Effectiveness and Treatment Compliance of Salmeterol–Fluticasone Easyhaler® Among Patients with Asthma, COPD, or Asthma–COPD Overlap Syndrome: Real-World Study Findings

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ABSTRACT

Introduction: For inhalation therapies to be effective, it is crucial that patients manage inhaler use correctly in their everyday life and achieve treatment compliance. We investigated the effectiveness of the salmeterol–fluticasone propionate Easyhaler® (SF EH) device-metered dry powder inhaler in a real-world setting in Hungary among adult patients with asthma, chronic obstructive pulmonary disease (COPD), or asthma–COPD overlap syndrome (ACO).

Methods: A prospective, open-label, multicenter, noninterventional, investigator-sponsored study was conducted in outpatient pneumology centers. Eligible patients were aged ≥ 18 years with either a new diagnosis of asthma, COPD, or ACO, or whose disease was not controlled with preexisting medication. Data were collected at baseline and 12 ± 4 weeks, including the asthma control test (ACT), COPD assessment test (CAT), spirometry parameters [including forced expiratory volume for 1 s (FEV₁)], and physician- and patient-reported outcomes.

Results: Five hundred sixteen patients were recruited from 103 centers: 376 with asthma; 104 with COPD; and 36 with ACO. At week 12, there were significant improvements from baseline in both mean ACT score in patients with asthma (14.4 ± 4.2 versus 21.4 ± 2.8; P < 0.001) and mean CAT score in patients with COPD (24.0 ± 6.1 versus 16.0 ± 5.8; P < 0.001). Significant improvement was observed when the switch from the most frequently used previous inhalers was analyzed separately. Mean FEV₁ improved from 76.0% ± 17.2 to 84.7% ± 16.1 (P < 0.001) and from 53.8% ± 15.0 to 59.9% ± 15.0 (P < 0.001) in patients with asthma or COPD, respectively. The study demonstrated improved physician-rated overall treatment compliance and patient preference for the SF EH over 3 months use compared with previous inhaler treatment, with patients effectively adopting the SF EH into everyday life.

Conclusions: Treatment with SF EH significantly improved patients’ lung function parameters and disease control.
INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent chronic respiratory diseases and leading causes of morbidity and mortality worldwide [1]. Both are characterized by chronic airway inflammation [2]. COPD is a progressive disorder characterized by severe airflow limitation and persistent respiratory symptoms, including dyspnea, cough, and sputum production [3]. Despite the presence of established treatment guidelines, many patients with asthma still experience persistent symptoms [4]. Some patients exhibit features of both diseases, with chronic respiratory symptoms and airflow limitation. Asthma–COPD overlap (ACO) describes older adults who often have a significant smoking history, persistent airflow limitation, and features of asthma in addition to COPD [5–7]. Asthma affected an estimated 262 million people in 2019 and caused 461,000 deaths [4]. Improvement of asthma control continues to be a public health concern, as adherence to asthma therapy is higher when symptoms are present, with treatment often avoided in the absence of persistent symptoms [8]. It is estimated that the number of COPD cases was 384 million in 2010, and around 3 million people die due to COPD each year [9]. In 2020, COPD ranked as the sixth leading cause of death in the USA [10]. COPD is likely to increase in coming years owing to higher smoking prevalence and aging populations in many countries [11].

Inhaled therapy is recommended as the primary route of administration for medication used to manage asthma [12, 13] and COPD [11]. Inhaled therapy enables direct delivery of medicines to the airways coupled with effective use of lower doses compared with other administration routes [14]. Many types of device for delivery of inhaled drugs are available [15]. Correct inhaler technique is crucial since a suboptimal inhalation technique will mean lower delivery of active substances and lower treatment effect [16]; however, it can be influenced by several factors, including age, gender, education, inhalation technique, and type of inhaler used [17, 18]. It has been shown that an
increase in patient inhaler satisfaction can lead to both an increase in treatment adherence and compliance followed by improvement of disease control [19].

Inhaled asthma and COPD medications are commonly delivered using either a dry powder inhaler (DPI) or a pressurized metered-dose inhaler (pMDI) [20, 21]. The pMDI device uses a pressurized propellant to deliver the required dose as an aerosol; however, despite being widely used, pMDIs require considerable patient coordination between inhalation and drug delivery from the canister, often making them difficult to use [20–22]. DPIs have advantages over pMDIs in that they are breath activated, easy and convenient to use, and are more environmentally friendly as they do not rely on propellants [20]. However, to guarantee adequate drug delivery to the lungs, DPIs rely on the patient generating sufficient inspiratory flow through the DPI to disaggregate the powder formulation into breathable-sized particles as efficiently as possible [23]. A peak inspiratory flow (PIF) rate of ≥ 30 L/min is considered sufficient to ensure delivery of an adequate dose to patients [24].

