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ORIGINAL ARTICLE

Salmeterol/fluticasone through breath-actuated inhaler versus pMDI: a randomized, double-blind, 12 weeks study

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Abstract

Objective: Salmeterol/fluticasone combination (SFC) formulated in a breath-actuated inhaler (BAI) overcomes the co-ordination problem associated with the pressurized-metered dose inhaler (pMDIs). Our aim was to compare the efficacy and the safety of SFC given through the BAI versus the conventional pMDI in moderate-to-severe asthmatics. **Methods:** In this randomized, double-blind, double-dummy, prospective, active-controlled, parallel group, multicenter, 12 weeks study, 150 asthmatics were randomized to receive SFC (25/125 mcg) through either BAI or pMDI. The primary efficacy endpoint was mean change in pre-dose morning PEFR value at 12 weeks and the secondary efficacy endpoints included, mean change in FEV₁, pre-bronchodilator FVC, pre-dose morning and evening PEFR, symptom scores at 2, 4, 8, and 12 weeks. Patient preferences for device and safety were also assessed. **Results:** At 12 weeks, the mean change in pre-dose morning PEFR in BAI and pMDI groups was 50.72 L/min and 48.82 L/min, respectively ($p < 0.0001$; both groups) and the difference between the two groups was not significant. Both the treatment groups showed a statistically significant improvement in secondary endpoints at all-time points compared with baseline. The usability questionnaire assessment results showed that the BAI device was preferred by 75% of patients as compared with 25% preferring pMDI. SFC in both BAI and pMDI devices was found to be safe and well tolerated. **Conclusion:** This is the first study to demonstrate that SFC given through the BAI produces comparable efficacy and safety endpoints as pMDI. Additionally, BAI was the preferred inhaler by patients compared to conventional pMDI.

Keywords

Asthma, breath-actuated inhaler, pressurized metered dose inhaler, preference, Salmeterol/Fluticasone, SFC BAI, SFC pMDI

History

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Introduction

Inhalation therapy is the most effective and preferred mode for delivering medications in patients with asthma. It offers the advantage of targeted lung delivery, smaller doses, rapid onset of action, and reduced side effects when compared with systemic administration of medications. The combination of inhaled corticosteroids (ICS) and long-acting beta₂-agonists (LABAs) is the foundation for the long-term management and effective control of moderate-to-severe asthma [1].

Since the introduction of the pressurized metered dose inhaler (pMDI) in 1956, [2] inhalation therapy has evolved and there are now a plethora of inhaler devices, to suit the varied needs of different patients. pMDIs still remain one of the most widely prescribed and used inhalers since they have

the advantages of being compact, portable, convenient and provide highly reproducible dosing [3]. One of the most commonly reported drawbacks of the pMDIs is the difficulty in co-ordinating the actuation with inhalation [2,3]. Patients with poor pMDI technique showed a substantial lower lung deposition (7.2%) [4]. Using spacers with pMDIs does overcome the problem of coordination [5–7]. The dry powder inhalers (DPIs) were introduced in the late 1960s. Unfortunately, patients with compromised inspiratory flow rates find it difficult to achieve the rapid and forceful inhalation required to actuate the DPIs [8,9]. Improper medication use and incorrect inhaler technique have been associated with suboptimal disease control and poor quality of life [10,11]. For achieving adequate disease control, both the right device and the right drug play a critical role.

The breath-actuated inhaler (BAI) is an advance in inhalation therapy since it overcomes the limitations experienced by patients with the use of other inhalation devices. The BAI senses the patient's inhalation through the actuator and

