THERAPEUTIC ADVANCES in
Respiratory Disease

Original Research

Effectiveness and safety of salmeterol/fluticasone fixed-dose combination delivered through Synchrobreathe® in patients with asthma: the real-world EVOLVE study

Santhalingam Balamurugan, Dalal Sonia, Deshmukh Vikrant, Khanra Monotosh, Sundar Raj Shyam, Akhtar Shamim, Kumar Vinay, Nandagopal Velayuthaswamy, Ahmed Masood, Gupta Manohar Lal, Godse Ajay, Chhowala Sushmeeta, Lopez Meena, Sawant Sandesh, Jadhav Sonali, Vaidya Abhijit and Gogtay Jaideep

Ther Adv Respir Dis

2022, Vol. 16: 1–13

DOI: 10.1177/17534666221137272

Correspondence to:
Vaidya Abhijit
Medical Affairs, Clinical Research Division, Cipla Ltd., Mumbai 400013, India.
abhijit.vaidya@cipla.com

Santhalingam Balamurugan
Chest Research Center, Chennai, India

Dalal Sonia
Kalyan Hospital, Vadodara, India

Deshmukh Vikrant
Nagpur Chest Center, Nagpur, India

Khanra Monotosh
Disha Clinic, Howrah, India

Sundar Raj Shyam
Sreshta Hospital, Hyderabad, India

Akhtar Shamim
Life Line Clinic, New Delhi, India

Kumar Vinay
Surya Chest Clinic, Karimnagar, India

Nandagopal Velayuthaswamy
Karthick Polyclinic, Coimbatore, India

Ahmed Masood
Chest Clinic, Aurangabad, India

Gupta Manohar Lal
Dr. Manohar Gupta's Chest Clinic, Jaipur, India

Godse Ajay
Sun Chest, Endocrine & Sleep Medicine Clinic, Mumbai, India

Chhowala Sushmeeta
Lopez Meena
Sawant Sandesh
Jadhav Sonali
Vaidya Abhijit
Gogtay Jaideep
Medical Affairs, Cipla Ltd., Mumbai, India

Abstract

Background: Inhalation therapy with corticosteroids and long-acting β_2-agonists has been the mainstay of asthma management. However, choosing the correct inhaler technique is essential to effectively deliver the medication to the lungs to attain good asthma control.

Objective: This study aimed to evaluate asthma control and device usability with salmeterol/fluticasone fixed-dose combination (FDC) administered through Synchrobreathe®, a breath-actuated inhaler (BAI), in Indian patients with persistent asthma (EVOLVE study).

Design: The present study was a prospective, open-label, non-comparative, multi-center, observational study.

Methods: The study enrolled 490 patients with documented diagnoses of asthma who were treatment-naive or uncontrolled due to poor inhaler technique associated with a previous device. The primary endpoint was a change from baseline in the Asthma Control Questionnaire-6 (ACQ-6) score at week 12.

Results: Mean ACQ-6 score reduced from 2.2 ± 1.07 (baseline) to 0.4 ± 0.49 (mean change: -1.9 ± 1.12, $p < 0.0001$) at week 12 in the intention-to-treat (ITT) population, and minimal clinically important difference of 0.5 was observed from week 4 onwards. Peak expiratory flow rate improved by 82.5 ± 75.74 ml/min ($p < 0.0001$) at week 12 in the ITT population. The proportion of well-controlled responders increased from 39.9% (week 4) to 77.1% (week 12). Most (91%) patients preferred the Synchrobreathe® and rated it very high for usability, portability, patient confidence, and satisfaction. Salmeterol/fluticasone FDC administered through Synchrobreathe® was well tolerated.

Conclusion: Treatment with salmeterol/fluticasone FDC administered through Synchrobreathe® for 12 weeks persistently improved asthma control and lung function and was well tolerated. Most patients were satisfied with it and preferred Synchrobreathe® BAI over their previous device.

Registration: The study was registered with the Clinical Trial Registry of India (CTRI/2018/12/016629).

Keywords: ACQ-6 score, asthma, BAI, salmeterol/fluticasone, Seroflo, Synchrobreathe®

Received: 23 June 2022; revised manuscript accepted: 20 October 2022.

Introduction

Asthma is a chronic inflammatory disorder of the airways, which is characterized by airway hyperresponsiveness that leads to recurrent breathlessness, shortness of breath, wheezing, coughing, and tightness in the chest due to variable widespread airflow obstruction within the lungs, and this airway limitation may become persistent at later stages.[1] The recent Global Burden of Disease (GBD, 1990–2019) study estimated the total burden of asthma in India as 34.3 million, which accounted for 13.09% of the global burden.[2,3] In India, asthma accounted for 13.2 thousand deaths. It also accounted for 27.9% of disability-adjusted life years (DALYs) in Indians. The target of asthma treatment is to achieve good asthma control and, primarily, to minimize the burden of symptoms and the risk of exacerbations.[4] Cornerstone for long-term management and control of moderate-to-severe asthma is treated with inhaled corticosteroids (ICS) with/without long-acting β_2-agonists (LABAs).[5] They help reduce the frequency of exacerbations and improve asthma control. Despite the availability of various therapeutic options for treating asthma in India, asthma control rates remain poor.[6] As reported in the Asia-Pacific Asthma Insight and Management (AP-AIM) study, asthma remains uncontrolled in 90% of Indian asthmatic patients.[7] Thus, there is a pressing need to introduce newer approaches that can improve asthma control rates in India.

