

# Budesonide/formoterol via the Elpenhaler® device in asthmatic patients: A real-world effectiveness study (The BOREAS Study)

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## ABSTRACT

**INTRODUCTION** Very limited real-world data have been captured in the Greek asthmatic population regarding the effects of treatment with a fixed-dose combination of budesonide/formoterol via the Elpenhaler® device, on the course of the disease and its impact on the patients' quality of life score.

**METHODS** In this multicenter, observational study, 1230 adult asthmatic patients in Greece that had been recently prescribed a fixed-dose combination budesonide/formoterol, Elpenhaler® were enrolled. The primary endpoint was the evaluation of the effectiveness of the treatment at six months in symptom control using the 7-item Asthma Control Questionnaire (ACQ-7). The secondary endpoints included the quality of life score using the Mini Asthma Quality of Life Questionnaire (MiniAQLQ), pulmonary function, patients' satisfaction with the Elpenhaler® device, and safety.

**RESULTS** In total, 60.3% (742/1230) of the participants were female and the mean age was 51.10±16.98 years. A statistically significant improvement of the mean ACQ-7 score was noted at 3 months (1.01±0.70) and 6 months (0.79±0.66), compared to baseline (2.18±0.91). Similar statistically significant results were noted for the MiniAQLQ score with an improvement from 4.58±1.06 at baseline to 5.95±0.79 at 3 months, and 6.21±0.74 at 6 months. The mean Forced Expiratory Volume at 1 second (FEV1) showed continuing improvement, being 2.36±0.86, 2.58±0.88, and 2.64±0.88 L, at baseline, 3, and 6 months, respectively.

**CONCLUSIONS** These real-world data showed that the administration of a fixed dose combination of budesonide/formoterol using the Elpenhaler® device was well-tolerated and effective in significantly reducing the symptoms of asthma and improving the quality of life.

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## INTRODUCTION

The health-related quality of life (HRQoL) of patients with asthma is affected by the presenting symptoms and their limiting effects on their physical, work and social aspects of their everyday life<sup>1</sup>. Hence, early and effective control of the disease can significantly impact their HRQoL, as assessed through various tools, and, in turn, decrease the use of healthcare resources<sup>1,2</sup>.

When referring to disease control in asthmatic patients, two aspects should be considered, the repression of symptoms and the reduction of the risk for potentially unfavorable outcomes, which include the incidence of exacerbations, persistent effects on lung function, and adverse events emerging from the treatment itself. In prospect, inadequate symptom control usually results in increased exacerbations and overall a negative effect on the quality of life<sup>2</sup>. Spirometry and, particularly, persistent airway obstruction are additive parameters for predicting future risk<sup>2</sup>.

Self-reported outcomes and physician-assessed tools

provide a method for harmonizing and quantifying asthmatic patients' initial state and changes occurring thereafter. The Asthma Control Questionnaire (ACQ) is a 7-item questionnaire that incorporates and evaluates symptoms and the treating guidelines. Certain cut-off scores, ranging from 0.75–1.50 have been proposed to differentiate between 'well controlled' and 'not well controlled' patients<sup>3</sup>. Validated translations of the ACQ-7 questionnaire in different languages, including Greek, are available<sup>4</sup>. The concurrent use of more than one of these assessment tools may not offer practical advantages to the clinician, as the available questionnaires may not exhibit the same correlation to the patient's symptoms<sup>5</sup>.

The initial evaluation and monitoring of the patient's quality of life are often overlooked in daily clinical practice, in favor of time conservation and clinical and laboratory examinations. However, in conditions such as asthma, where the disease can produce debilitating symptoms that affect the person's health perception and their ability for social

activity, the assessment of the quality of life can significantly steer the therapeutic goals required. The Asthma Quality of Life Questionnaire (AQLQ) was developed specifically for asthmatic patients, compared to other generic tools that provide only a general representation<sup>6</sup>. To address the limited resources and time available in clinical trials, a shorter version, the Mini Asthma Quality of Life Questionnaire (MiniAQLQ), was constructed with 15 instead of 32 self-reported items, which has been validated and translated in the Greek language<sup>7-9</sup>.

The combined use of ACQ-7 and MiniAQLQ has wide acceptance among clinicians and offers measurable insights into disease control. Long-term follow-up studies comparing these tools to lung function tests have noted a high interpatient variability of the latter without a necessary correlation to the self-assessment presented by patients. These results suggest that clinical indicators alone cannot provide an accurate measurement of the effect of treatment on the patient's quality of life, which may be obtained instead through validated questionnaires<sup>10</sup>.

The Feeling of Satisfaction with Inhaler-10 (FSI-10) questionnaire is a self-reported instrument containing 10 questions, each with 5 possible responses on a 5-point Likert scale (5='very', 4='fairly', 3='somewhat', 2='not very', 1='hardly at all') with maximum total score 50. It assesses the level of satisfaction of the patients with the inhaler and includes items on ease or difficulty of use, portability, and usability. FSI-10 has been validated and translated into the Greek language<sup>11,12</sup>.

According to Global Initiative for Asthma (GINA) 2021 guidelines, for patients receiving maintenance inhaled corticosteroid (ICS) treatment with as-needed short-acting beta-agonist (SABA), adding long-acting beta-agonist (LABA) in a combination inhaler provides additional improvements in symptoms and lung function with a reduced risk of exacerbation compared with the same dose of ICS<sup>13,14</sup>.

Very limited published data of the effectiveness of the fixed-dose combination budesonide/formoterol (BUD/FORM) administered via the Elpenhaler® device in a real-world setting are available for Greece. The present study, the BOREAS study, aimed to additionally collect information on the patients' asthma control, quality of life, comorbidities, treatment effectiveness regarding the absolute number of patients' eosinophils count, safety, and the satisfaction from the use of the Elpenhaler® inhalation device.