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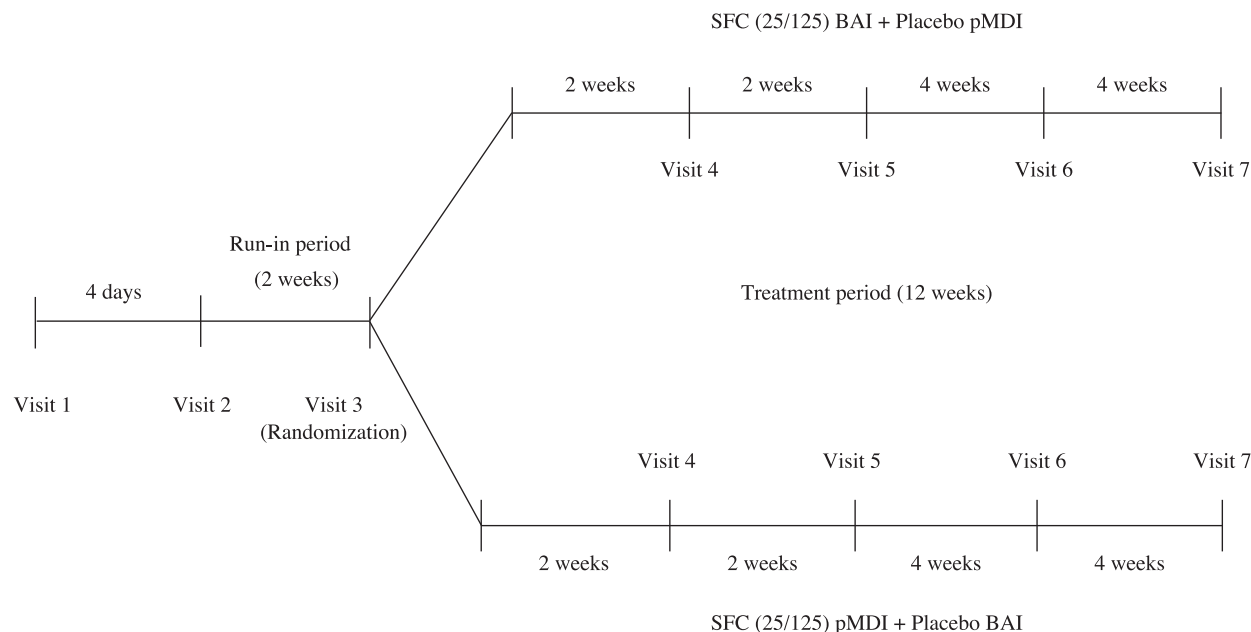


Figure 1. Study design. SFC, Salmeterol Fluticasone combination; BAI, breath-actuated inhaler; pMDI, pressurized metered dose inhaler.

releases the drug automatically in synchrony. Hence, unlike DPIs, the delivered dose does not depend on patient's inhalation effort [12,13].

Salmeterol/fluticasone combination (SFC) is a well-established and widely used LABA/ICS combination approved for the long-term management of patients with asthma and COPD. A number of studies have supported the role of inhaled SFC in improving lung function, quality of life, reducing exacerbations, and providing better disease control in patients with asthma [14–16].

The LABA/ICS combination of SFC has now been formulated in a BAI. The aim of this study was to compare the efficacy and the safety of SFC delivered by the BAI versus the same combination delivered by the pMDI in patients with moderate to severe asthma over 12-weeks. In addition, we also compared patient preference for device use between BAI and pMDI.

Methods

Study design

This was a randomized, double-blind, double-dummy, prospective, active-controlled, parallel group, multi-centre, 12 weeks study in moderate-to-severe asthma.

Patients visited the clinic at the beginning (screening visits 1 and 2), at the end of run-in (visit 3) and after 2, 4, 8, and 12 weeks of treatment (Figure 1). At visit 1, patients were screened for eligibility by history, physical examination, and laboratory investigations including chest X-ray, electrocardiogram (ECG) and blood tests. At visit 2, selected patients were assessed for reversibility test (spirometry: forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), and % predicted FEV₁). Patients fulfilling the required criteria entered a 2-week run-in period, in which all previous asthma medications were withdrawn and all patients prescribed fluticasone propionate pMDI 50 mcg two puffs

twice daily. Levosalbutamol pMDI was provided as rescue medication throughout the study duration.

Double dummy is a technique for retaining the blind when administering supplies in a clinical trial, when the two treatments cannot be made identical [17]. In this study, treatments were masked in a double-dummy fashion, whereby subjects randomized to receive BAI were given SFC BAI and a placebo pMDI, and subjects randomized to receive pMDI were given SFC pMDI and a placebo BAI.

After the run-in period, patients satisfying the randomization criteria were randomized (1:1) to receive either SFC 25/125 mcg (Seroflo[®] BAI, Cipla Ltd, Mumbai, India) + pMDI (placebo) or SFC 25/125 mcg (Seroflo[®] pMDI, Cipla Ltd, Mumbai, India) + BAI (placebo) for a period of 12 weeks.