The amount of drug that reaches the lungs is an important factor that determines the treatment efficacy and varies with the type of inhaler device and inhalation technique used. Incorrect choice of inhalers, poor inhaler technique, and poor patient adherence to inhalers are key obstacles to attaining good asthma control.[8]

Pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the most widely used drug delivery systems for administering the drug by inhalation. However, the need for coordinating actuation and inhalation with pMDIs, and ensuring forceful inspiration in DPIs are their major shortcomings.[5,9,10] Breath-actuated inhalers (BAIs) are designed to overcome these limitations. In BAIs, the drug is released in response to a negative pressure generated in the device during inhalation. BAIs show better lung deposition of the medication than pMDIs in patients with poor technique and coordination.[11] Recently, a BAI device with a dose counter, the Synchrobreathe®, has been introduced with salmeterol/fluticasone (SFC) as active drugs. The device is actuated at low inspiratory flow rates of approximately 27–30 L/min.[11] When selecting the inhalation device for a patient, in addition to drug safety and efficacy, the patient's preference and acceptance of the device, ease of training, and device usability are important considerations for the physician.[12] We conducted a real-world study to evaluate the efficacy, safety, and usability of the BAI, Synchrobreathe®, containing SFC in patients with persistent asthma in India.

Materials and methods

Study settings and patient selection

This was an open-label, observational, prospective, non-comparative, multi-center study conducted at 48 outpatient centers across India, from December 2018 to May 2019, to **EV**aluate asthma c**O**ntro**L** and de**V**ice Usability of salm-**E**terol/fluticasone propionate FDC administered through Synchrobreathe® in patients with persistent asthma (EVOLVE study). The study enrolled patients above 12 years of age who had a documented diagnosis of asthma, were treatment-naive or were uncontrolled due to poor inhaler technique associated with a previous device based on investigator discretion and the clinical status of the patient on existing therapy, and were deemed suitable for initiating treatment with an SFC FDC delivered *via* BAI (Synchrobreathe®) at the investigator's discretion. Key exclusion criteria were hypersensitivity toward SFC, patients with acute episodes of asthma needing intensive measures, and status asthmaticus. Patients with prior experience using the Synchrobreathe® device were also excluded. The study was conducted following the ethical principles that have their origin in the current Declaration of Helsinki (2013) and was consistent with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP), Indian Good Clinical Practice Guidelines issued by the Central Drugs Standard Control Organisation, local regulations, and Ethical Guidelines for Biomedical Research on Human Participants issued by the Indian Council of Medical Research. The protocol was approved by an independent ethics committee and was registered with the Clinical Trial Registry of India (CTRI/2018/12/016629). All patients and their legally acceptable representatives provided informed consent before participation.

Study procedure and data collection

All those patients that were prescribed either SFC Synchrobreathe® 25/125 µg or 25/250 µg as a part of their asthma management consented to participate in this 12-week study. Patients were required to purchase the Synchrobreathe® BAI for their asthma control throughout the study period. They were instructed on the use of Synchrobreathe® during their routine visit by the physician or study staff. All other concomitant medications were continued as usual. The patients were followed up at 4, 8, and 12 weeks following treatment initiation. The adherence was assessed through verbal communication between the physician and the patient/caretaker.

The demographic characteristics, history of asthma, medical and surgical history, previous and concomitant medications, and previous inhalers used by the patient were noted at screening. Physical examination was also performed at screening and at the end of the study at 12 weeks. Vital signs were recorded throughout the treatment. Asthma control was evaluated using the ACQ-6[13] at all visits. The ACQ-6 comprises a total of six questions regarding dyspnea and wheezing, daytime and night-time symptoms, limitation in activity, and use of rescue bronchodilator in the past 7 days.[14] Each item is scored on a 7-point scale ranging from 0 to 6 and the final score is generated by averaging the total score for the six questions, where higher scores indicate worse asthma control. The minimal clinically important difference (MCID) level for the ACQ-6 score is 0.5 and represents the smallest clinically meaningful change.[15] The peak expiratory flow rate (PEFR) was measured at weeks 4, 8, and 12 using a peak flow meter (Breathometer, Cipla Ltd). The PEFR was recorded with a window period of ±2 h. To reduce diurnal variation, the recording time was uniformly maintained for every subject at each visit, that is, either in the morning or evening. In addition, a questionnaire to evaluate the device's usability was administered in week 4.