The salmeterol–fluticasone propionate Easyhaler® (SF EH; Safumix Easyhaler® Orion Corporation, Espoo, Finland) device-metered DPI containing 50 µg of salmeterol (as salmeterol xinafoate) and 250 µg or 500 µg of fluticasone propionate in each metered dose has been developed for the treatment of asthma and COPD [25]. It has been designed specifically for ease of use, with salmeterol, a selective long-acting β2 adrenoceptor agonist that produces long duration of bronchodilation, and fluticasone propionate, an inhaled corticosteroid (ICS) that has glucocorticoid anti-inflammatory action within the lungs, resulting in reduced asthma and COPD symptoms [25, 26]. This real-world study conducted in Hungary investigated the effectiveness of the SF EH inhaler treatment in patients with asthma, COPD, and ACO, including measures of physician-assessed patient compliance in a real-world setting.

METHODS

Patients

Patients included in the study were aged ≥ 18 years with a new diagnosis of asthma, COPD, or ACO, or whose disease could not be controlled with preexisting asthma [according to the Global Initiative for Asthma (GINA) 2018 guidelines [27]] or COPD therapy [according to the Global Initiative for COPD (GOLD) 2018 guidelines [28]], or whose proficiency in the usage of the previously prescribed inhaler was unsatisfactory. Patients were excluded if they had any evidence of hypersensitivity (allergy) to salmeterol, fluticasone propionate, or the excipient lactose, which contains a small amount of milk proteins. Patients who were pregnant or lactating, or currently participating in other clinical or real-world evidence studies were also excluded. Consecutive patients presenting to the outpatient pneumonology centers and fulfilling the recruitment criteria were enrolled.

The study protocol was approved by the local Ethics Committee in Hungary: Scientific and Research Ethics Committee and National Institute of Food and Drug administration, OGYÉI/13041–5/2019. All patients provided written informed consent in Hungarian and the study was conducted according to the Declaration of Helsinki.

Study Design

This prospective, open-label, multicenter, non-interventional, real-world, investigator-sponsored study was conducted in outpatient pneumonology centers in Hungary. Patients were diagnosed according to GINA or GOLD guidelines [27, 28] and received treatment with the SF EH according to the current clinical practice and the Hungarian Summary of Product Characteristics (SmPC) [25]. All asthma and COPD patients were diagnosed by respiratory specialists. Asthma diagnosis was confirmed either by spirometry [with reversibility of obstruction detected by forced expiratory volume for 1 s (FEV1)] increase ≥ 12%
and ≥ 200 mL after 400 µg salbutamol inhalation] or by bronchial provocation tests in all patients. COPD diagnosis was confirmed by post-bronchodilator FEV₁ < 70% and lack of reversibility during spirometry with reversibility testing. ACO diagnosis was defined when both asthma and COPD criteria were met. Eligible patients were either not receiving inhaled therapy and were considered inhaler treatment-naive or switched from their current inhaler to the SF EH treatment at the start of the study as decided by the treating physician as a part of normal routine treatment practices in Hungary. For patients with a new diagnosis of asthma, COPD, or ACO, the treating physician decided the dose of SF EH based on patient symptoms and according to local guidelines. A similar procedure was followed for patients who had received prior treatment, and for whom treatment alterations were considered necessary by the treating physician. As this was a real-world study, SF EH treatment was not provided to the patients but was prescribed as per the real-world setting. No diagnostic or therapeutic procedures beyond those used in current clinical practice in Hungary were performed on patients enrolled in the study.