The study was approved by the local ethics review committees and was conducted in accordance with the principles of Declaration of Helsinki. The study was conducted according to ICH-GCP guidelines. Written informed consent was obtained from all the study participants. This study is registered with clinical trial registry of India CTRI/2011/11/002165.

Patients

Patients ≥ 18 years of age with a confirmed diagnosis of asthma according to Global Initiative For Asthma (GINA) guidelines, demonstrating reversibility (FEV₁ of $\geq 12\%$ and ≥ 200 ml, 20 min after administering 200 mcg levosalbutamol delivered through the pMDI) or with a documented reversibility within the last 6 months were enrolled in the study. Eligible patients had a documented history of asthma for at least past 6 months and were receiving a dose of ICS or ICS + LABA for at least 4 weeks prior to the screening visit.

Patients with, known or suspected hypersensitivity to the medicinal product, history of serious uncontrolled medical condition which might compromise safety of the subject, clinically relevant upper respiratory tract infection for

4 weeks or lower respiratory tract infection for 8 weeks were excluded from the study. Also, pregnant and lactating females were not included in the study.

Those patients showing an $FEV_1 \geq 50\%$ and $\leq 80\%$ of the predicted normal value when not on short-acting bronchodilator medication for the past 6 h and ICS + LABA combination for the past 24 h, prior to screening visit 2 were included in the 2 week run-in period.

At the end of 2 weeks, patients with a pre-dose $FEV_1 \geq 50\%$ and $\leq 80\%$ of the predicted normal value and FEV_1 within $\pm 15\%$ of visit 2 value were randomized. Patients with an exacerbation requiring hospitalization or oral steroids or additional asthma therapy (including change in dose of ICS) and those suffering from respiratory tract infections during the run-in period were excluded from the study. Current smokers or past smokers with a smoking history of ≥ 10 pack years were excluded from the study.

Assessments

The primary efficacy endpoint was mean change in pre-dose morning PEFR recorded at the end of 12 weeks, using the peak flow meter (Breathe-o meter™, Cipla Ltd., Mumbai, India)

The secondary endpoints included lung function measurements, symptoms, rescue medication use, safety assessments and patient preference for the inhaler device. Lung function measurement included mean change in pre-dose morning and evening PEFR, measured using peak flow meter; mean change in FEV_1 and FVC measured using spirometer at 2, 4, 8, and 12 weeks. Spirometry was performed according to ATS/ERS 2005 standards. Symptom scores and rescue medication usage were recorded at 2, 4, 8, and 12 weeks. To assess the preference for a particular device, each patient answered a two-page self-administered validated questionnaire at week 12. Questionnaires were provided in regional languages if required. Safety was evaluated in terms of adverse events and drug-related adverse events throughout the study period. Laboratory investigations (hematology, liver function tests, renal function tests, and urine analysis) were done at screening visit 1 and at the end of the study. Vital parameters – blood pressure (systolic and diastolic in mmHg) and pulse (beats/min) – were recorded at every visit.

Statistical analysis

The primary efficacy variable was the mean change in morning PEFR over 12 weeks and the minimum sample size required for the study was determined in relation to its statistical power to detect no treatment difference in mean change in morning PEFR between the two study arms. Assuming a true standard deviation of mean change in morning PEFR of 50 L/min and using two-sided significance test at the 5% level, a sample size of 126 evaluable patients were determined to give the study a power of 80% with an equivalence limit difference in the mean of 25 L/min between the two groups. Assuming a 20% dropout rate, a total of 150 patients were determined to be randomized in the study.

Intention-to-treat (ITT) population included all randomized patients who received at least one dose of study drug with one post-baseline visit data. The statistical significance

of the difference at week 12 from baseline for the primary and secondary endpoints was analyzed using paired *t*-test at 5% level of significance. The statistical significance between the groups across the visits for mean values was analyzed using unpaired *t*-test at 5% level of significance. The mean change between the two groups was analyzed, for each end point using unpaired *t*-test at 5% level of significance; and for usability questionnaire using chi-square or fisher's exact test at 5% level of significance.

Results

A total of 180 patients were screened, out of which 161 fulfilled the selection criteria and entered the run-in-period (Figure 2). Of these, 11 patients failed to meet the randomization criteria and 150 eligible patients were randomized (1:1) to SFC BAI ($n = 75$) and SFC pMDI ($n = 75$). A total of 14 patients ($n = 5$ SFC BAI, $n = 9$ SFC pMDI) dropped out of the study due to protocol violation. The intent to treat (ITT) population consisted of 136 patients ($n = 70$ SFC BAI, $n = 66$ SFC pMDI). Baseline characteristics were comparable between the two treatment groups (Table 1).