Study outcomes

The primary endpoint was a change from baseline in the ACQ-6 score at week 12. Secondary endpoints included change in the ACQ-6 score at weeks 4 and 8, the proportion of patients who responded to treatment, change from baseline in the PEFR at weeks 4, 8, and 12, and assessment of device usability at week 4. Patient response was categorized based on the ACQ-6 score at week 12 as follows: responders (improvement in ACQ-6 > 0.5), well controlled (ACQ-6 < 0.75), partially controlled ($0.75 <$ ACQ-6 < 1.5), and uncontrolled (ACQ-6 > 1.5).

Safety endpoints were adverse events (AEs) and serious adverse events (SAEs) recorded throughout the study period (12 weeks).

Statistical analysis

Since the study was observational, sample size calculation was not carried out; instead, a group of 500 patients was planned to be screened.

Primary and secondary analyses were conducted on the ITT and modified ITT (mITT) populations. The mITT population included patients who received study treatment and had at least one postbaseline assessment. Results for various subgroups based on baseline characteristics, for example, previous DPI use, previous pMDI use, and SFC use were analyzed. Continuous and quantitative variables were summarized using descriptive statistics and were compared using a paired *t*-test. Categorical data were presented as frequency count (*n*) and percentages (%). All statistical analyses were done using SAS® for Windows version 9.4 or above (SAS® Institute Inc., Cary, NC, USA).

Results

Of the 500 planned patients, 490 patients with persistent asthma were enrolled in 48 outpatient clinics. Of these, 26 patients discontinued the study for various reasons and 419 patients completed the study as per protocol (Figure 1). A total of 490 patients were analyzed in the ITT and safety population and 476 in the mITT population.

The mean age of the study population was 43.2 ± 16.4 years and included 269 (54.9%) men (Table 1). The mean duration of asthma was 3.1 ± 6.9 years. Most patients were non-smokers ($n = 465$, 94.9%). At baseline, the mean PEFR was 262.2 ± 102.2 L/min, and the ACQ-6 score was 2.2 ± 1.07. Treatment-naive or newly diagnosed cases constituted 36.7% ($n = 180$) of the ITT population, while 63.3% ($n = 310$) of patients were already receiving asthma treatment. Within

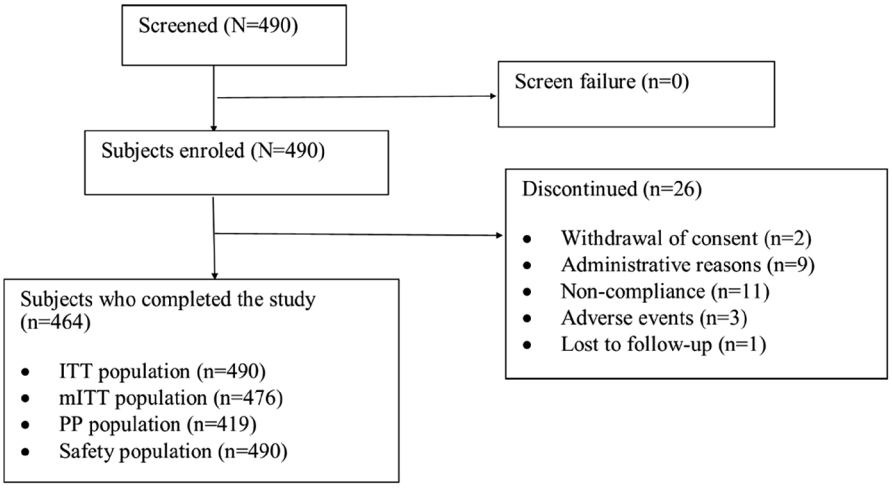

Figure 1. Flowchart representing patient disposition.
ITT, intention-to-treat; mITT, modified intention-to-treat; PP, per protocol.

Table 1. Demographic and baseline characteristics.

Parameters	Overall (ITT, *N* = 490)
Age (years)	43.2 ± 16.4
Gender (male/female)	269 (54.9)/221 (45.1)
Duration of asthma (years)	3.1 ± 6.9
Smoking habits	• Non-smoker: 465 (94.9) • Former smoker: 19 (3.9) • Current smoker: 6 (1.2)
Smoking history (pack-years)	11.5 ± 17.3
PEFR (L/min)	262.2 ± 102.2
ACQ-6 score	2.2 ± 1.07
Currently on treatment	310 (63.3)
Treatment-naive or newly diagnosed	180 (36.7)
Past inhalers (*n* = 296)	• DPI: 97 (19.7) • pMDI: 178 (36.3) • Soft Mist™ Inhaler: 1 (0.2) • Others: 20 (4.1)
Investigational product strength (mcg)	• Seroflo (SFC) Synchrobreathe® 125:119 (24.3) • Seroflo (SFC) Synchrobreathe® 250:371 (75.7)

ACQ-6, Asthma Control Questionnaire-6; DPI, dry powder inhaler; ITT, intention-to-treat; PEFR, peak expiratory flow rate; pMDI, pressurized metered-dose inhaler.
Data presented as mean ± SD or *n* (%) unless specified otherwise.

the ITT population, the majority received SFC 250 (*n* = 371, 75.7%) and 119 patients (24.3%) received SFC 125 delivered *via* Synchrobreathe®.