All patients completed three visits during the study: a screening and baseline visit (visit 1) to assess patient eligibility, collect baseline data and instruct patients on how to use the inhaler according to normal practice; an optional interim visit (visit 2) at 4 ± 1 weeks after the beginning of treatment to check the SF EH inhaler technique as judged by the treating physician; and a final visit (visit 3) at 12 ± 4 weeks after visit 1. Data were collected from the patient’s medical record including questionnaires such as the asthma control test (ACT), COPD assessment test (CAT), modified Medical Research Council (mMRC) dyspnea scale, and spirometry values, which were entered into the electronic case report forms. FEV₁ and forced vital capacity (FVC) were recorded from the spirometry printout when spirometry was performed. During visit 1, study physicians filled in a questionnaire on previous inhaler use and preference for those patients who had been treated with inhaler medications previously. In addition, they recorded the following for all patients: How easy was it to teach the use of SF EH? (“very easy”—“easy”—“medium”—“it was not easy”); How long did it take to teach the use of SF EH? (5 min, 5–10 min, 10–20 min, > 20 min). In addition, patients recorded how easy it was to learn the use of the SF EH on a six-point scale (“very easy” to “difficult”) and how they evaluated their previous inhaler in general, on a six-point scale (“very good” to “unsatisfactory”). On study visit 3, physicians recorded the following on a questionnaire for all patients: How well did the patient adopt the use of SF EH to the everyday life? (“very well”—“well”—“moderately”); How do you evaluate the patient compliance? (“very good”—“good”—“medium”—“weak”). In addition, patients recorded how they evaluated the SF EH in general on a six-point scale (“very good” to “unsatisfactory”). Adverse events (AEs) and serious AEs (SAEs) associated with the use of SF EH were collected from visit 1 until study completion or withdrawal according to the study protocol. All questionnaires were completed by the study physician at the study visit during an interview with the patient.

Outcomes

The primary objective was to investigate the clinical effectiveness of the SF EH inhaler in patients with asthma, COPD, or ACO. Clinical effectiveness was determined using the following measures recorded at baseline (visit 1) and at visit 3: ACT for patients with asthma (0 to ≤ 15: not controlled; 16 to ≤ 19: partially controlled; 20–25: controlled) [29]; CAT for patients with COPD (< 10: low impact; 10–20: medium impact; 21–30: high impact; > 30: very high impact); and, both CAT and ACT for patients with ACO. For COPD and ACO patients, the mMRC scale was also used [30] [dyspnea only with strenuous exercise (0); dyspnea when hurrying or walking up a slight hill (+ 1); walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace (+ 2); stops for breath after walking 100 yards (91 m) or after a few minutes (+ 3); too dyspneic to leave house or breathless when dressing (+ 4)]. Additional assessments of
effectiveness included FEV\textsubscript{1}, percent predicted FEV\textsubscript{1} values, and FVC derived from spirometry measured at baseline and visit 3.

Secondary objectives included assessment of changes in asthma control levels based on GINA 2018 (GINA steps 1–4 [27]); ABCD classification for patients with COPD based on GOLD 2018 (GOLD Groups A–D [28]); change in clinical symptoms among patients with asthma, COPD, or ACO, when SF EH was given as a first ICS/-long-acting beta-agonist (ICS/LABA) combination (i.e., among inhaler-naive patients), and when switching from the most frequently used devices in Hungary to the SF EH. Study physicians also recorded on study questionnaires their perceptions of how well patients used the SF EH, including perceptions of how easily and quickly use of the SF EH could be taught, patient compliance, overall use of SF EH, and integration of the inhaler into patients’ everyday life, as well as an evaluation of the overall health of patients using the SF EH. In addition, patients recorded their perception of their previous inhaler as well as that of SF EH.

Additional assessments included patient age, sex, height and weight, smoking history, highest education level, concomitant treatments, and current medical health.

Screening of patients with COPD also included assessment of exacerbation history/symptom burden and exacerbation risk (ABCD classification) [28, 31].

**Statistical Methods**

Power calculations were not conducted owing to the real-world nature of the study. Continuous variables such as ACT, CAT, FEV\textsubscript{1}, and FVC between visits were tested by Wilcoxon signed rank test. Categorical (ordinal) variables between visits were tested with Cochran-Mantel–Haenszel statistics. A \( P \)-value < 0.05 was considered statistically significant. Data for continuous variables are presented as means with corresponding standard deviation. Categorical variables are presented with frequencies and percentages.

**RESULTS**

**Patient Disposition**

In total, 376 patients with asthma, 104 patients with COPD, and 36 patients with ACO were recruited from 103 centers throughout Hungary. Of the 376 patients with asthma, 372 completed ACT and 291 completed FEV\textsubscript{1} and FVC measurements at visit 3, and 103 of the 104 patients with COPD completed CAT and mMRC, while 80 completed FEV\textsubscript{1} and FVC measurements. During the COVID-19 pandemic, it was not possible to perform spirometry for all patients, resulting in missing FEV\textsubscript{1} and FVC data (for details see Table 1). Interim visit 2 was optional and offered for patients if they had problems regarding their treatment. Of patients with asthma, 103/376 (27.4%) attended visit 2; however, 101/103 (98.1%) used their SF EH inhaler correctly, and hence no extra training was performed. Among patients with COPD and ACO, respectively, 16/104 (15.4%) and 11/36 (30.6%), attended visit 2, and all of these patients used the SF EH inhaler correctly. Hence, compared with the normal clinical practice, additional instruction on SF EH inhaler use was not required at visit 2 for any patients, and was not considered to cause deviation from the real-world study setting.

