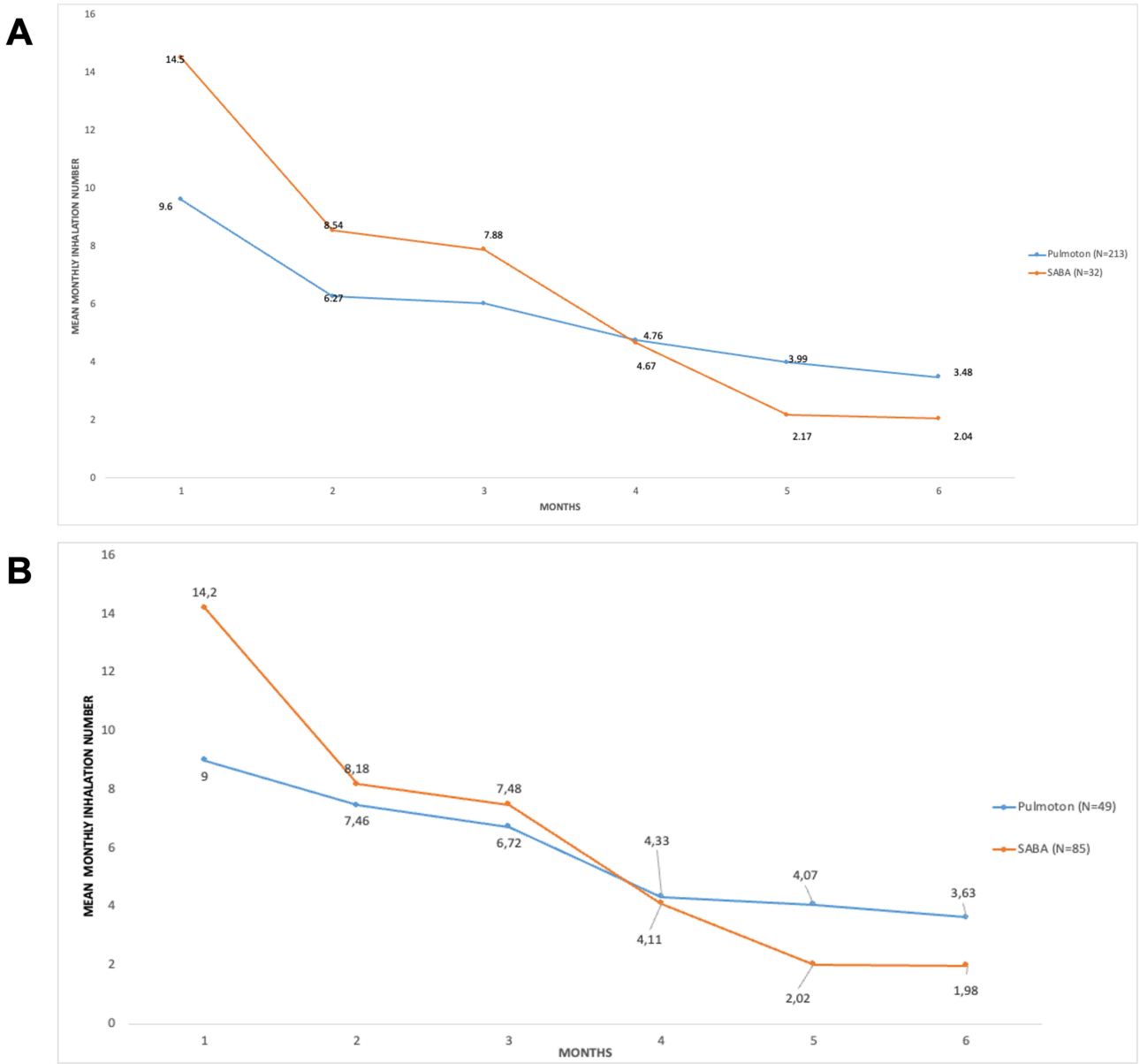

Figure 5 Need for rescue therapy with low dose budesonide/formoterol (BUD/FOR) or short-acting β_2 agonist (SABA) (**A**) in Group B and (**B**) in Group C.

month, respectively. (Figure 5a and b) shows the reduction over time in the use of rescue therapy with BUD/FOR or SABA in groups B and C, respectively.