Change in the ACQ-6 score

The mean ACQ-6 score significantly reduced from 2.2 ± 1.1 at baseline to 0.4 ± 0.5 at week 12 (mean

Table 2. Change in ACQ-6 score and PEFR as per ITT analysis.

	Baseline	Week 4	Week 8	Week 12
ACQ-6 score				
Overall population	2.2 ± 1.1 (*n* = 490)	1.1 ± 0.8 (*n* = 474)	0.7 ± 0.6 (*n* = 471)	0.4 ± 0.5 (*n* = 464)
Change from baseline	–	−1.2 ± 1.0 (*n* = 474)	−1.6 ± 1.1 (*n* = 471)	−1.9 ± 1.1 (*n* = 464)
p-value	–	<0.0001	<0.0001	<0.0001
Subgroup: previous DPI use	2.1 ± 1.0 (*n* = 97)	1.0 ± 0.7 (*n* = 93)	0.7 ± 0.5 (*n* = 92)	0.5 ± 0.5 (*n* = 89)
Change from baseline	–	−1.1 ± 0.9 (*n* = 93)	−1.4 ± 1.0 (*n* = 92)	−1.7 ± 1.0 (*n* = 89)
p-value	–	<0.0001	<0.0001	<0.0001
Subgroup: previous pMDI use	2.1 ± 1.1 (*n* = 178)	1.0 ± 0.8 (*n* = 173)	0.7 ± 0.8 (*n* = 173)	0.4 ± 0.5 (*n* = 171)
Change from baseline	–	−1.1 ± 0.9 (*n* = 173)	−1.5 ± 1.0 (*n* = 173)	−1.7 ± 1.1 (*n* = 171)
p-value	–	<0.0001	<0.0001	<0.0001
Subgroup: previous SFC use	2.3 ± 1.0 (*n* = 62)	1.2 ± 0.6 (*n* = 61)	0.9 ± 0.5 (*n* = 61)	0.6 ± 0.6 (*n* = 61)
Change from baseline	–	−1.1 ± 0.9 (*n* = 61)	−1.5 ± 1.0 (*n* = 61)	−1.8 ± 1.1 (*n* = 61)
p-value	–	<0.0001	<0.0001	<0.0001
PEFR (L/min)				
Overall population	262.2 ± 102.2 (*n* = 490)	298.8 ± 108.4 (*n* = 474)	323.6 ± 109.5 (*n* = 471)	346.6 ± 106.8 (*n* = 464)
Change from baseline	–	35.1 ± 53.1 (*n* = 474)	60.1 ± 65.5 (*n* = 471)	82.5 ± 75.7 (*n* = 464)
p-value	–	<0.0001	<0.0001	<0.0001
Subgroup: previous DPI users	247.1 ± 96.2 (*n* = 97)	280.8 ± 98.4 (*n* = 93)	306.9 ± 110.3 (*n* = 92)	317.1 ± 98.4 (*n* = 89)
Change from baseline	–	33.6 ± 40.3 (*n* = 93)	58.5 ± 60.3 (*n* = 92)	68.9 ± 64.5 (*n* = 89)
p-value	–	<0.0001	<0.0001	<0.0001
Subgroup: previous pMDI users	275.5 ± 110.3 (*n* = 178)	307.8 ± 110.8 (*n* = 173)	331.2 ± 105.5 (*n* = 173)	349.9 ± 101.0 (*n* = 171)
Change from baseline	–	29.9 ± 51.2 (*n* = 173)	53.6 ± 55.7 (*n* = 173)	72 ± 63.5 (*n* = 173)
p-value	–	<0.0001	<0.0001	<0.0001
Subgroup: previous SFC users	275.2 ± 98.1 (*n* = 62)	305.7 ± 101.6 (*n* = 61)	325.5 ± 111.9 (*n* = 61)	332.2 ± 98.0 (*n* = 61)
Change from baseline	–	30.3 ± 37.2 (*n* = 61)	50.0 ± 54.6 (*n* = 61)	56.7 ± 52.8 (*n* = 61)
p-value	–	<0.0001	<0.0001	<0.0001

DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler; PEFR, peak expiratory flow rate.
Data presented as mean ± SD.