**Patient Baseline Characteristics**

Patient baseline demographic and clinical characteristics are summarized in Table 1. Baseline ACT scores were 14.4 ± 4.2 for patients with asthma and 13.8 ± 4.4 for patients with ACO. Baseline CAT scores were 24.0 ± 6.1 for patients with COPD and 19.4 ± 7.8 for patients with ACO. Approximately 92% of patients with asthma entered the study at GINA step 3 (66.0%) or step 2 (26.1%). Most patients with COPD were GINA step 3 at baseline [27/36 (75.0%)]. The majority of patients with COPD entered the study at GOLD Group C (44.2%) or GOLD Group D (45.2%). Most patients with ACO were in GOLD Group B or C at baseline [27/36 (75.0%)]. (Table 1).
### Table 1  Patient baseline characteristics

|                       | Asthma  |
|-----------------------|---------|
|                       | \((n = 376)\) | COPD \((n = 104)\) | ACO \((n = 36)\) | Total \((n = 516)\) |
| Age, years (SD)       | 55.9 (15.1) | 64.1 (9.7) | 64.4 (8.2) | 58.1 (14.3) |
| Gender, \(n\) (%)     |          |          |          |          |
| Female                | 253 (67.3) | 53 (51.0) | 27 (75.0) | 333 (64.5) |
| Male                  | 123 (32.7) | 51 (49.0) | 9 (25.0)  | 183 (35.5) |
| Height, cm (SD)       | 167 (8.9)  | 165 (13.6)| 164 (8.5) | 167 (10.0) |
| Weight, kg (SD)       | 79.0 (16.9)| 77.7 (20.1)| 76.6 (21.4)| 78.6 (17.9) |
| FEV\(_1\) (%)—1. Visit, \(a\) mean (SD) | 76.0 (17.2) | 53.8 (15.0) | 67.7 (19.3) | 70.9 (19.1) |
| Education, \(n\) (%)  |          |          |          |          |
| Higher education      | 59 (15.7)  | 3 (2.9)   | 3 (8.3)   | 65 (12.6)  |
| Secondary school      | 236 (62.8)| 40 (38.5) | 18 (50.0) | 294 (57.0) |
| Primary school (8 years) | 81 (21.5) | 61 (58.7) | 15 (41.7) | 157 (30.4) |
| Disease control, mean (SD) |          |          |          |          |
| ACT                   | 14.4 (4.2) | 13.8 (4.4) | 14.3 (4.2) |          |
| CAT                   | 24.0 (6.1) | 19.4 (7.8) | 22.9 (6.9) |          |
| mMRC                  | 1.9 (0.8)  | 1.3 (1.0)  | 1.7 (0.9)  |          |
| Smoking status, \(n\) (%) |          |          |          |          |
| Never smoked          | 280 (74.5)| 20 (19.2) | 6 (16.7)  | 306 (59.3) |
| Current smoker        | 50 (13.3)  | 52 (50.0) | 18 (50.0) | 120 (23.3) |
| Previously smoked     | 46 (12.2)  | 32 (30.8) | 12 (33.3) | 90 (17.4)  |
| Severity, \(n\) (%)   |          |          |          |          |
| GINA Step 1\(^b\)    | 1 (0.3)   | 1 (2.8)   | 2 (0.5)\(^c\) |          |
| GINA Step 2           | 98 (26.1) | 6 (16.7)  | 104 (25.2)\(^c\) |          |
| GINA Step 3           | 248 (66.0)| 27 (75.0) | 275 (66.7)\(^c\) |          |
| GINA Step 4           | 29 (7.7)  | 2 (5.6)   | 31 (7.5)\(^c\) |          |
| GOLD Group A\(^d\)    | 0 (0.0)   | 4 (11.1)  | 4 (2.9)\(^e\) |          |
| GOLD Group B          | 11 (10.6) | 20 (55.6) | 31 (22.1)\(^e\) |          |
| GOLD Group C          | 46 (44.2) | 7 (19.4)  | 53 (37.9)\(^e\) |          |
| GOLD Group D          | 47 (45.2) | 5 (13.9)  | 52 (37.1)\(^e\) |          |
| Inhaler naïve patients, \(n\) | 46 | 4 | 1 | 51 |