Number of Severe Exacerbations

At 3 months, 13 patients (1,21%) had at least one exacerbation, and only one of them had two leading to corticosteroid use in 8 patients and in treatment increase in 9 patients. At 6 months, 18 (1,73%) of the patients had at least one exacerbation and only two of them had two, leading to corticosteroid use in 16 patients and in treatment increase in 13 patients. Only one hospitalization was recorded at V2, in a patient having exacerbation for the first time. Most patients that exacerbated belonged in group C (Number of exacerbations recorded in groups across visits V1; A: 0, B:4, C:8, V2; A:1, B:3, C:12).

https://doi.org/10.2147/JAA.S517932

Adverse Events

No serious adverse events attributed to the treatment were recorded throughout the study. Only one patient complained of leg cramps.

Group Analysis of the Patients with Treatment Change (n=89)

Similarly to the whole cohort, improvements in asthma control (ACQ-6 mean (SD) at V0: 2.78 (1.30), V1:1,09 (0,78), V2:0,51 (0,58), mean change from V0 to V1 and V2: −1.72 and −2.29, respectively), in lung function (mean FEV_1 increase (L) V1-V0: 0.33, V2-V0: 0.44) and in quality of life (MiniAQLQ score increase at V1: 2.18 and at V2: 2.69), compared to V0 were observed.

Discussion

NOTOS is the first study to evaluate the real-life effectiveness of the fixed BUD/FOR combination administered via the Elpenhaler® device prescribed as maintenance and/or "as needed" reliever treatment in asthmatic patients according to usual clinical practice. The study showed clinically meaningful improvements in asthma control, as assessed by the ACQ-6 questionnaire, in a Greek population with asthma after 3 and 6 months of treatment with the fixed-dose combination BUD/FOR via Elpenhaler, used either as controller and/or reliever, according to GINA recommendations and usual clinical practice. These improvements were evident at 3 months and were more pronounced at 6 months, with the mean change exceeding the MCID of 0.5 points. Furthermore, improvement was noticed in all sub-populations of the study, irrespective of the dose of maintenance treatment or the use of rescue medication, with the most pronounced improvements achieved in patients receiving maintenance treatment with BUD/FOR 400/12 μg. There were also significant improvements in quality of life at 3 months, further improved at 6 months, irrespective of the presence of comorbidities. Finally, we observed improvement of lung function and reduction in the need for rescue therapy at six months, with an acceptable safety profile of the two doses of BUD/FOR.

The NOTOS study advances the previously available evidence by studies on real-life effectiveness of BUD/FOR administered via the Elpenhaler® prescribed only as maintenance treatment by pulmonologists[12,13] or primary care physicians.[14] The improvements in asthma control, QoL, and FEV_1 in our study further support the previously reported data[12,14] over the clinical effectiveness of the FDC of BUD/FOR, in patients with asthma in the real-life BOREAS study. That study showed that after six months of treatment with the fixed-dose combination BUD/FOR (both doses) via the Elpenhaler as maintenance treatment, asthma control and QoL of asthmatic patients were significantly improved.[12,14] Our data add valuable information on the use of the BUD/FOR FDC in the Elpenhaler device not only as maintenance but also as maintenance and/or reliever therapy (MART). These improvements in asthma control, health status and lung function, are likely attributed to the fact that most of the patients included in our study had a step-up in their previous treatment, either addition of formoterol in their ICS maintenance treatment, and/or addition of ICS/formoterol on demand in patients not adequately controlled with maintenance treatment. Importantly, around 40% of the patients were treatment-naive prior to enrollment and the overall population had poor asthma control at baseline, with a mean score of ACQ-6 was 2.16, with values ≥1.5 indicating uncontrolled asthma.[18,19]