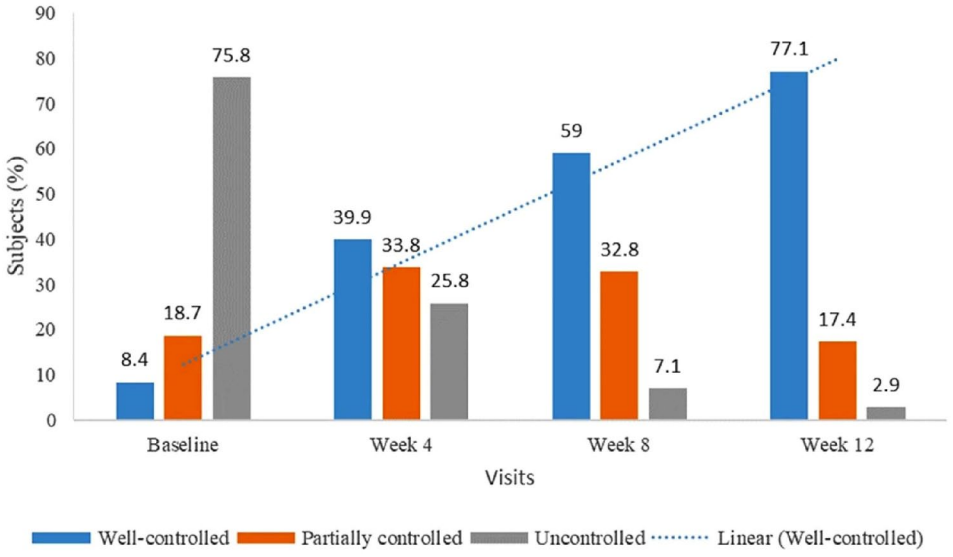

Figure 2. Proportion of patients with well-controlled, partially controlled, and uncontrolled asthma at all visits.

change: -1.9 ± 1.1, $p < 0.0001$) in the ITT population. Similar trends were observed in the mITT analysis. A consistent and statistically significant improvement in the ACQ-6 scores was observed as early as week 4 (Table 2). The MCID of 0.5 for the ACQ-6 was achieved in the patients from their first follow-up visit at week 4 (Table 2). Statistically significant improvements in the ACQ-6 scores were also observed in the subgroup analyses conducted, viz. patients previously using DPIs, patients previously using pMDIs, and those previously using SFC FDC with any inhaler device (Table 2). Similarly, mean change from baseline at week 4, week 8, and week 12 in treatment-naive and treatment-experienced patients was also found statistically significant (Supplementary Table 1).

A linear increase was observed in the proportion of well-controlled responders from 39.9% at week 4 to 77.1% at week 12 in the ITT population (Figure 2). This pattern of change in asthma control was similar in the mITT population.

Change in PEFR

The baseline PEFR in the ITT population increased by 35.1 ± 53.1 ml/min ($p < 0.0001$), 60.1 ± 65.5 ml/min ($p < 0.0001$), and 82.5 ± 75.7 ml/min ($p < 0.0001$) at weeks 4, 8, and 12, respectively (Table 2). Similar results were also seen in the mITT population. Statistically significant improvements in the PEFR were also observed in the three patient subgroups: patients previously using DPIs, patients previously using pMDIs, and those previously using the SFC FDC with any inhaler device (Table 2). Subgroup analysis demonstrated significantly improved PERF at week 4, week 8, and week 12 from baseline in treatment-naive and treatment-experienced patients (Supplementary Table 1).

Questionnaire for assessment of device usability

Most (91%) patients preferred using Synchrobreathe® over their previous inhaler device; 92.4% found it easy to use, and 91.3% found it very easy to inhale from Synchrobreathe®. In addition, Synchrobreathe® was rated very high on other parameters of usability, portability, patient confidence, and satisfaction (Table 3).

Safety evaluation

A total of 15 AEs and two SAEs were reported. Out of the 490 subjects enrolled, 11 had at least one AE. Of the 15 AEs, eight were mild, three were moderate, and four were severe (Table 4). The most commonly reported AE was respiratory tract infection (0.6%). Due to AEs, three subjects discontinued the study. Of the total 15 AEs, two were related to the study drug and 13 were unrelated. The two SAEs were death cases unrelated to the study drug.

Table 3. Patient responses from the device-usability questionnaire.

Category/response, *n* (%)	Overall (*N* = 490)
How easy was it to understand how to use the Synchrobreathe® inhaler?	
Very easy	351 (71.6)
Somewhat easy	102 (20.8)
Neither easy nor uneasy	11 (2.2)
Not very easy	10 (2.0)
How easy was it to remember how to use the Synchrobreathe® inhaler?	
Very easy	340 (69.4)
Somewhat easy	114 (23.3)
Neither easy nor uneasy	17 (3.5)
Not very easy	3 (0.6)
How easy was it to inhale from the mouthpiece of the Synchrobreathe® inhaler?	
Very easy	336 (68.6)
Somewhat easy	111 (22.7)
Neither easy nor uneasy	17 (3.5)
Not very easy	10 (2.0)
Overall, how easy was it to use the Synchrobreathe® inhaler?	
Very easy	366 (74.7)
Somewhat easy	84 (17.1)
Neither easy nor uneasy	17 (3.5)
Not very easy	7 (1.4)
How easy was it to carry the Synchrobreathe® inhaler in your pocket/bag?	
Very easy	332 (67.8)
Somewhat easy	114 (23.3)
Neither easy nor uneasy	20 (4.1)
Not very easy	8 (1.6)
How confident are you about using the Synchrobreathe® inhaler correctly?	
Very confident	366 (74.7)
Somewhat confident	84 (17.1)
Neither confident nor unsure	20 (4.1)
Somewhat unsure	2 (0.4)
Not confident at all	2 (0.4)