## METHODS

The study was conducted with a non-interventional design that did not impose any therapeutic restriction or evaluations, in order to capture the typical clinical practice of physicians in Greece. A summary of the study has been published at [clinicaltrials.gov](https://clinicaltrials.gov) (ID: NCT03033758). The study was conducted between February and December 2017 and included hospitals in Athens, Thessaloniki, Chania, Kozani, and Lamia, and private medical offices from a wide

geographical area in Greece. In total, 1230 adult asthmatic patients were enrolled from 73 sites. To be enrolled, patients should have been recently prescribed a fixed-dose combination of BUD/FORM via the Elpenhaler® device in doses of 200/6 µg, or 400/12 µg as a maintenance treatment for diagnosed asthma (according to the investigator) and not be concomitantly receiving another combination of ICS and LABA. Exclusion criteria included age <18 years, chronic obstructive pulmonary disease, the use of any ICS/LABA combination, inappropriate use and non-adherence to inhalation treatments. Evaluations were performed at baseline, 3 months, and 6 months, and included ACQ-7, MiniAQLQ, spirometry parameters, and the FSI-10 questionnaire.

The primary objective of the study was the effect of the fixed-dose combination BUD/FORM Elpenhaler® treatment, using a steady daily dose, on the frequency and severity of asthmatic symptoms, as evaluated by the ACQ-7 at 6 months. Secondary objectives were the impact on the QoL as evaluated by the change in the MiniAQLQ total score, lung function evaluation through FEV<sub>1</sub> and forced vital capacity (FVC) changes, as well as the incidence of adverse events, disease exacerbations, and hospitalizations. Product satisfaction with the Elpenhaler® device was additionally assessed using the FSI-10 questionnaire at 3 months.

Endpoints also included the evaluation of blood biomarkers, such as the eosinophils count where available, vital signs, and concomitantly used medications and comorbidities, for a possible correlation with the treatment response.

The calculation of the sample size was based on the primary endpoint, namely the change in the ACQ-7 questionnaire from the start of treatment with BUD/FORM Elpenhaler® to 6 months ( $\pm$  2 weeks). According to the SMARTASIA study, which was conducted on inadequately controlled asthmatic patients, the administration of budesonide formoterol resulted in a statistically significant improvement in the ACQ questionnaire by 0.58 units (SD=0.93 units) after a 12-week treatment period. In addition, according to the study of Kuna et al.<sup>15</sup>, the administration of budesonide formoterol resulted in a statistically significant improvement in the ACQ questionnaire by at least 0.7 units after a 24-week treatment period. Therefore, based on the aforementioned data, a sample size of 1200 patients was considered to be adequate in order to estimate a change from baseline to 6 months in the ACQ-7 questionnaire of at least 0.7 units, with a 95% confidence level and the power exceeding 90%.

Continuous characteristics are presented in the form of mean $\pm$ SD values, as well as in the form of median and IQR (interquartile range, between the 25th and 75th percentile). Categorical characteristics are presented in the form of frequencies and percentages. The paired samples t-test was used in order to investigate the change in the examined characteristics between two visits, while the repeated

measures analysis of variance (ANOVA) was used in order to investigate the change of the examined characteristics among the three visits (baseline, 3 months, and 6 months).

RESULTS

Overall, 96% (1181/1230) of the patients enrolled successfully completed the visit at 3 months and 94.3% (1160/1230) at 6 months. The mean age was 51.10±16.98 years, with 60.3% (742/1230) of the participants being female and 63.7% (783/1230) never smokers (Table 1).

Of the total population, 41.0% (504/1230) of the enrolled patients did not receive any treatment for their asthma before starting the fixed-dose combination BUD/FORM treatment, and 56.9% (700/1230) had a previous treatment (Table 1).

Primary objective

The mean ACQ-7 score was statistically improved between baseline and the visits at 3 and 6 months. The ACQ-7 score decreased from 2.18±0.91 at baseline to 1.01±0.70 at 3 months and 0.79±0.66 at 6 months (Table 1).

Secondary objectives

Similar to the ACQ-7, the MiniAQLQ score significantly increased from 4.58±1.06 (Table 1) to 5.95±0.79 and 6.21±0.74, at the respective time points (Figure 2). A significant, strong, negative, linear correlation between the change at 6 months in ACQ-7 score (-1.4) and MiniAQLQ score (1.6) (rs=0.758, p<0.001) was observed. The FSI-10 tool was used to assess the functionality and ease of use of the Elpenhaler® device, reporting a mean score 44.4±5.0 out of 50.

The most commonly reported comorbidities were diseases of the upper respiratory system (34.7%, 427/1230), followed by cardiovascular diseases (20.0%, 246/1230), metabolic diseases (16.2%, 199/1230), respiratory infections (10.9%, 134/1230), gastroesophageal reflux disease (GERD) (10.6%, 130/1230), psychiatric disorders (5.9%, 73/1230), skin diseases-eczema (2.0%, 25/1230) and obstructive sleep apnea (OSA) syndrome (2.0%, 25/1230).

The mean forced expiratory volume at 1 second (FEV<sub>1</sub>) also exhibited a gradual improvement with treatment (p<0.0001), from 2.36±0.86 at baseline to 2.58±0.88 and 2.64±0.88 L at 3 and 6 months, respectively.

The incidence of adverse events (AE) was very low, with only 7 patients with AEs, of whom 4 were deemed as having AEs possibly-related with the treatment (hoarseness and oropharyngitis) and 3 other non-related events documented. There were no reported discontinuations of treatment due to AEs. Disease exacerbations were reported in 14 patients, however without any need for hospitalization.

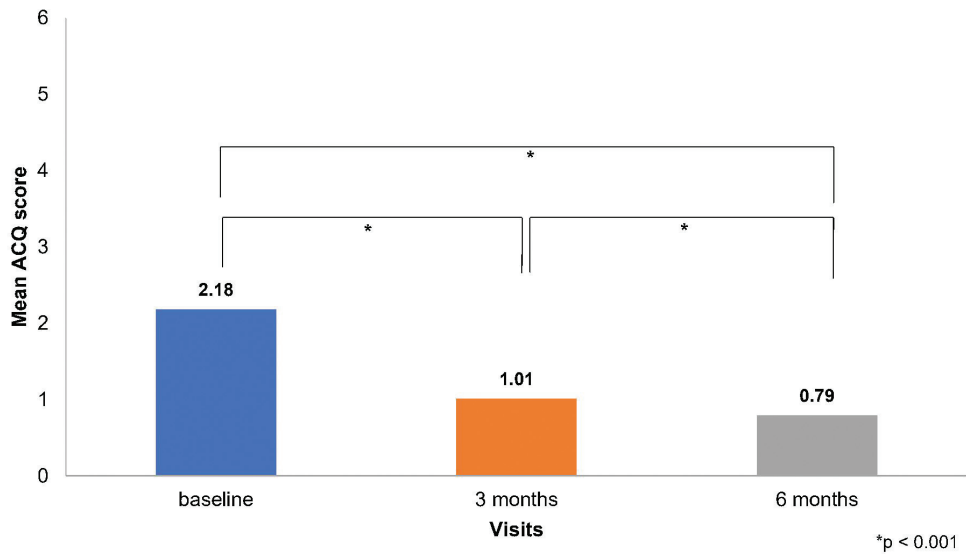
An analogous decrease in the ACQ-7 and increase in the MiniAQLQ (Table 2) score over time was noted when contrasting patients without any comorbidity to those with at least one comorbidity, without identifying any other trends