Mean change in pre-dose morning and evening PEFR

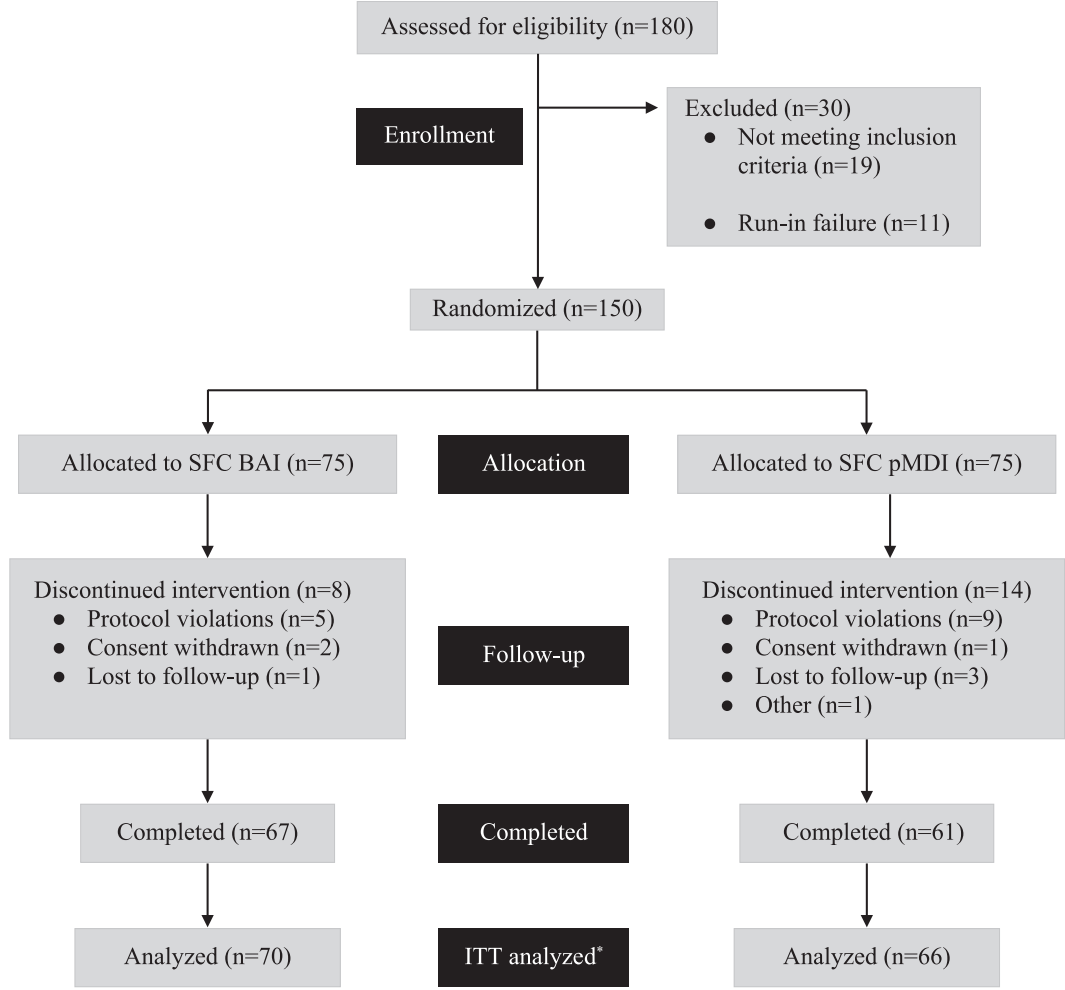
Both the treatment groups showed a statistically significant improvement in morning and evening PEFR values at all the time points throughout the study period. The morning PEFR values at baseline for SFC BAI and SFC pMDI group were 269.20 L/min and 266.65 L/min while after 12 weeks treatment the improvement in morning PEFR were 319.92 L/min ($p < 0.0001$) and 315.47 L/min ($p < 0.0001$), respectively. At week 12 a significant improvement ($p < 0.0001$) in morning PEFR was recorded with a mean change from baseline in BAI and pMDI groups being reported as 50.72 L/min and 48.82 L/min, respectively, with no statistically significant difference ($p = 0.35$) between the two treatment groups (Figure 3, Online Supplements 1 and 2)