Our study assessed the use of the BUD/FOR FDC in the Elpenhaler device as maintenance and reliever therapy (MART), as proposed for the ICS/formoterol combinations in current asthma recommendations.[1] The use of reliever treatments has evolved significantly over time, with the MART technique appearing as a reliever option from step 3 onwards in GINA 2014,[23] leading to the fundamental change In GINA 2019[6] that excluded SABA alone treatment and introduced "as needed" ICS/formoterol as preferred controller in step 1 and 2 (alternative to daily LD ICS), and as preferred reliever as well, in all steps. GINA 2020 clarified and reinforced GINA 2019, stating that I CS-formoterol is the preferred reliever for patients prescribed maintenance therapy with ICS-formoterol (MART), while for other ICS-LABAs, the reliever was still SABA.[9] Finally, GINA 2021[24,25] onwards[1] recommends a two-track approach, where in the ("preferred") track 1 LD ICS/formoterol is recommended as reliever at all steps: as needed only in Steps 1–2 (mild asthma), and with daily maintenance ICS/formoterol (MART) in Steps 3–5. The elimination of SABA use alone from mild asthma was based on existing evidence that even these patients are at risk of serious adverse events and regular use

of SABA was linked with serious complications, while higher use was associated with higher risk of severe exacerbations and much higher risk of death.[26,27] Conversely, inhaled corticosteroids reduce the risk of asthma deaths, hospitalization, and exacerbations requiring oral corticosteroids (OCS),[28–30] but adherence is poor, particularly in patients with mild or infrequent symptoms. The SYGMA 1 and 2 trials showed that BUD/FOR as needed was better than SABA on asthma control days[31] and that BUD/FOR as needed was non-inferior to low dose ICS on exacerbation prevention.[32] The NOTOS study is the first observational, multicenter study of BUD/FOR administered as maintenance and reliever therapy (MART) with the Elpenhaler device in 1107 Greek patients with asthma of variable severity, for whom the treatment choice was based on the treating physicians' decision. Our results confirm the effectiveness and safety of BUD/FOR FDCs as anti-inflammatory reliever (AIR) and as maintenance and reliever therapy (MART) in a real-world setting, further supporting the results of the aforementioned randomized controlled trials and existing recommendations.

The NOTOS study further focused on the analysis of patient subsets based on controller dose and the use of as needed treatment, either with ICS/formoterol (MART) or SABA in order to assess the impact of inhaled medication in each set. Improvements in asthma control and QoL were consistent across all subgroups, irrespective of the dose of the controller, although improvements in ACQ-6 and MiniAQLQ were more pronounced in the 400/12 μg subgroup, indicating the effectiveness of the higher dose combination in more advanced steps. Furthermore, significant improvements were observed both in patients receiving ICS/formoterol FOR or SABA as a reliever, with small trends for superiority of the MART technique, especially in the HD BUD/FOR maintenance group. In this study, patients used SABA as a reliever because of personal preference, possibly due to long-standing habits and inertia. Notably, asthma control and quality of life improved further between 3 and 6 months of treatment, while the need for rescue therapy decreased significantly throughout the study, supporting the effectiveness of ICS/formoterol combination as a controller, in the context of an observational study and in accordance with previous observations.[11]

The dry powder inhaler (DPI) combination of budesonide and formoterol administered via Elpenhaler has been shown to have equivalent lung deposition compared to the same formulation delivered by the Turbuhaler® device in a pharmacokinetic study including patients with asthma.[33] Furthermore, previous evidence of high satisfaction by Elpenhaler and a use-friendly device contributes to increased adherence and compliance to treatment and therefore better outcomes and reduced healthcare use. In two comparative Greek studies of different inhalers, participants' satisfaction from the use of the Elpenhaler was significantly higher compared to the other devices,[34,35] whereas a study of 755 patients with asthma and COPD showed that Elpenhaler presented lower rates of critical errors that affect drug delivery to the lungs compared with the Diskus® and Turbuhaler® devices.[36] Our data further support the use of BUD/FOR in the Elpenhaler device as anti-inflammatory reliever in mild asthma and in the context of MART strategy as treatment choice in moderate-to-severe asthma in a real-life setting.