Table 1. Baseline characteristics of participants (N=1230)

Characteristics	%
Age (years), mean ± SD	51.1 ± 17.0
BMI (kg/m²), mean ± SD	28.3 ± 5.6
Sex	
Female	60.3
Male	39.7
Race	
White	99.6
Black	0.3
Other	0.1
Smoking status	
Non-smoker	63.7
Current smoker	18.2
Former smoker	18.1
Vaccination	
Influenza vaccine	27.4
Pneumococcus	20.6
Onset from diagnosis	
Previously diagnosed patients	50.2
Newly diagnosed	49.8
Previous treatment for asthma	
Without previous treatment, % (n)	41.0 (504)
With previous treatment, % (n)	56.9 (700)
SABA	21.5
ICS+SABA	14.4
ICS+SAMA	0.2
ICS	9.5
ICS+SABA+THEOPHYLLINE	0.1
LABA	2.1
ICS+LABA	1.6
ICS+LABA+SABA	0.1
LABA+LTRA	0.1
ICS+LTRA	0.2
ICS+LTRA+SABA	0.4
LTRAs	0.7
LTRA+SABA	0.9
Other*	5.1
Missing data	2.1
Evaluation of asthma control (n=1210)	
ACQ-7 score, mean ± SD	2.18 ± 0.91
Evaluation of QoL (n=1228)	
MiniAQLQ score, mean ± SD	4.58 ± 1.06

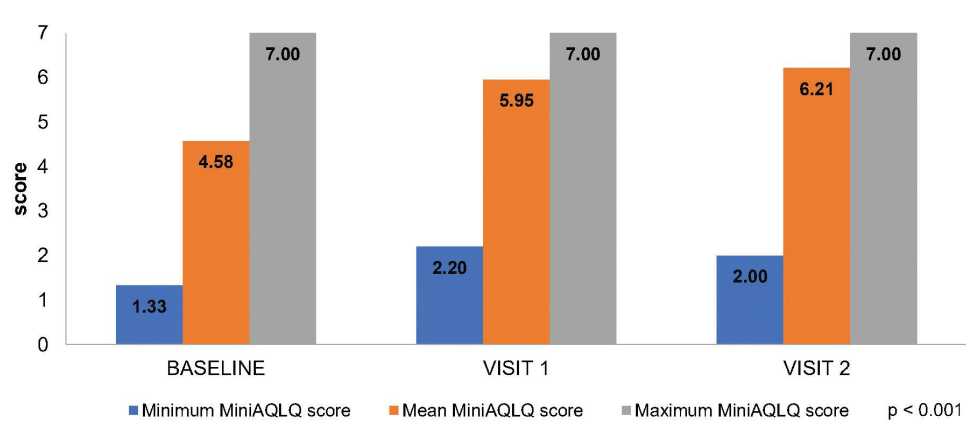
\*Previous treatments for asthma labelled as 'Other' include: anti-IgE, antibiotics, antihistamines, and other various combinations of the treatments included in the table in small percentages. SD: standard deviation. BMI: body mass index. SABA: short-acting beta-agonist. ICS: inhaled corticosteroid. SAMA: short-acting muscarinic antagonist. LABA: long-acting beta-agonist. LTRA: leukotriene receptor antagonist. ACQ-7: seven-item asthma control questionnaire. QoL: quality of life. MiniAQLQ: mini asthma quality of life questionnaire.

Figure 1. ACQ-7 score at 0, 3, and 6 months



ACQ-7=7-item Asthma Control Questionnaire

Figure 2. MiniAQLQ score at 0, 3, and 6 months



MiniAQLQ=Mini Asthma Quality of Life Questionnaire

compared to the respective results in the total population. The additional analysis in the subgroup of asthmatic patients (47.1%, 579/1230) with the following five most common comorbidities according to GINA: an upper respiratory tract infection (URTI) (34.7%), GERD (10.6%), obesity (7.8%), psychiatric disorders (5.9%), and OSA (2%), at baseline, the median score of ACQ-7 was  $2.2\pm1.0$  (Table 3, Figure 3) and of the MiniAQLQ was  $4.5\pm1.1$  (Table 4, Figure 4). After six months of treatment, there was a significant decrease in the ACQ-7 score ( $p<0.001$ ) and an increase in the MiniAQLQ score ( $p<0.001$ ).

A subgroup analysis was performed in 14.6% (180/1230) of patients with an absolute number of eosinophils/mL in peripheral blood greater than 150. In the subgroup

with a mean of  $352\pm202.9$  eosinophils/mL in peripheral blood at baseline, the mean ACQ-7 score was  $2.29\pm0.91$  (Supplementary file Material 1) and the mean MiniAQLQ score was  $4.35\pm1.07$  (Supplementary file Material 2). These are significantly lower values compared with the subgroup of 6.3% (77/1230) patients with an absolute number of eosinophils/mL in peripheral blood  $\leq150$  and a mean of  $88\pm51.1$  eosinophils/mL of peripheral blood (ACQ-7 score =  $2.10\pm1.11$ ; MiniAQLQ score =  $4.43\pm1.17$ ). Following six months of treatment, there was a statistically significant decrease in the ACQ-7 score ( $p<0.001$ ) with a mean of  $0.77\pm0.59$ , as well as a significant increase in the MiniAQLQ score ( $p<0.001$ ) with a mean of  $6.27\pm0.66$ .