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Most recruited patients were switched from their previous inhaler to the SF EH device, particularly those with asthma (330 patients switched inhaler versus 46 device-naive patients). The most frequently used previous inhalers included Airflusol/C210 (Sandoz Limited, Surrey, UK), Diskus/C210 (GlaxoSmithKline, North Carolina, USA), Elpenhaler/C210 (Elpen Pharma, Pikiemi, Greece), and MDI for asthma (various manufacturers). Of the 104 COPD patients, there were 100 who switched inhaler and four device-naive patients. The most frequently used previous inhalers included Airflusol/C210 (Sandoz Limited, Surrey, UK), Breezhaler/C210 (Novartis Pharmaceuticals, London, UK), Genuair® (AstraZeneca UK Limited, Bedfordshire, UK), and MDI (various manufacturers). Among patients with ACO, 35 switched inhaler and one was device-naive.

Clinical Effectiveness of SF EH — asthma

Significant clinical improvement occurred in patients with asthma following treatment with SF EH (Table 2). At visit 3, mean ACT score improved from baseline in patients with asthma (14.4 ± 4.2 versus 21.4 ± 2.8; \( P < 0.001 \); Table 2). Similar mean ACT results were observed in patients with ACO (baseline 13.8 ± 4.4 versus visit 3 20.1 ± 2.7; \( P < 0.001 \); data not shown). There was also an improvement in FEV1 and FVC after 12 weeks of SF EH treatment (\( P < 0.001 \); Table 2). Well-controlled asthma was detected at visit 3 in 83.6% of patients with asthma (Fig. 1A) and 69.4% of patients with ACO. Rescue medication use in patients with asthma reduced between visit 1 and visit 3, with those taking rescue medication at least three times per day falling from 28 patients (7.4%) to zero, and substantial growth for categories “not once” and “once a week or less,” indicating reduced rescue medication use (Fig. 2). There were significant improvements (\( P < 0.001 \)) in mean ACT scores when patients with asthma were switched from the most frequently used previous inhaler (visit 1) to SF EH (visit 3; Fig. 3A).

Clinical Effectiveness of SF EH — COPD

A significant and relevant clinical improvement was detected in patients with COPD following treatment with SF EH (Table 3). At visit 3, mean CAT score improved from baseline in patients with COPD (24.0 ± 6.1 versus 16.0 ± 5.8; \( P < 0.001 \); Table 3). Similar mean CAT results were observed in patients with ACO (19.4 ± 7.8 versus 12.8 ± 6.3; \( P < 0.001 \); data not shown). There was also improvement in FEV1 and FVC after 12 weeks of SF EH treatment (\( P < 0.001 \); Table 3). By visit 3, 63.1% of patients had “medium impact” and 12.6% of patients had

### Table 1 continued

| Inhaler switching patients, n | Asthma (n = 376) | COPD (n = 104) | ACO (n = 36) | Total (n = 516) |
|------------------------------|-----------------|---------------|-------------|---------------|
| Asthma-COPD overlap syndrome, ACT asthma control test, CAT COPD assessment test, COPD chronic obstructive pulmonary disease, FEV1 forced expiratory volume for 1 s, GINA Global Initiative for Asthma, GOLD Global Initiative for COPD, mMRC modified Medical Research Council, SD standard deviation. 
≥During the COVID-19 pandemic, the performance of spirometry could not be achieved for all patients, which resulted in missing FEV1 and FVC data; during visit 1 for patients with asthma (nine), COPD (none), and ACO (one), and during visit 3 for patients with asthma (85), COPD [24], and ACO (10). 
≤For details of GINA see ref. [27]. 
©The denominator for calculating the GINA results for the total column is total patients with asthma + total patients with ACO (376 + 36 = 412). 
∂For details of GOLD see ref. [28]. 
≤The denominator for calculating the GOLD results for the total column is total patients with COPD + total patients with ACO (104 + 36 = 140).
“low impact” COPD, as compared with baseline, where 61.5% of patients had “high impact” and 15.4% had “very high impact” COPD (Fig. 1B). A “high impact” CAT score indicates exercise is not safe, being breathless walking around the house and washing, being breathless when talking, and chest symptoms including a cough causing daytime tiredness and sleep disturbance. A “medium impact” CAT score is an improvement; however, this still means doing activities slowly and being breathless at times, e.g., bending over, and having chest tightness or wheeze in the morning [32]. Similar trends were found by visit 3 for the ACO COPD symptom control. There were significant improvements ($P < 0.001$) in mean CAT score when patients with COPD were switched from the most frequently used previous inhalers (visit 1) to SF EH (visit 3; Fig. 3B).