The evening PEFR values at baseline for SFC BAI and SFC pMDI group were 268.00 and 269.66 L/min while after 12 weeks treatment the improvement in evening PEFR were 323.44 L/min ($p < 0.0001$) and 316.55 L/min ($p < 0.0001$), respectively. SFC BAI group showed a significantly greater increase in evening PEFR at weeks 2 ($p = 0.0477$) and 4 ($p = 0.04$) compared with the SFC pMDI group (Figure 4). At week 12, difference between the treatment groups for mean change in evening PEFR was 8.55 L/min (95% CI 3.42, 9.03) respectively. (Online Supplement 3).

Mean change in FEV_1

Both the treatment groups showed statistically significant improvement in the FEV_1 values at all-time points (2, 4, 8, and 12 weeks) compared with baseline (Figure 5). The mean FEV_1 at baseline for SFC BAI and SFC pMDI group were 1.63 L and 1.67 L, while after 12 weeks treatment, the improvement in mean FEV_1 were 1.83 L ($p < 0.0001$) and 1.82 L ($p < 0.0001$), respectively.

There was a significant difference between the two groups at the end of 2 weeks (SFC BAI: 0.13 L; SFC pMDI: 0.06 L; $p < 0.05$). At week 12, difference between the treatment groups for mean change in FEV_1 was 0.06 L (95% CI -0.05,



*ITT population included patients who received atleast one dose of the study drug with one post baseline visit data

Figure 2. Patient disposition.

Table 1. Patient demographics and baseline characteristics.

Parameters	Salmeterol/Fluticasone		<i>p</i> Value
	BAI (<i>n</i> = 72)	pMDI (<i>n</i> = 71)	
Gender (M/F)	32/40	32/39	0.936
Age (years), mean ± SD	44.85 ± 12.30	43.25 ± 12.39	0.4397
Height (cm), mean ± SD	158.33 ± 9.96	158.08 ± 9.07	0.8756
Weight (kg), mean ± SD	61.51 ± 14.07	58.94 ± 11.23	0.2298
Duration of asthma (months)	72.38 ± 85.31	70.77 ± 88.28	0.9119
Smoking history in pack years	6.16 ± 4.06	7.0 ± 0.0	0.0853
Pre-bronchodilator FEV ₁ (L)	1.60 ± 0.48	1.60 ± 0.47	0.999
Pre-bronchodilator FEV ₁ % of predicted	63.99 ± 7.57	63.51 ± 8.36	0.719
Pre-bronchodilator FVC (L)	2.26 ± 0.64	2.31 ± 0.71	0.658
Reversibility (%)	22.77 ± 9.12	24.50 ± 10.93	0.306

0.17), higher in the BAI group, but not statistically significant (Online Supplement 4).

Mean change in FVC

Both the BAI and pMDI groups showed statistically significant improvement in pre-bronchodilator FVC at the end of 2, 4, 8, and 12 weeks compared with baseline. The mean FVC

values at baseline for the SFC BAI and the SFC pMDI group were 2.28 L and 2.35 L, while after 12 weeks treatment, the improvement in mean FVC was 2.43 L (*p* < 0.0004) and 2.50 L (*p* < 0.0045), respectively.

There was no difference in the change in FVC between the two groups. SFC BAI and SFC pMDI showed an increase of 0.15 L and 0.14 L, respectively, for mean change in FVC, at 12 weeks. At week 12, difference between the treatment groups for mean change in FVC was 0.01 L (95% CI –0.17, 0.19) (Figure 6, Online Supplement 5).

Rescue medication

There was a significant reduction in rescue medication use in both the groups compared with baseline (*p* < 0.05). This reduction was seen throughout the 12-week treatment period. The mean rescue medication puffs at baseline for the SFC BAI and the SFC pMDI group were 12.40 and 13.85, while after 12 weeks treatment, the reduction in rescue medication puffs were 4.69 (*p* < 0.0004) and 4.88 (*p* < 0.0001), respectively.

At week 12, difference between the treatment groups for mean change in the number of puffs of rescue medication was 0.76 (95% CI –0.63, 2.15) (Online Supplements 6 and 7).