Furthermore, asthma control and QoL were assessed in

**Table 2. Evaluation of the asthma control via the ACQ-7 scale and MiniAQLQ scale at baseline, 3 months and 6 months among patients with at least one comorbidity and patients without any comorbidity**

	Baseline	3 months	6 months
<b>ACQ-7 scale</b>			
<b>Patients with at least one comorbidity</b>	719	620	645
Mean $\pm$ SD	2.23 $\pm$ 0.93	1.01 $\pm$ 0.69	0.76 $\pm$ 0.64
Median (IQR)	2.14 (1.57–2.86)	0.86 (0.43–1.43)	0.57 (0.29–1.00)
Range	0.14–5.00	0.00–3.86	0.00–3.14
<b>Patients without any comorbidity</b>	511	461	474
Mean $\pm$ SD	2.12 $\pm$ 0.88	1.02 $\pm$ 0.71	0.83 $\pm$ 0.69
Median (IQR)	2.14 (1.43–2.57)	0.86 (0.43–1.43)	0.71 (0.29–1.29)
Range	0.00–5.57	0.00–3.86	0.00–3.57
<b>MiniAQLQ scale</b>			
<b>Patients with at least one comorbidity</b>	719	675	669
Mean $\pm$ SD	4.51 $\pm$ 1.08	5.92 $\pm$ 0.80	6.20 $\pm$ 0.73
Median (IQR)	4.53 (3.80–5.33)	6.07 (5.53–6.53)	6.40 (5.87–6.73)
Range	1.40–7.00	2.93–7.00	2.00–7.00
<b>Patients without any comorbidity</b>	511	496	489
Mean $\pm$ SD	4.66 $\pm$ 1.02	5.99 $\pm$ 0.78	6.23 $\pm$ 0.76
Median (IQR)	4.67 (4.00–5.47)	6.13 (5.53–6.60)	6.47 (5.80–6.80)
Range	1.33–7.00	2.20–7.00	2.60–7.00

SD: standard deviation. IQR: interquartile range 25th–75th percentile. ACQ-7: seven-item asthma control questionnaire. MiniAQLQ: mini asthma quality of life questionnaire.

**Table 3. Evaluation of the asthma control via the ACQ-7 scale at baseline, 3 months, and 6 months in relation to the five most common comorbidities according to GINA**

	Baseline	3 months	6 months
<b>Patients with at least one comorbidity belonging to the five most common</b>	559	495	522
Mean $\pm$ SD	2.21 $\pm$ 0.96	0.97 $\pm$ 0.66	0.73 $\pm$ 0.62
Median (IQR)	2.14 (1.57–2.86)	0.86 (0.43–1.29)	0.57 (0.29–1.00)
Range	0.14–5.00	0.00–3.86	0.00–3.14
<b>Patients without any comorbidity belonging to the five most common</b>	651	586	597
Mean $\pm$ SD	2.15 $\pm$ 0.87	1.05 $\pm$ 0.72	0.84 $\pm$ 0.69
Median (IQR)	2.14 (1.57–2.71)	0.86 (0.43–1.57)	0.71 (0.29–1.29)
Range	0.00–5.57	0.00–3.86	0.00–3.57

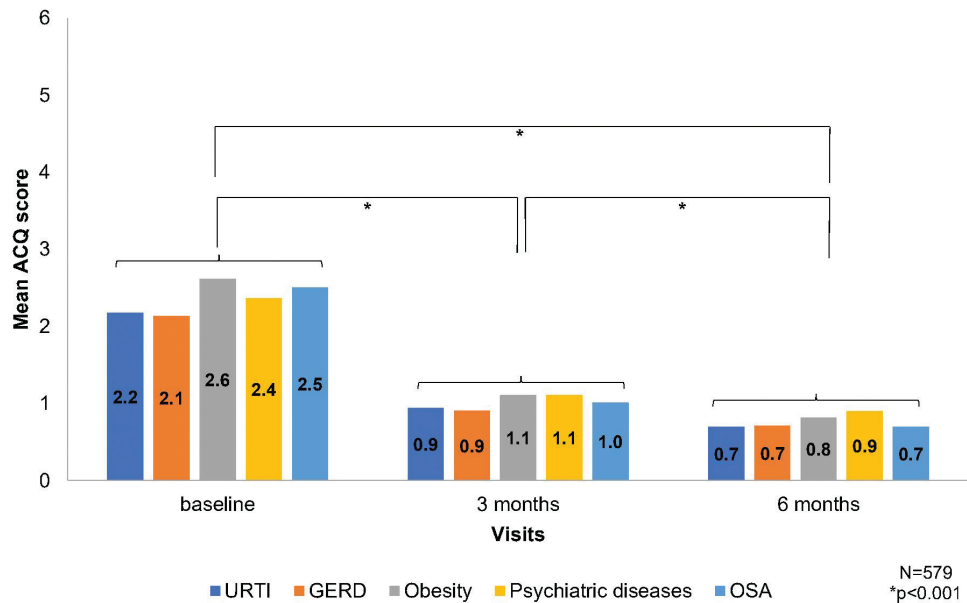
SD: standard deviation. IQR: interquartile range 25th–75th percentile. ACQ-7: seven-item asthma control questionnaire.

a subgroup of 16.2% patients (199/1230) with metabolic disorders among other comorbidities (i.e. obesity, type 2 diabetes mellitus (T2DM), and dyslipidaemia). At baseline, the mean ACQ-7 and MiniAQLQ scores were 2.45 $\pm$ 0.97 and 4.21 $\pm$ 1.13, respectively, for the group of patients with metabolic disorders, whereas the mean ACQ-7

and MiniAQLQ scores were 2.13 $\pm$ 0.89 and 4.65 $\pm$ 1.03, respectively, for the group of patients without metabolic disorders. After 6 months, a significant decrease in the ACQ-7 score ( $p<0.001$ ), a significant increase in the MiniAQLQ score ( $p<0.001$ ), and a significant, strong, negative, linear correlation between the change in the ACQ-7 (-1.61) and



Figure 3. ACQ-7 score in relation to five common categories of comorbidities at 0, 3, and 6 months



ACQ-7=7-item Asthma Control Questionnaire, URTI=Upper Respiratory Tract Infection, GERD=Gastroesophageal Reflux Disease, OSA=Obstructive Sleep Apnoea

Table 4. Evaluation of quality of life via the MiniAQLQ scale at baseline, 3 months and 6 months in relation to the five most common comorbidities according to GINA