**Physician and Patient Assessment of Inhaler Treatment**

Use of SF EH was considered by physicians either “very easy to teach” (62.1%) or “easy to teach” (35.0%). The ease of teaching was slightly higher in patients with asthma (65.7%) “very easy to teach” and 31.1% “easy to teach”) compared with patients with COPD (49.0% for both “very easy to teach” and “easy to teach”). The use of SF EH was also generally “very easy” or “easy to teach” for physicians treating patients with ACO (data not shown). Use of SF EH took physicians less than 5 min to teach for 78.5% of patients with asthma, 72.1% of patients with COPD, and 86.1% of patients with ACO. In addition, 5–10 min of teaching time was sufficient for 20.5%, 25.0%, and 13.9%, of patients, respectively.

Physicians evaluated compliance as good or better for almost all patients with asthma (“very good” 68.5%; “good” 29.4%), COPD (“very good” 48.5%; “good” 50.5%), and ACO (“very good” 72.2%; “good” 27.8%). Physicians’ perceptions of how well the SF EH had been adopted into everyday life were rated “very well” for 78.2% of patients with asthma, 60.2% of patients with COPD, and 75.0% of patients with ACO. At visit 3, the overall physician evaluation of SF EH was “very good” for 81.7% of patients with asthma compared with 7.7% for the previous inhaler/no inhaler at visit 1. For COPD patients, there was an overall evaluation of “very good” for 72.8% of patients with SF EH.

| Table 2 | Assessment of asthma parameters at visit 1 and visit 3 |
|---------|---------------------------------|
|          | Asthma ($n = 376$) | Asthma ($n = 372$) | $P$-value |
| **Visit 1** | **Visit 3** | **Visit 1** | **Visit 3** | **Visit 1** | **Visit 3** | **Visit 1** | **Visit 3** |
| Mean (SD) ACT | 14.4 (4.2) | 21.4 (2.8) | < 0.001 |
| FEV$_1$ (% predicted),$^a$ mean (SD) | 76.0 (17.2) | 84.7 (16.1)$^b$ | < 0.001 |
| FVC (% predicted),$^a$ mean (SD) | 86.5 (17.8) | 92.6 (16.0)$^b$ | < 0.001 |
| GINA 1, n (%)$^c$ | 1 (0.3) | 1 (0.3)$^d$ | 0.867 |
| GINA 2, n (%) | 98 (26.1) | 75 (24.9)$^d$ |  |
| GINA 3, n (%) | 248 (66.0) | 206 (68.4)$^d$ |  |
| GINA 4, n (%) | 29 (7.7) | 19 (6.3)$^d$ |  |

$^a$ACT asthma control test, FEV$_1$ forced expiratory volume for 1 s, FVC forced vital capacity, GINA Global Initiative for Asthma, SD standard deviation

$^b$n = 291

$^c$see details of GINA in ref. [27]

$^d$n = 301 (1 + 75 + 206 + 19) as denominator to calculate the percentage values

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- Baseline: Controlled (60.9%), Partially controlled (28.2%), Not controlled (10.9%)
- 12 weeks with SF EH: Controlled (12.4%), Partially controlled (83.6%), Not controlled (4%)

Controlled: ACT score of 20 to 25; Partially controlled: ACT score of 16 to ≤19; Not controlled: ACT score of 0 to ≤15

B

- Baseline: Low impact (15.4%), Medium impact (61.5%), High impact (18.3%), Very high impact (4.8%)
- 12 weeks with SF EH: Low impact (23.3%), Medium impact (63.1%), High impact (12.6%), Very high impact (1%)

Low impact: CAT score of <10; Medium impact: CAT score of 10–20; High impact: CAT score of 21–30; Very high impact: CAT score of >30
at visit 3, compared with 2.0% for alternative inhaler/no inhaler at visit 1. At visit 3, the overall physician evaluation of SF EH was “very good” for 80.0% of patients with ACO compared with 5.6% for previous inhaler/no inhaler at visit 1. No AEs or SAEs were recorded. Only 4.7% of patients considered SF EH as difficult to learn to use, with 8.5% considering it “very easy.” The majority of patients evaluated the SF EH overall as “very good” (80.5%) compared with their previous inhaler (“very good” 6.4%).

DISCUSSION

The results of this real-world study performed in patients with symptomatic, uncontrolled asthma, COPD, or ACO in pulmonology centers throughout Hungary showed that following 3 months of SF EH treatment, there were significant improvements in ACT, CAT, mMRC, FEV1, and FVC in all three patient groups. Furthermore, the study demonstrated a very high overall physician-rated preference and compliance evaluation, as well as a patient-reported overall evaluation for the SF EH over 3 months use, compared with other commonly used inhalers in Hungary. Physicians’ assessments included perception of how easily and quickly use of the SF EH could be taught, and how easily patients incorporated use of the SF EH into their everyday lives.