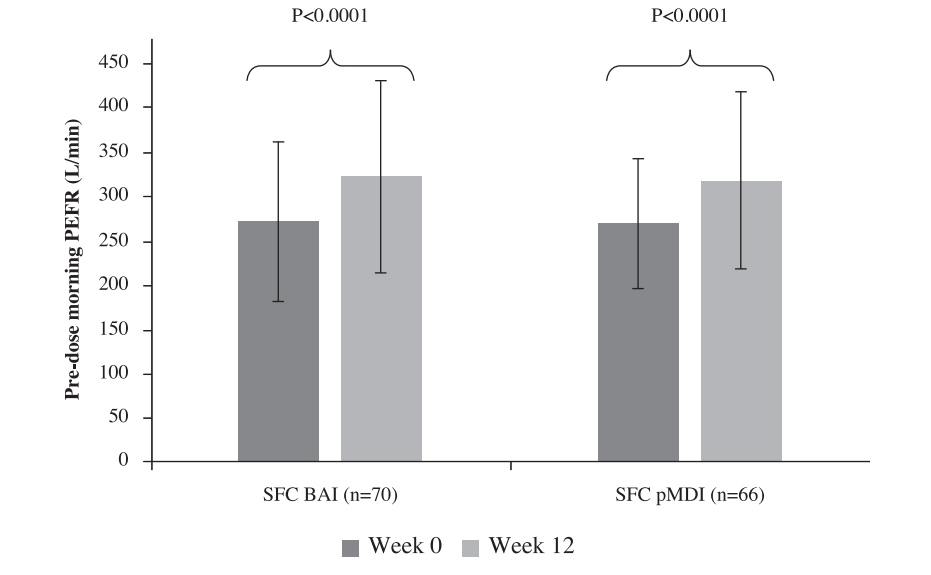


Figure 3. Mean (± SD) pre-dose morning PEFR values at weeks 0 and 12.

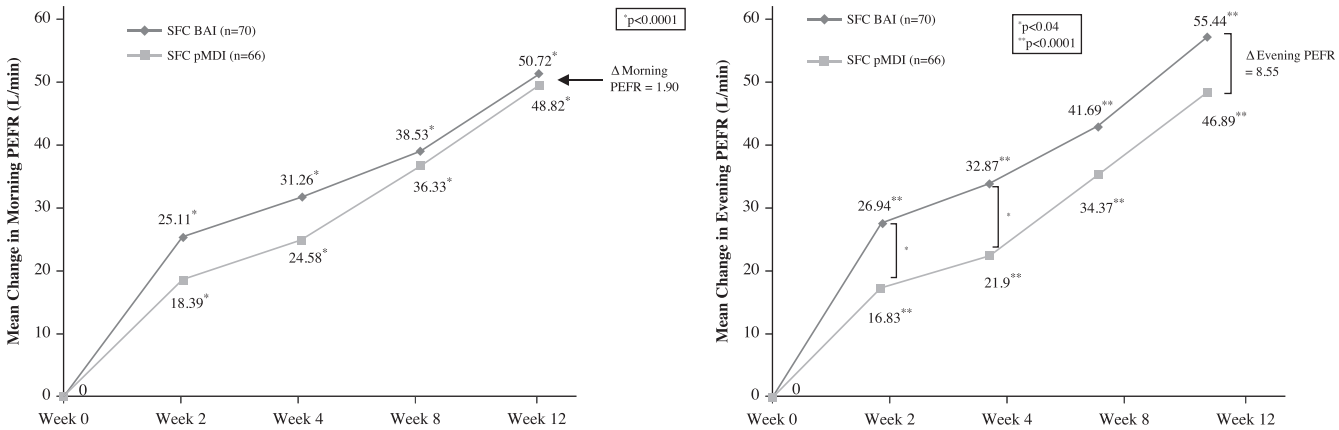


Figure 4. Mean change (± SE) in pre-dose morning and evening PEFR (L/min) at 2, 4, 8, and 12 weeks.

Symptom score

There was a significant improvement ($p < 0.0001$) in day time (Online Supplement 8) and night time symptom scores (Online Supplement 9) in both the groups from week 2 onwards with no difference between the groups.

The mean day time symptom score at baseline for the SFC BAI and the SFC pMDI group were 0.67 and 0.71, while after 12 weeks treatment, the mean day time symptom score decreased to 0.23 ($p < 0.0001$) and 0.24 ($p < 0.0001$), respectively. The mean night time symptom score at baseline for the SFC BAI and the SFC pMDI group were 0.51 and 0.54, while after 12 weeks treatment, the mean night time symptom score decreased to 0.10 ($p < 0.0005$) and 0.12 ($p < 0.0001$), respectively.