	Baseline	3 months	6 months
Patients with at least one comorbidity belonging to the five most common			
Mean ± SD	578	545	542
Median (IQR)	4.55 ± 1.10	5.96 ± 0.78	6.23 ± 0.70
Range	4.53 (3.87–5.40)	6.07 (5.60–6.53)	6.47 (5.87–6.73)
	1.40–7.00	2.93–7.00	3.27–7.00
Patients without any comorbidity belonging to the five most common			
Mean ± SD	650	626	616
Median (IQR)	4.60 ± 1.02	5.95 ± 0.80	6.19 ± 0.78
Range	4.60 (4.00–5.40)	6.07 (5.47–6.53)	6.40 (5.80–6.80)
	1.33–7.00	2.20–7.00	2.00–7.00

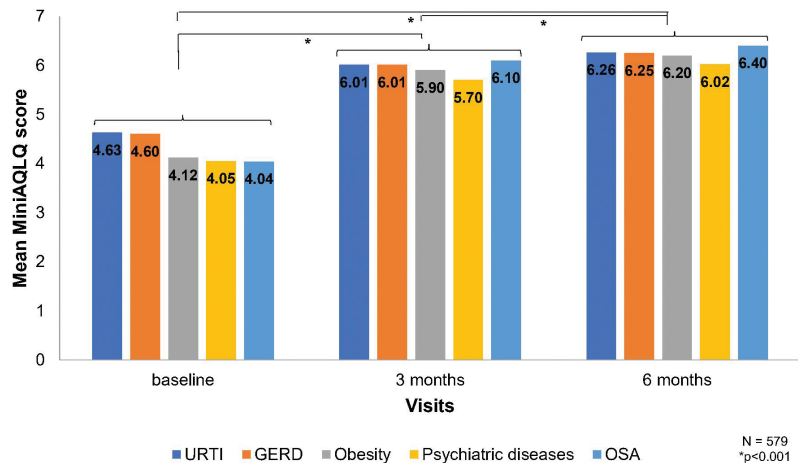
SD: standard deviation. IQR: interquartile range 25th–75th percentile. MiniAQLQ: mini asthma quality of life questionnaire.

MiniAQLQ (1.93) score ( $p<0.001$ ) between visits, were noted for the group of patients with metabolic disorders (Supplementary file Materials 3 and 4). Similar results were also observed in patients without metabolic disorders.

Asthma control and QoL were also assessed in a subgroup of 5.9% patients (73/1230) with psychiatric disorders (i.e. depression, anxiety, and panic disorder). At baseline, the mean ACQ-7 and MiniAQLQ scores were  $2.37\pm1.23$  and  $4.05\pm1.31$ , respectively, in patients with psychiatric disorders and  $2.17\pm0.89$  and  $4.61\pm1.03$  in patients without psychiatric disorders, respectively. After

6 months, a significant decrease in the ACQ-7 score ( $p<0.001$ ), a significant increase in the MiniAQLQ score ( $p<0.001$ ), and a significant, strong, negative, linear correlation between the change in the ACQ-7 (-1.48) and MiniAQLQ (1.95) score ( $p<0.001$ ) between visits, were noted in patients with psychiatric disorders (Supplementary file Materials 5 and 6). Similar results were also observed in patients without psychiatric disorders.

No other important change resulting from treatment was noted between baseline measurements and the observational visits in the vital signs (blood pressure, cardiac frequency).

**Figure 4. MiniAQLQ score in relation to five common categories of comorbidities at 0, 3, and 6 months**

MiniAQLQ=Mini Asthma Quality of Life Questionnaire, URTl=Upper Respiratory Tract Infection,  
GERD=Gastroesophageal Reflux Disease, OSA=Obstructive Sleep Apnoea

## DISCUSSION

After six months of treatment with the fixed-dose combination BUD/FORM via the Elpenhaler®, there was a clinically significant improvement in asthma control and QoL of asthmatic patients, as shown using the difference in the ACQ-7 and MiniAQLQ scores, respectively.

Furthermore, a clinically significant improvement in asthma control and QoL were noted in asthmatic patients with five common comorbidities, especially, in those with OSA and obesity, despite the absolute eosinophil number/mL in peripheral blood. Similar results in the ACQ-7 and MiniAQLQ scores were noted when comparing data from patients with one to four comorbidities and those free from other diseases, to the overall analysis population.

The presence of metabolic or psychiatric disorders followed the statistically significant trends of the total population and did not produce any meaningful correlation with the course of the disease.

The results of large-scale epidemiologic studies in Greece indicate that the prevalence of asthma and asthma-related symptoms is higher than the relevant global metrics<sup>16,17</sup>. Despite this, real-world studies that aim to elucidate the effect of maintenance treatment with fixed-dose combination BUD/FORM via Elpenhaler® device in this regional pool of asthmatic patients are very scarce.

The BOREAS study aimed to analyze the information captured by self-reported and physician-evaluated tools that is integral to the clinical and functional tests evaluated in asthma. Such data can play a decisive role in the treatment goals set for these patients, especially in those with a stable over-time lung function or an inconsistency between their symptomatology and paraclinical tests. The ACQ-7 and MiniAQLQ were chosen since they have both been translated

and validated in the Greek language and are widely accepted in everyday practice. Since this was an observational study, no imposition was set on the choice of treatment, clinical and paraclinical evaluations, or visiting schedule of asthmatic patients, to minimize the limitations on generalizability associated with the rigidly defined evaluations of an interventional trial.

No comparative analyses were planned for the different dosing groups since no significant differences were expected using an individualized treatment approach.

The main finding of the BOREAS study was that asthma control with steady maintenance therapy of a fixed-dose combination BUD/FORM was significantly improved as early as 3 months and continued to do so at 6 months. The rapid therapeutic improvement, as assessed by the ACQ-7, could be anticipated, since other reports have shown this effect to take place as early as 2 weeks after treatment initiation<sup>18</sup>. The sustainability and further improvement at 6 months without a dose increase in the fixed-dose combination BUD/FORM regimen has similarly been described in a retrospective analysis of clinical trials, despite that it involved the use of reliever or rescue medications<sup>19</sup>.