In addition to the results observed in patients with COPD and asthma, the SF EH was effective in the management of both COPD and asthma symptoms in patients with ACO. Improvements in ACT and CAT scores for ACO patients were proportional to those for patients with either asthma or COPD, indicating that one SF EH inhaler can bring dual relief to ACO patients. Both the GINA and GOLD guidelines

Fig. 1 Clinical effectiveness of SF EH in improving the asthma control test (ACT) score (panel A) and the COPD assessment test (CAT) score (panel B). ACT asthma control test, CAT COPD assessment test, COPD chronic obstructive pulmonary disease, SF EH salmeterol–fluticasone propionate Easyhaler

Fig. 2 Rescue medication use for patients with asthma. SF EH salmeterol–fluticasone propionate Easyhaler

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recommend treating patients with ACO according to the dominant phenotype [33].

Good asthma control is one of the main goals in asthma treatment. Despite recent advances in asthma treatment, there is still a substantial associated morbidity and cost burden. A key aim is to increase patient treatment compliance and adherence, thus leading to better disease control [19]. Asthma control is assessed with symptom control and the risk of future exacerbations. The ACT test is a helpful simple tool to assess asthma control in clinical practice [27]. In our study, asthma control improved markedly to the target level “controlled” (defined as an ACT score of 20–25) both among patients with asthma and those with ACO. These results highlight the importance of active follow-up measures in treatment-naive patients, and also among patients whose asthma is not well controlled.

Similarly, symptoms play a crucial role in COPD management. Lung function, symptom

Fig. 3 Clinical effectiveness of switching inhaler treatment from the most frequently used previous inhaler to SF EH among patients with asthma (panel A) or patients with COPD (panel B). COPD chronic obstructive pulmonary disease, SF EH salmeterol–fluticasone propionate Easyhaler
control, exacerbations, and comorbidities have to all be considered in COPD assessment, and treatment choice is guided by exacerbation history and symptoms [28]. COPD patients included in our study were symptomatic at enrollment but showed major improvement in CAT scores during the follow-up period. In addition, under-treatment is a major problem in COPD. The results of our study showed that inhaler treatment initiation, or a switch from a previous non-preferred inhaler, together with appropriate training on how to use the inhaler, significantly improved symptom control in COPD patients.

Of note, in Hungary, all asthma and COPD patients are diagnosed by respiratory physicians in approximately 550 centers across the country, of which 103 took part in the present study. Asthma and COPD medications are also prescribed solely by respiratory specialists. Patients may be referred to specialists by general practitioners or may decide themselves to visit a respiratory specialist. A limitation of this study was that only patients who were symptomatic on their previous treatment or who were untreated were included. These inclusion criteria were used as this was a noninterventional real-world study, where the initiation of a new therapy was appropriate for study patients according to routine practice.

Demonstrating the effectiveness of SF EH for both asthma and COPD symptoms in these patients suggests that the SF EH would be an appropriate choice for disease management. In a previous study comparing a SF EH inhaler and a fluticasone propionate inhaler in adolescent and adult patients with asthma, fewer severe asthma exacerbations were noted for the combination product [34]. This combination product also reduced moderate-to-severe exacerbations in patients with COPD compared with placebo, with improved health status and FEV1 across GOLD stages [35]. The GINA or GOLD categorization of patients after 12 weeks of SF EH treatment did not substantially change, demonstrating that the SF EH was effective at controlling symptoms as shown by the ACT and CAT data, whilst not changing the need for ongoing treatment or the severity of the underlying asthma, COPD, or ACO. For many of the patients with asthma, the use of rescue medication was greatly reduced or

### Table 3 Assessment of COPD parameters at visit 1 and visit 3

| Parameter | COPD (n = 104) | COPD (n = 103) | P-value |
|-----------|----------------|----------------|---------|
| CAT | 24.0 (6.1) | 16.0 (5.8) | < 0.001 |
| mMRC | 1.9 (0.8) | 1.0 (0.8) | < 0.001 |
| FEV1 (% predicted), a mean (SD) | 53.8 (15.0) | 59.9 (15.0) | < 0.001 |
| FVC (% predicted), a mean (SD) | 73.6 (18.0) | 76.1 (18.9) | < 0.001 |
| GOLD B, n (%) | 11 (10.6) | 10 (10.5) | 0.898 |
| GOLD C, n (%) | 46 (44.2) | 45 (47.4) | | |
| GOLD D, n (%) | 47 (45.2) | 40 (42.1) | | |