(Continued)

Table 3. (Continued)

Category/response, *n* (%)	Overall (*N* = 490)
Overall, how satisfied are you with the Synchrobreathe® inhaler?	
Very satisfied	384 (78.4)
Somewhat satisfied	81 (16.5)
Neither satisfied nor not satisfied	7 (1.4)
Not satisfied	1 (0.2)
In case you were using an inhaler previously for your treatment of asthma, then which device do you prefer?	
Synchrobreathe® (the study device)	270 (91.2)
Or your previous device	17 (5.7)
Missing	9 (3.1)

Discussion

This study assessed the asthma control and device usability of the SFC FDC delivered *via* Synchrobreathe® in a real-world setting in India. The use of the SFC Synchrobreathe® showed significant and consistent improvements in asthma control (ACQ-6 scores) and lung function (PEFR) starting from week 4 until the end of the study (week 12). The proportion of well-controlled responders increased from 39.9% at week 4 to 77.1% at week 12. The device was rated high in usability and patient satisfaction, with most subjects (91%) preferring Synchrobreathe® to their existing inhalation devices. Similar results have been reported by Dhar *et al.* from a randomized, controlled trial, evaluating the safety and efficacy of the SFC FDC administered through a BAI *versus* a pMDI. A significant mean change in the PEFR from baseline was seen for the BAI and pMDI groups (50.72 L/min *versus* 48.82 L/min). Although the difference was not statistically significant between the groups, 75% of the patients preferred using a BAI and 25% preferred the pMDI.[16] Patients who were already using SFC at baseline in our study showed significant improvements in their ACQ-6 scores and PEFR after switching to Synchrobreathe®. It should be noted that among past inhalers the poor inhaler technique was based on investigator discretion and the clinical status of the patients on the existing therapy. There was no run-in to prove it by enhancing the inhaler technique and later verifying it. This finding indicates that in patients who are already using guideline-recommended medications, the introduction of user-friendly devices, such as Synchrobreathe®, may lead to improved asthma control.

Similar results have been reported from various studies that assessed the effectiveness of BAIs in asthmatics. A retrospective observational database study involving more than 450 general practices in the United Kingdom found that inhaler devices might have a bearing on clinical outcomes in the real world. Adjusted odds ratios [95% confidence intervals (CI)] for asthma control were significantly better for BAIs [1.08 (1.02–1.14)] and DPIs [1.13 (1.06–1.21)] compared with pMDIs, while adjusted exacerbation rate ratios (95% CI) were 1.00 (0.93–1.08) and 0.88 (0.81–0.95), respectively.[17] In another real-world study comparing the effectiveness of traditional pMDI and BAI using the primary care medical record database ($n = 5556$ patients), children and adults using BAIs appeared to have better asthma control compared with those using pMDIs.[18] Characteristics of inhaler devices and patient factors (primarily inhaler technique) play a significant role in determining the amount of drug deposited in the lungs, which can, in turn, impact asthma control.[17,18] In a previously reported gamma-scintigraphy study, drug deposition in the lungs was found to be significantly higher when SFC was delivered *via* the Synchrobreathe® device compared with a conventional pMDI (22.33% *versus* 17.32%).[19] Moreover, studies

Table 4. Summary of adverse events.

	Events (*n*)	Percentage
Total	15	2.2
Serious adverse event	2	0.4
Seriousness criteria		
Fatal	2	0.4
Severity		
Mild	8	1.2
Moderate	3	0.4
Severe	4	0.6
Discontinuation of study medication	2	0.2
Interruption of study medication	2	0.2
Relation to investigational product		
Probable	2	0.2
Not related	13	2.0
Outcome		
Recovered	13	1.8
Fatal	2	0.4
Description of adverse events	1	0.2
Cardiac arrest	1	0.2
Glossodynia	1	0.2
Pyrexia	1	0.2
Respiratory tract infection	3	0.6
Upper respiratory tract infection	1	0.2
Pancreatic carcinoma	1	0.2
Dizziness	1	0.2
Asthma	1	0.2
Cough	1	0.2
Dyspnea	1	0.2
Allergic rhinitis	1	0.2
Pruritus	1	0.2
Rash	1	0.2

have shown that a BAI can improve asthma control even in patients who were previously using a DPI or a pMDI.[20,21] Congruent with these studies, switching to Synchrobreathe® improved asthma control in a subgroup of patients who were using a DPI or a pMDI at baseline in our study before enrollment in the study.