If the suggested judicious cut-off point of 1.5 to identify ‘not well controlled’ patients is used, then the population overall did not meet the criterion for adequate control at the time of enrolment, with the opposite being true for the two follow-up evaluations<sup>3</sup>. It could be assumed that the significant improvement in the ACQ-7 score could be attributed to: 1) the step-up of treatment since 56.9% (700/1230) were receiving some type of anti-asthmatic treatment including ICS standalone, ICS plus SABA, ICS or SABA as needed, LTRAs, LTRA+SABA, as has been shown in other studies with inadequately controlled patients who

switched to a fixed-dose combination BUD/FORM<sup>20</sup>; and 2) the 41% (504/1230) of patients that were naïve to treatment. Furthermore, it has been suggested that the future risk of a patient not being regulated by treatment is inversely tied to the extent of their current disease control<sup>19,21</sup>. Despite their initial disease status of not being adequately controlled, the population of the BOREAS study did achieve asthma control at the end of their observation.

As it was anticipated, the results of the MiniAQLQ correlated with those of the ACQ-7 for symptom control and treatment goal attainment, nonetheless in a statistically significant fashion in both visits. Similar observations on the significant improvement in the quality of life, as measured through the MiniAQLQ, have been published even for short regimens of a fixed-dose combination BUD/FORM of 4, 8, or 12 weeks. A one-year follow-up study in patients with asthma has shown that improvements in the AQLQ were maintained over time in a similar fashion between dosing of 200 and 800 µg of budesonide, with and without formoterol<sup>10</sup>.

No direct effect on the disease course could be identified from the analyses of the study's endpoints in subgroups according to the eosinophil count and type of comorbidities. Similar findings came to light from a recent open-label controlled trial in 668 patients either receiving albuterol, budesonide, or budesonide plus formoterol. According to their results, no clear effect to the disease's exacerbations or ACQ-5 score could be deduced from the age, sex, baseline smoking status, history of exacerbations, baseline SABA use, baseline score on the ACQ-5, FEV<sub>1</sub>%, and baseline blood eosinophil count<sup>22</sup>.

Among the patients who participated in the study, a subgroup of 47.1% (579/1230) of patients had at least one of the five most frequently encountered comorbidities that according to GINA guidelines<sup>13</sup>, are present in patients with asthma (URTI, GERD, psychiatric disorders, obesity, and OSA). These have been commonly reported in other studies, with various possible mechanisms being proposed as the link with asthma, including affected levels of inflammatory mediators, cellular stress, and mechanical anatomic effects<sup>23-27</sup>. Since multiple chronic conditions tend to occur concurrently, affect the patient's overall quality of life and exposure to healthcare services, and influence the severity of the disease, the management of asthma patients with comorbidities should be addressed as a whole<sup>24,27-29</sup>.

Exacerbations were documented in just over 1% (14/1230) of the participants. Despite an annualized rate could not be objectively calculated due to the 6 months follow-up, the projected rate of exacerbations of any severity is in alignment with the range noted from other interventional and observational studies<sup>22,30-33</sup>. Contrary to the findings of certain randomized trials with high-dose ICS, metaanalyses of interventional and observational studies concluded that fewer exacerbations occur with a fixed-dose combination of ICS/LABA than with an ICS alone<sup>34,35</sup>.

Furthermore, the rate at which the improvement occurred was much faster with a fixed-dose combination BUD/FORM versus budesonide monotherapy<sup>18</sup>.

It has been shown that adding formoterol in patients already using an ICS, such as budesonide, significantly reduces the risk of severe exacerbations and improves lung function, compared to up-titrating the dose of the ICS<sup>36</sup>.

The analyzed scores of the FSI-10 reflected very high levels of participants' satisfaction from the use of the Elpenhaler® inhalation device<sup>11</sup>. Essentially, an improved satisfaction with the inhaler has shown to result in increased adherence and compliance, improved disease control, and therefore reduced healthcare use and associated costs<sup>37</sup>. Comparative studies between different types of inhalers have shown that switching from one to another might indeed significantly affect the control of asthma<sup>38</sup>. Therefore, clinicians should be aware not only of the efficacy of the drugs that are planned for administration but also of the effectiveness and compliance rates of the specific inhaling devices that these are contained in. A comparative study of different inhalers available in the Greek market has shown that Elpenhaler® is met with significantly higher satisfaction in most of the domains of the FSI-10 compared to the other devices<sup>39</sup>.

### Limitations

The main limitations of BOREAS arise from its observational nature in order to simulate real-life conditions, namely the lack of validity via a control group, patient selection bias, and positive reinforcement of patients through participation in a clinical study.

### CONCLUSIONS

The real-life evidence from this study confirms the effectiveness and satisfaction from the use of a fixed-dose combination of BUD/FORM via the Elpenhaler® device in controlling patients' asthma symptoms and improving their quality of life in a significant and constant manner.

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### CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE Form for Disclosure of Potential Conflicts of Interest. P. Bakakos, D. Papakosta and S. Loukides have received in the past consultation fees from the product's marketing authorization holder.

### FUNDING

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### ETHICAL APPROVAL AND INFORMED CONSENT

The protocol was approved by all the relevant local ethics and scientific committees (Approval number and Date) and was conducted in accordance with the provisions of the



Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice (ICH-GCP) and Good Pharmacoeconomics Practice (GPP). Written informed consent was obtained from all the patients before the performance of any study procedures.

## DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

## AUTHOR CONTRIBUTIONS

All authors contributed equally to the development of this manuscript.

## PROVENANCE AND PEER REVIEW

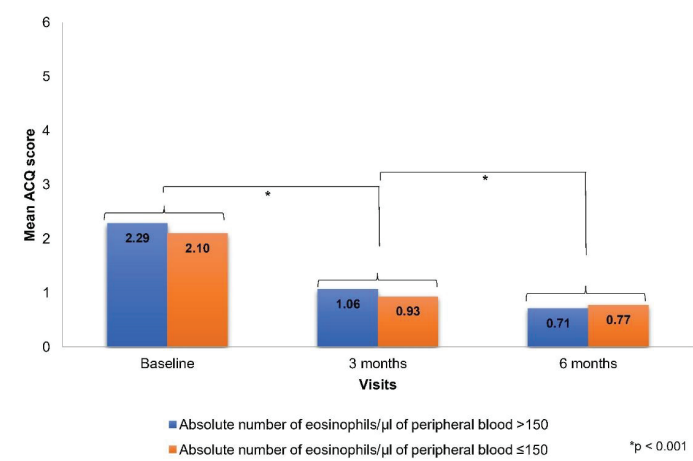
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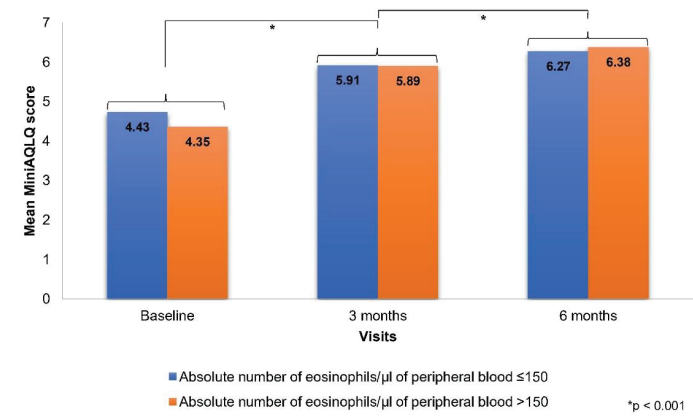
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**Supplementary Material 1: ACQ-7 score in patients with absolute number of eosinophils > or ≤ 150/μl of peripheral blood at 0, 3 and 6 months**