**CAT** COPD assessment test, **COPD** chronic obstructive pulmonary disease, **FEV1** forced expiratory volume for 1 s, **FVC** forced vital capacity, **GOLD** Global Initiative for COPD, **mMRC** modified Medical Research Council, **SD** standard deviation

a During the COVID-19 pandemic, the performance of spirometry could not be achieved for all patients which resulted in missing FEV1 and FVC data for 0 patients (visit 1) and 24 patients (visit 3)

b n = 80
c for details of GOLD see ref. [28]
d n = 95 patients (10 + 45 + 40) as denominator to calculate the percentage values
eliminated. The COPD and ACO patient populations contained a large majority of smokers or previous smokers, which indicated further that the SF EH was effective in the more difficult-to-treat patient populations [36].

Physicians evaluated the SF EH as being “easy” or “very easy” to teach in as little as less than 5 min or 5–10 min, for the majority of patients. Compliance ratings were “very good” or “good” for most patients, with the majority of patients being considered by physicians to have adopted the SF EH into everyday life either “very well” or “well.” The overall evaluation of the SF EH by physicians was “very good” for the majority of patients, which was much higher than the previous overall evaluation of alternative inhalers at the baseline visit. In accordance with this, 8.5% of patients considered SF EH as “very easy” to learn how to use, and the majority of patients evaluated the SF EH overall as “very good.”

Study limitations included the open-label design with no comparator inhaler during the treatment period [37]. Open-label designs can lead to bias, including patient-selection bias in which patients who are not optimally treated by their current inhaler may be preferentially selected, and performance- or reporting-bias owing to the absence of blinding [38]. The large majority of patients had either “not controlled” or “partially controlled” asthma ACT results, and “high impact” or “very high impact” COPD CAT results using the previous inhaler, therefore the study does not compare patients who were previously satisfied with their inhaler to those who switched to the SF EH. Hungarian data on patient adherence to the previous inhaler or the level of specific inhaler training for the previous inhaler were not available for comparison to the data in this study [37]. The GOLD Group A–D classifications describe increasing severity of symptoms and categorize the number and severity of exacerbations [27]. Data on total number of previous or current exacerbations of asthma, COPD, or ACO were not available for each patient prior to the study start and during treatment. It was therefore not possible to determine if the frequency of exacerbations was reduced during SF EH use during the study. The study design would have been stronger if direct comparisons between inhalers had been performed, rather than the performance of patients switching from a range of inhalers to SF EH. This was a prospective, open, multicenter, noninterventional, real-world, investigator-sponsored study in outpatient pneumonology centers in Hungary. The strengths of this real-world study include the generation of data on the real-world use of the SF EH inhaler, with no additional interventions that could introduce their own biases and that the majority of outpatient pulmonology centers from Hungary were included in the study.

Rescue medication use among patients with asthma was high at the start of the study, with one-third of patients using it at least three times per day or one to two times per day, and a further one-third using it two to three times per week. Rescue medication use was substantially lower after 3 months of SF EH use with no patients using it at least three times per day, approximately 10% using it one to two times per day or two to three times per week and nearly 90% of patients either not using it or using it once per week or less. This implies that asthma is successfully managed with maintenance SF EH and the need for additional therapy through rescue medication use is substantially lower. This is important as when symptoms worsen, patients prefer to use reliever therapies that could result in overuse of rescue medication [8]. Indirect evidence suggests that overuse of beta-agonists alone, e.g., as rescue medication, is associated with increased risk of death from asthma or near-fatal asthma [8].

CONCLUSIONS

After 3 months of SF EH treatment, patients with previously uncontrolled obstructive pulmonary disease had significantly improved lung function parameters and disease control. Most patients with asthma, COPD, or ACO could achieve well-controlled disease for asthma/asthma symptoms or reduced symptom burden for COPD/COPD symptoms when treated with SF EH. Subjective physician ratings for ease and speed of teaching, patient compliance, incorporation into everyday life, and overall
evaluation were very high for SF EH after 3 months treatment and in accordance with high patient ratings on ease of learning and overall evaluation.

Declarations

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Compliance with Ethics Guidelines This study was conducted in accordance with ethical principles of the Declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. The study protocol was approved by the local Ethics Committee in Hungary: Scientific and Research Ethics Committee and National Institute of Food and Drug administration, OGYÉI/13041–5/2019. All patients provided written informed consent in Hungarian.

Data Availability The data generated for this study is the property of Semmelweis University and is not publicly available.

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