A major strength of the NOTOS study is its real-life design, including a wide range of patients selected with broad inclusion criteria, with various characteristics and comorbidities, unlike the necessary restrictions of randomized controlled trials. This is particularly important in asthma, a disease with significant variability. Moreover, we have achieved a large sample size with considerable heterogeneity in access to healthcare resources, consisting of patients recruited in hospital settings and in private practice, with variable disease severity. Another study strength is the low number of patients who were excluded (n=7) or stopped treatment (n=10), that is likely due to the fact that all patients were included and followed-up by their treating physicians in real-life settings. The subgroup analysis of the population with unchanged treatment throughout the study represents an additional strength, as it has provided more robust results in each category. A possible limitation is the observational open-label design of the study that cannot rule out the potential selection bias, yet the inclusion of a large population of >1000 patients in various settings may have – at least partially – compensated for this. Moreover, we were not able to assess potential superiority of ICS/formoterol on exacerbation prevention compared to SABA, due to the small numbers of exacerbations in our study. Finally, the absence of placebo arms and the open-label design cannot rule out a possible Hawthorne effect, but the improvements in both subjective (ACQ-6, MiniAQLQ) and objective measures (lung function) represent an additional factor that supports the effectiveness of ICS/formoterol via Elpenhaler as controller and/or reliever option.

Conclusions

The evidence from the real-life NOTOS study showed significant and clinically meaningful improvement in asthma control, lung function, and asthma-related quality of life in 1107 patients receiving FDC BUD/FOR via Elpenhaler, as anti-inflammatory reliever or as maintenance and/or reliever therapy, after 6 months of treatment in primary care settings. These data further add to the body of evidence supporting the effectiveness of the combination of ICS/formoterol, this time with the Elpenhaler device, in a wide range of asthma patients under various clinical settings.

Data Sharing Statement

The data can be made available from ELPEN after appropriate review of a request.

All data generated or analyzed during this study are included in this published article. Anonymized data will be shared by request from any qualified investigator.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Acknowledgments

The authors would like to thank the following respiratory physicians for their participation in the conduct of the study: Anastasopoulos Andreas, Andri-Vasilescu Camelia, Anevlavis Stavros, Angelis Nikolaos, Argiana Evaggelia, Asimomyti Kyriaki, Babalis Christos, Barouchos Nikolaos, Bartziokas Konstantinos, Boglou Panagiotis, Bousmoukilia Stavroula, Chaloulou Eftychia, Chamerzokova Iliadi Eleni, Charitopoulos Konstantinos, Chatziapostolou Panagiotis, Chatziparaskeva Polyxeni, Christou Konstantinos, Chytiroglou Konstantinos, Damianakos Damianos, Delaveri Aikaterini, Dimoulis Andreas, Efthimiou Maria, Eleftheriou Kleio, Fragkos Konstantinos, Georgitsa-Galarioti Kalliopi, Georgoudakis Grigorios, Kalampoka Dionysia, Kalfountzos George, Kalitsounaki Anna-Maria, Kapetangiorgis Athanasios, Kareklas Nikolaos, Karianou Evgenia, Kasiola Maria, Katsoni Athanasia, Katsourakis Georgios, Kazanas Kosmas, Kolovos Dimitrios, Kostanta Soultana, Kotsifou Efstathia, Kouloumenta Vassiliki, Kourtidou-Papadeli Chrysoula, Krommidas Georgios, Kyriakaki Chara, Kyriakakis Athanasios, Lampropoulos Lampros, Latsios Dimitrios, Lazaridou Athena, Leontaridi Christina, Markatos Miltiadis, Michailidis Dimitrios, Michailidou Athanasia, Michailidou Makrina, Michailopoulos Pavlos, Moysiadis Nikolaos, Mytilinaiou Styliani, Nikas Konstantinos, Ntanasis Andreas, Ntaoulas Konstantinos, Organtzis Ioannis, Panagiotou Marios, Panselinas Efstratios, Papadaki Georgia, Papageorgiou Lazaros, Papaioannou Antonios, Papalexatos Dionysios, Papapetrou Dimosthenis, Parisis Chrysovalantis, Pechlivanidis Theofilos, Peristeri Sofia, Pililitsis Leonidas, Politis Alexios, Politis Ioannis, Siakouli Panagiota, Siganaki Maria-Anna, Sioutkou Agni, Skliris Athanasios, Skopas Vlasios, Sofiadis Lampros, Spiliotopoulou Andromachi, Thomoglou Eleni, Titopoulos Iraklis, Tryfon Ir. Stavros, Tsafaridou Paraskevi, Tsarouchis Georgios, Tsavlis Drosos, Tsitsaras Charalampos, Tsouliaga Athina, Tzelepi Vassiliki, Tzortzaki Eleni, Tzouvelekis Argyrios, Vakouti Eleftheria, Valkanou Eleni, Vassalos Dimitrios, Vassiliou Christos, Vittorakis Stylianos, Xafenias Athanasios, Zakaki Semiramis, Zias Nikolaos, Zikiri Andriani, Zois Panagiotis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The study was funded by ELPEN Pharmaceutical Co. Inc.