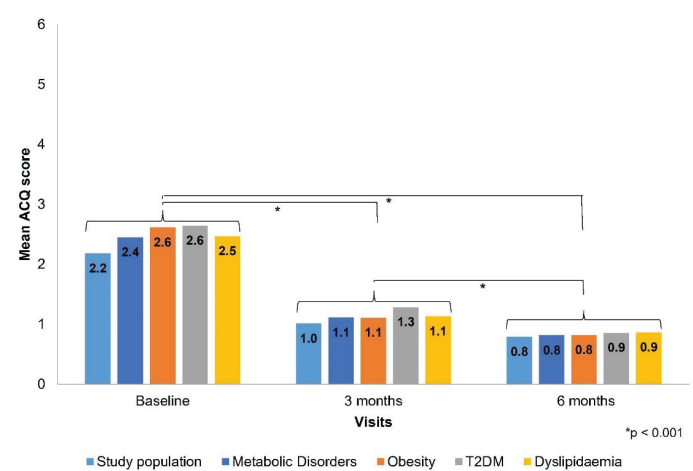
ACQ-7=7-item Asthma Control Questionnaire

**Supplementary Material 2: MiniAQLQ score in patients with an absolute number of eosinophils > or ≤ 150/μl of peripheral blood at 0, 3 and 6 months**



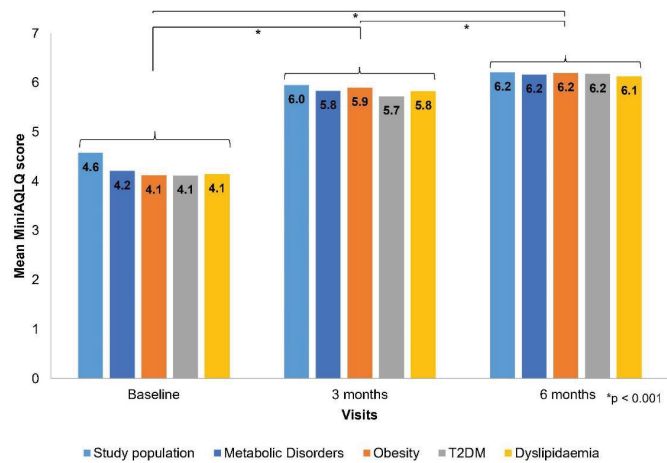
MiniAQLQ=Mini Asthma Quality of Life Questionnaire

**Supplementary Material 3: ACQ-7 score in relation to metabolic disorders at 0, 3 and 6 months**



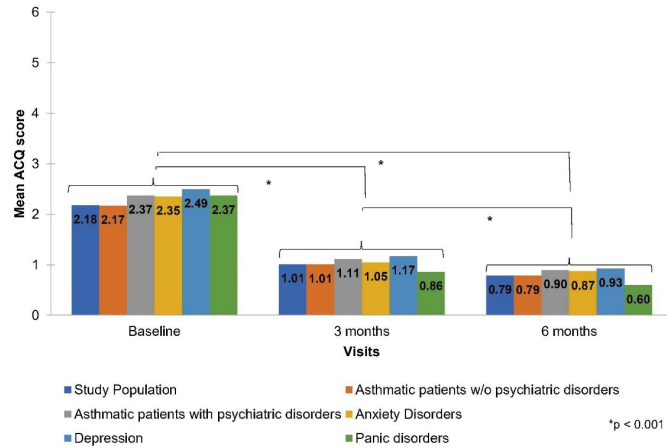
ACQ-7=7-item Asthma Control Questionnaire, T2DM=Type 2 Diabetes Mellitus

Supplementary Material 4: MiniAQLQ score in relation to metabolic disorders at 0, 3 and 6 months



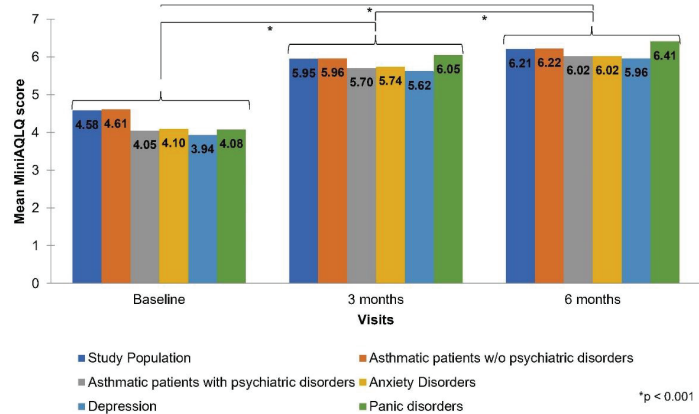
MiniAQLQ=Mini Asthma Quality of Life Questionnaire, T2DM=Type 2 Diabetes Mellitus

Supplementary Material 5: ACQ-7 score in relation to psychiatric disorders at 0, 3 and 6 months



ACQ-7=7-item Asthma Control Questionnaire

Supplementary Material 6: MiniAQLQ score in relation to psychiatric disorders at 0, 3 and 6 months



MiniAQLQ=Mini Asthma Quality of Life Questionnaire

# Real-life effectiveness of ICS/LABA inhalers in asthma: The evidence generated and future needs for optimal patient management