Accurate use of inhaler devices remains a significant challenge for improving therapeutic efficacy in chronic diseases such as asthma and Chronic obstructive pulmonary disease (COPD). Certain patient populations are prone to having problems in adopting correct inhaler techniques while using DPIs and pMDIs, which leads to poor asthma control and increased healthcare costs. Cognitive difficulties, impaired vision, and inadequate physical strength are the common reasons for poor device technique in elderly people. Patients with physical or cognitive impairment are often unable to coordinate the actuation with the inhalation. Children under the age of 5 years may not be able to generate sufficient suction to use DPIs correctly. Thus, BAIs have emerged as the preferred device for most of these patients.[22]

Real-world evidence on the handling and preference of inhalational devices varies, and a closer evaluation through larger, well-designed prospective trials is needed.[17] In a recent study, Synchrobreathe® was compared with a pMDI in patients with asthma and COPD, and in inhaler-naive healthy volunteers ($n=460$). After 14 days, the percentage of participants using the device without any error was higher with Synchrobreathe® *versus* the pMDI (68.19% *versus* 56.21%, $p<0.001$) while the number of errors before and after training, the time required for correctly performing the inhalation technique and the number of attempts to perform the correct technique were significantly lower with Synchrobreathe® *versus* the pMDI. Overall, Synchrobreathe® was preferred and rated highly over the pMDI by the study participants.[11] In another randomized study, it was demonstrated that BAIs were correctly used by over 90% of patients.[22] A similar preference for BAIs over pMDIs was also seen in an observational study that assessed the adequacy of the inhaler technique and patient preferences in the elderly.[23] BAIs have also been shown to result in greater patient satisfaction in clinical practice.[24] These results correlate with those in our study, which indicated that most (91%) patients preferred Synchrobreathe® over their previous device.[25]

The results of this study should be interpreted by taking into account its limitations. The present study was an open-label study, and there was no comparator arm. Furthermore, due to the nonavailability of electronic medical records, we were unable to establish a historical control. Notably, more than one-third of the patients were treatment-naive which could lead to overestimation of improved ACQ and PEF with the use of the study device/Synchrobreathe®. However, the remaining group (that included 296 patients who had been mostly using DPIs, and pMDI, for asthma control) also showed the benefit when switched to Synchrobreathe inhaler. SFC treatment *via* Synchrobreathe® was initiated in patients based on the clinical judgment of the treating physician. The selection of the dose was also left at the discretion of the investigator. Hence, there was a possibility that treatment-experienced patients were likely to be prescribed a higher dose of SFC, which could affect treatment outcomes. Since we included patients receiving SFC through other devices, the treatment adherence before our study was not known. Compliance with and adherence to SFC, when delivered *via* Synchrobreathe®, was also not assessed. However, it reflects the use of SFC Synchrobreathe® in a real-world setting where compliance and device techniques are not limiting factors to consider the patients for efficacy analysis as done in a controlled clinical trial. Hence, we believe that the findings of our study reflect the benefits of SFC Synchrobreathe® which is seen in clinical practice.

Conclusion

Treatment with SFC FDC delivered *via* Synchrobreathe® resulted in consistent improvement in asthma control and lung function over 12 weeks. Furthermore, most patients reported satisfaction with and a preference for Synchrobreathe® BAI over their previous device. However, long-term studies are needed to be conducted to reciprocate study results.

Thus, SFC delivered *via* Synchrobreathe® offers good efficacy and safety, and could have significant clinical implications for improving asthma control in real-world clinical settings. Overall, SFC Synchrobreathe® is a new option for patients with asthma, including those who currently have poor inhaler techniques.

Declarations

Ethics approval and consent to participate

The protocol was approved by an independent ethics committee (Anand Institutional Ethics Committee; registration number: ECR/725/Inst/GJ/2015/RR-21). All patients and/or their legally acceptable representatives provided informed consent before participation.

Consent for publication

None.

Author contributions

Santhalingam Balamurugan: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Dalal Sonia: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Deshmukh Vikrant: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Khanra Monotosh: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Sundar Raj Shyam: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Akhtar Shamim: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Kumar Vinay: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Nandagopal Velayuthaswamy: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Ahmed Masood: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Gupta Manohar Lal: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Godse Ajay: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Chhowala Sushmeeta: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Writing – original draft; Writing – review & editing.

Lopez Meena: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Sawant Sandesh: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Writing – original draft; Writing – review & editing.

Jadhav Sonali: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Writing – original draft; Writing – review & editing.

Vaidya Abhijit: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Gogtay Jaideep: Conceptualization; Funding acquisition; Methodology; Writing – original draft; Writing – review & editing.

Acknowledgements

The authors thank Dr Kapila Chawda, Clinical Research Group, Medical Services, Cipla Ltd, the investigator's teams, and JSS Medical Research, India, for their assistance in conducting the study. The medical writing support was provided by Leena Patel from CBCC Global Research.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Cipla Ltd., India.