Disclosure

Athena Gogali has no conflict of interest within the scope of the submitted work and has received honoraria and consultancy fees from Boehringer Ingelheim, Chiesi, ELPEN, GSK, and Menarini.

Nikoletta Rovina has no conflict of interest within the scope of the submitted work and has received consultancy fees and/or funding from Chiesi, Menarini, AstraZeneca, ELPEN, and CSL Behring.

Konstantinos Samitas has no conflict of interest within the scope of the submitted work and has received consultancy fees and/or funding from Novartis, Elpen, Bristol, Medi-Globe, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Menarini, MSD, Guidotti, and Special Therapeutics.

Paschalis Steiropoulos has no conflict of interest within the scope of the submitted work and has received honoraria and consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Elpen, Menarini, and Specialty Therapeutics.

Dimitrios Potonos has no conflicts of interest to declare.

Maria Bertoli, Polyanthi Papanastasiou, and Alexandros Ginis are employees of ELPEN Pharmaceutical Co. Inc.

Konstantinos Kostikas has no conflict of interest within the scope of the submitted work and has received honoraria and consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GSK, Guidotti, Menarini, Pfizer, Sanofi, and Specialty Therapeutics; he was an employee of AstraZeneca from 02 September to 29 November 2024.

The authors report no other conflicts of interest in this work.

References

1. 2024 GINA main report. global initiative for asthma - GINA. 2024. Available from: https://ginasthma.org/2024-report/. Accessed December 15, 2024.
2. Zervas E, Loukides S, Kostikas K, Bakakaos P, Tzortzaki E, Gaga M. Asthma and asthma-like symptoms in Greece. The Greece asthma national preva- lence survey. *Eur Respir J*. 2012;40.
3. Wertz DA, Pollack M, Rodgers K, Bohn RL, Sacco P, Sullivan SD. Impact of asthma control on sleep, attendance at work, normal activities, and disease burden. *Ann Allergy Asthma Immunol*. 2010;105(2):118–123. doi:10.1016/j.anai.2010.05.009
4. Beasley R, Braithwaite I, Semprini A, et al. ICS-formoterol reliever therapy stepwise treatment algorithm for adult asthma. *Eur Respir J*. 2020;55 (1):1901407. doi:10.1183/13993003.01407-2019
5. Jenkins CR, Bateman ED, Sears MR, O'Byrne PM. What have we learnt about asthma control from trials of budesonide/formoterol as maintenance and reliever?: BUD/FORM MART for asthma. *Respirology*. 2020;25(8):804–815. doi:10.1111/resp.13804
6. Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J*. 2019;53(6):1901046. doi:10.1183/13993003.01046-2019
7. Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med*. 2019;380 (21):2020–2030. doi:10.1056/NEJMoa1901963
8. Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet*. 2019;394 (10202):919–928. doi:10.1016/S0140-6736(19)31948-8
9. Ish P, Malhotra N, Gupta N. GINA 2020: what's new and why? *J Asthma*. 2021;58(10):1273–1277. doi:10.1080/02770903.2020.1788076
10. Barnes PJ. Using a combination inhaler (budesonide plus formoterol) as rescue therapy improves asthma control. *BMJ*. 2007;335(7618):513. doi:10.1136/bmj.39273.537778.AD
11. Ställberg B, Naya I, Ekelund J, Eckerwall G. Real-life use of budesonide/formoterol in clinical practice: a 12-month follow-up assessment in a multi-national study of asthma patients established on single-inhaler maintenance and reliever therapy. *Int J Clin Pharmacol Ther*. 2015;53 (06):447–455. doi:10.5414/CP202224
12. Bakakos P, Papakosta D, Loukides S. Budesonide/formoterol via the Elpenhaler® device in asthmatic patients: a real-world effectiveness study (The BOREAS Study). *Pneumōn*. 2021;1–10.
13. Exarchos KP, Rovina N, Krommidas G, Latsios D, Gogali A, Kostikas K. Correction to: adherence and quality of life assessment in patients with asthma treatment with budesonide/formoterol via the Elpenhaler device: the COMPLETE study. *BMC Pulm Med*. 2022;22(1):322. doi:10.1186/s12890-022-02117-5
14. Steiropoulos P, Exarchos K, Bertoli M, et al. Effectiveness and quality of life in asthmatic patients treated with budesonide/formoterol via Elpenhaler® device in primary care. The "SKIRON" real world study. *J Asthma*. 2023;60(6):1104–1114. doi:10.1080/02770903.2022.2132957
15. Kostikas K. Real-life effectiveness of ICS/LABA inhalers in asthma: the evidence generated and future needs for optimal patient management. *Pneumōn*. 2021;1–3.
16. Archived Reports. Global Initiative for Asthma - GINA. 2016. Available from: https://ginasthma.org/archived-reports/. Accessed January 11, 2025.
17. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902–907. doi:10.1034/j.1399-3003.1999.14d29.x
18. Juniper EF, Bousquet J, Abetz L, Bateman ED. GOAL committee. identifying "well-controlled" and "not well-controlled" asthma using the asthma control questionnaire. *Respir Med*. 2006;100(4):616–621. doi:10.1016/j.rmed.2005.08.012

19. Uniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened ver- sions of the asthma control questionnaire. *Respir Med*. 2005;99(5):553–558. doi:10.1016/j.rmed.2004.10.008
20. Grammatopoulou E, Skordilis E, Koutsouki D, Baltopoulos G. An 18-item standardized asthma quality of life questionnaire-AQLQ(S). *Qual Life Res*. 2008;17(2):323–332. doi:10.1007/s11136-007-9297-y
21. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the mini asthma quality of life questionnaire. *Eur Respir J*. 1999;14(1):32–38. doi:10.1034/j.1399-3003.1999.14a08.x
22. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338. doi:10.1183/09031936.05.00034805
23. Reddel HK, Bateman ED, Becker A, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J*. 2015;46(3):622–639. doi:10.1183/13993003.00853-2015
24. 2021 GINA main report. 2016. Available from: https://ginasthma.org/gina-reports/. Accessed July 24, 2021.
25. Reddel HK, Bacharier LB, Bateman ED, et al. Global initiative for asthma strategy 2021: executive summary and rationale for key changes. *Eur Respir J*. 2022;59(1):2102730. doi:10.1183/13993003.02730-2021
26. Suissa S, Ernst P, Boivin JF, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):604–610. doi:10.1164/ajrccm.149.3.8118625
27. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J*. 2020;55(4):1901872. doi:10.1183/13993003.01872-2019
28. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med*. 2000;343(5):332–336. doi:10.1056/NEJM200008033430504
29. Suissa S. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax*. 2002;57(10):880–884. doi:10.1136/thorax.57.10.880
30. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet*. 2003;361(9363):1071–1076. doi:10.1016/S0140-6736(03)12891-7
31. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide–formoterol as needed in mild asthma. *N Engl J Med*. 2018;378(20):1865–1876. doi:10.1056/NEJMoa1715274
32. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med*. 2018;378(20):1877–1887. doi:10.1056/NEJMoa1715275
33. Grekas N, Athanassiou K, Papataxiarchou K, Rizea Savu S, Silvestro L. Pharmacokinetic study for the establishment of bioequivalence of two inhalation treatments containing budesonide plus formoterol. *J Pharm Pharmacol*. 2014;66(12):1677–1685. doi:10.1111/jphp.12303
34. Zervas E, Samitas K, Gaga M. Assessment of satisfaction with different dry powder inhalation devices in Greek patients with COPD and asthma: the ANASA study. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1845–1855. doi:10.2147/COPD.S113870
35. Karampitsakos T, Hillas G, Zervas E, et al. Prospective evAluatIon foR inhalation devices in Greek patients with COPD and asthma: the PAIR study. *Pulm Pharmacol Ther*. 2020;60(101882):101882. doi:10.1016/j.pupt.2019.101882
36. Bouros D, Evangeliou MN. Critical steps: a non-interventional, multicenter, prospective, observational study on critical handling errors with DPI use, in asthma and COPD patients. *J Pulm Respir Med*. 2016;6(4). doi:10.4172/2161-105x.1000360