Konstantinos Kostikas<sup>1,2,3</sup>

The fixed-dose combinations (FDC) of inhaled corticosteroids (ICS) with long-acting  $\beta_2$ -agonists (LABA) represent one of the most widely used controller options for the management of patients with asthma, worldwide. Recently, the Global Initiative for Asthma (GINA) reports recommended the use of ICS-containing regimens in all the steps of asthma management, suggesting that the preferred reliever option would be combinations of ICS/formoterol, setting consequently these inhalers as the preferred controller option for such patients<sup>1</sup>. In the quest of the selection of the appropriate inhaled medication for our patients with asthma, a broad choice of inhalers is currently available. The treating physician needs to take into consideration several characteristics of the inhalation device, involving both the substances included but also the characteristics of the device that will be most appropriate for the individual patient, in order to ensure the acceptability of the device by the patient that will consequently lead to better adherence to the inhaled treatment and better disease outcomes<sup>2</sup>. The 'ideal' inhaler should carry several properties, including being user- and environmental-friendly (e.g. being breath-actuated, being multi-dose and portable yet robust, avoiding harmful additives, e.g. propellants), allowing for control of the appropriate dosing by providing feedback and dose receipt confirmation, providing the dosing independently of environmental conditions and inspiratory flow rate, and achieving high lung deposition with high respirable fine particle fraction<sup>3</sup>. In the journey of the management of patients with airways disease, the treating physicians should be familiar with the properties of the inhalation devices that they prescribe, choose the appropriate device based on the characteristics of each individual patient, involve actively the patients in the device and treatment selection, evaluate the patients' inhalation technique and train them appropriately at each visit, and re-evaluate the need for a different device whenever they identify a potential gap in the use of the previous one, but switch to a new device only with the patients' involvement and appropriate education<sup>4</sup>.

The dry powder inhaler (DPI) combination of budesonide and formoterol in the Elpenhaler® has been shown to be bioequivalent in terms of lung deposition to the same formulation delivered by the Turbuhaler® device in a crossover pharmacokinetic study in 100 patients with asthma<sup>5</sup>. Moreover, there is evidence of high satisfaction and acceptability of the Elpenhaler® in patients with asthma and COPD using the Feeling of Satisfaction with Inhaler (FSI-10) questionnaire that was comparable or better to other DPI devices<sup>6,7</sup>, whereas it also presented lower rates of critical errors that affect drug delivery to the lungs when compared with the Diskus® and Turbuhaler® devices in a prospective study of 755 patients with asthma and COPD<sup>8</sup>.

In this issue of *Pneumon*, Bakakos et al.<sup>9</sup> provide further clinically relevant information on the real-life effectiveness of the ICS/LABA combination of budesonide/formoterol in the Elpenhaler® device in patients with asthma, by presenting the results of the BOREAS study. This is a 6-month prospective multicenter observational study that enrolled 1230 asthma patients who were prescribed either of the two doses of Elpenhaler® budesonide/formoterol (200/6 or 400/12  $\mu$ g). The authors were able to show significant

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improvements in the asthma control questionnaire (ACQ-7, that was the primary endpoint of the study) and the mini asthma quality of life questionnaire (Mini AQLQ) at 3 months that were sustained at 6 months. Interestingly, the mean improvements in both these patient-reported outcomes exceeded the minimal clinically important difference (MCID) of 0.5 points<sup>10,11</sup>. These improvements were evident in patients with higher and lower blood eosinophils (using the 150 cells/ $\mu$ L as cut-off point), as well as in patients with and without metabolic and psychiatric comorbidities. These results are accompanied by significant improvements in lung function, with an acceptable safety profile of the two doses of budesonide/formoterol. These improvements in asthma control, health status and lung function, are likely attributed to the fact that in more than 50% of the patients, the new treatment was a step-up from previous treatments, whereas 41% were treatment-naïve prior to the study enrollment. These results further support the clinical effectiveness of the FDC of budesonide/formoterol in the Elpenhaler® device, when prescribed as step-up or initial treatment in patients with asthma in real-life practice in various clinical settings. The study results are limited by the pre-post open-label design that did not involve a control group and the fact that the treating physicians made the conscious decision to provide these treatment options in patients with uncontrolled asthma (the baseline ACQ-7 value was 2.18, well-above the 1.5 cut-off point for uncontrolled asthma for this tool) as a step-up or initial treatment. Based on the study design, a significant placebo effect cannot be ruled out, however, the accompanying improvement in lung function (e.g. >200 mL in mean FEV<sub>1</sub>) further supports the clinically relevant effectiveness of these treatments.

External validity is critical for the generalization of the efficacy observed in randomized placebo-controlled appropriately blinded trials. This is important in asthma, a disease entity with significant variability in the course of time. As an example, in a study of patients of the Wessex Severe Asthma Cohort, less than 25% of patients with severe eosinophilic asthma would have been eligible in the phase III licensing trials of interleukin-5 biologics, due to their stringent inclusion criteria<sup>12</sup>. Therefore, we need real-life studies with broader inclusion criteria that engage patients with various characteristics that would have excluded them from the typical randomized controlled trials of asthma. The BOREAS study included 36.3% of current or ex-smokers, while it evaluated the effectiveness of the specific budesonide/formoterol combination in patients with various comorbidities, with consistent results. The absence of a placebo arm is partly compensated by the fact that the authors collected both subjective (ACQ-7 and MiniAQLQ) and objective (lung function) measures of effectiveness, and thus they need to be commended for this selection of outcomes. In a previous well-designed study in patients with asthma, placebo inhalers and sham acupuncture improved symptoms, but lung function was improved only by active bronchodilator

(albuterol)<sup>13</sup>. In open-label studies of inhaled medication, the inclusion of patient-reported and objective outcomes is necessary, and the authors of the BOREAS study are to be commended for their selection. The study also confirms previous data by reporting high patient satisfaction by the Elpenhaler® device, as well as the favorable safety profile of the budesonide/formoterol combination in patients with asthma. Future data generation could focus on the use of the budesonide/formoterol FDC in the Elpenhaler® device as maintenance and reliever therapy (MART), as proposed for the ICS/formoterol combinations in current asthma recommendations<sup>1</sup>.

## CONFLICTS OF INTEREST

The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported. K. Kostikas declares that he is the Editor-in-Chief of the journal Pneumon.

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## ETHICAL APPROVAL AND INFORMED CONSENT

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## DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created.

## PROVENANCE AND PEER REVIEW

Commissioned; internally peer reviewed.

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