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: C.S., L.M., S.S., J.S., V.A., and G.J. are the employees of Cipla Ltd., Mumbai, India. Other authors do not have any conflict of interest regarding the manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

ORCID iD

Vaidya Abhijit https://orcid.org/0000-0002-6046-9105

Supplemental material

Supplemental material for this article is available online.

References

1. Reddel HK, Bacharier LB, Bateman ED, *et al.* Global initiative for asthma strategy 2021: executive summary and rationale for key changes. *Eur Respir J* 2021; 59: 2102730.
2. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396: 1223–1249.
3. GBD compare, https://vizhub.healthdata.org/gbd-compare/ (2021, accessed 30 July 2021).
4. Papi A, Brightling C, Pedersen SE, *et al.* Asthma. *Lancet* 2018; 391: 783–800.
5. Salvi S, Gogtay J and Aggarwal B. Use of breath-actuated inhalers in patients with asthma and COPD – an advance in inhalational therapy: a systematic review. *Expert Rev Respir Med* 2014; 8: 89–99.
6. Price D, Roche N, Christian Virchow J, *et al.* Device type and real-world effectiveness of asthma combination therapy: an observational study. *Respir Med* 2011; 105: 1457–1466.
7. Salvi SS, Apte KK, Dhar R, *et al.* Asthma insights and management in India: lessons learnt from the Asia Pacific–Asthma Insights and Management (AP-AIM) Study. *J Assoc Physicians India* 2015; 63: 36–43.
8. Haughney J, Price D, Kaplan A, *et al.* Achieving asthma control in practice: understanding the reasons for poor control. *Respir Med* 2008; 102: 1681–1693.
9. Crompton GK, Barnes PJ, Broeders M, *et al.* The need to improve inhalation technique in Europe: a report from the Aerosol Drug Management Improvement Team. *Respir Med* 2006; 100: 1479–1494.
10. Giraud V and Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J* 2002; 19: 246–251.
11. Balamurugan S, Apte K, Singh BP, *et al.* Device-handling study of a novel breath-actuated inhaler, Synchrobreathe®, versus a pMDI. *Respir Med* 2020; 161: 105707.
12. Lavorini F, Janson C, Braido F, *et al.* What to consider before prescribing inhaled medications: a pragmatic approach for evaluating the current inhaler landscape. *Ther Adv Respir Dis* 2019; 13: 1753466619884532.
13. Jia CE, Zhang HP, Lv Y, *et al.* The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol* 2013; 131: 695–703.
14. Barnes PJ, Casale TB, Dahl R, *et al.* The Asthma Control Questionnaire as a clinical trial endpoint: past experience and recommendations for future use. *Allergy* 2014; 69: 1119–1140.
15. Meltzer EO, Busse WW, Wenzel SE, *et al.* Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. *J Allergy Clin Immunol* 2011; 127: 167–172.
16. Dhar R, Salvi S, Rajan S, *et al.* Salmeterol/fluticasone through breath-actuated inhaler versus pMDI: a randomized, double-blind, 12 weeks study. *J Asthma* 2015; 52: 1065–1072.
17. Price D, Haughney J, Sims E, *et al.* Effectiveness of inhaler types for real-world asthma management: retrospective observational study using the GPRD. *J Asthma Allergy* 2011; 4: 37–47.
18. Price D, Thomas M, Mitchell G, *et al.* Improvement of asthma control with a breath-actuated pressurised metred dose inhaler (BAI): a prescribing claims study of 5556 patients using a traditional pressurised metred dose inhaler (MDI) or a breath-actuated device. *Respir Med* 2003; 97: 12–19.
19. Gogtay J, Tambe A, Rote K, *et al.* Improvement in the drug delivery of salmeterol/fluticasone via a novel breath actuated pressurized metered dose inhaler with a dose counter. *Euro Resp J* 2019; 54: PA4222.
20. Diggory P, Bailey R and Vallon A. Effectiveness of inhaled bronchodilator delivery systems for elderly patients. *Age Ageing* 1991; 20: 379–382.
21. Giraud V and Allaert FA. Improved asthma control with breath-actuated pressurized metered dose inhaler (pMDI): the SYSTER survey. *Eur Rev Med Pharmacol Sci* 2009; 13: 323–330.

22. Gupta S. How to ensure the correct inhaler device is selected for each patient. *Clin Pharm* 2009; 1: 322–323.

23. Chapman KR, Love L and Brubaker H. A comparison of breath-actuated and conventional metered-dose inhaler inhalation techniques in elderly subjects. *Chest* 1993; 104: 1332–1337.

24. Gupta N and Darbar A. Satisfaction survey on the use of breath actuated Inhaler. *Euro Resp J* 2016; 48: PA970.

25. Molimard M, Raherison C, Lignot S, *et al.* Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. *J Aerosol Med* 2003; 16: 249–254.