Both the groups showed improvements in the number of patients with symptom-free days at week 12 ($n = 56/70$ SFC

BAI; $n = 55/66$ SFC pMDI) as compared with baseline ($n = 38$ SFC BAI; $n = 38$ SFC pMDI). Similarly, there was an improvement in number of patients with symptom free nights at week 12 ($n = 64/70$ SFC BAI; $n = 63/66$ SFC pMDI) as compared with baseline ($n = 43$ SFC BAI; $n = 39$ SFC pMDI).

Usability questionnaire assessment

The results of the usability questionnaire assessment revealed that the BAI was the preferred device and was easier in terms of learning and remembering the steps of usage as compared to the pMDI (Figure 7).

Ninety-seven (97%) patients found the BAI very easy/easy to use while 75% found pMDI very easy to use. Out of the 128 subjects, 96 (75%) showed a preference for the BAI while 32 (25%) preferred to use the conventional pMDI.

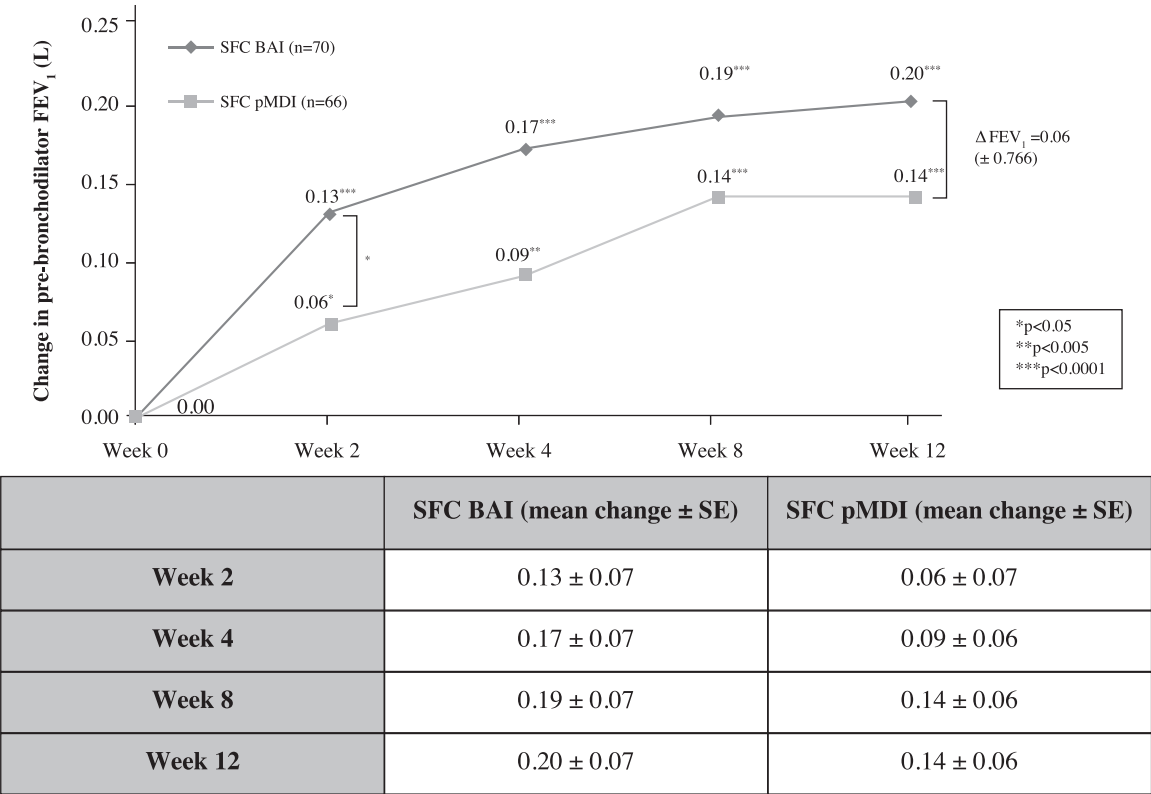


Figure 5. Mean change (± SE) in pre-bronchodilator FEV₁ at 2, 4, 8, and 12 weeks from baseline.

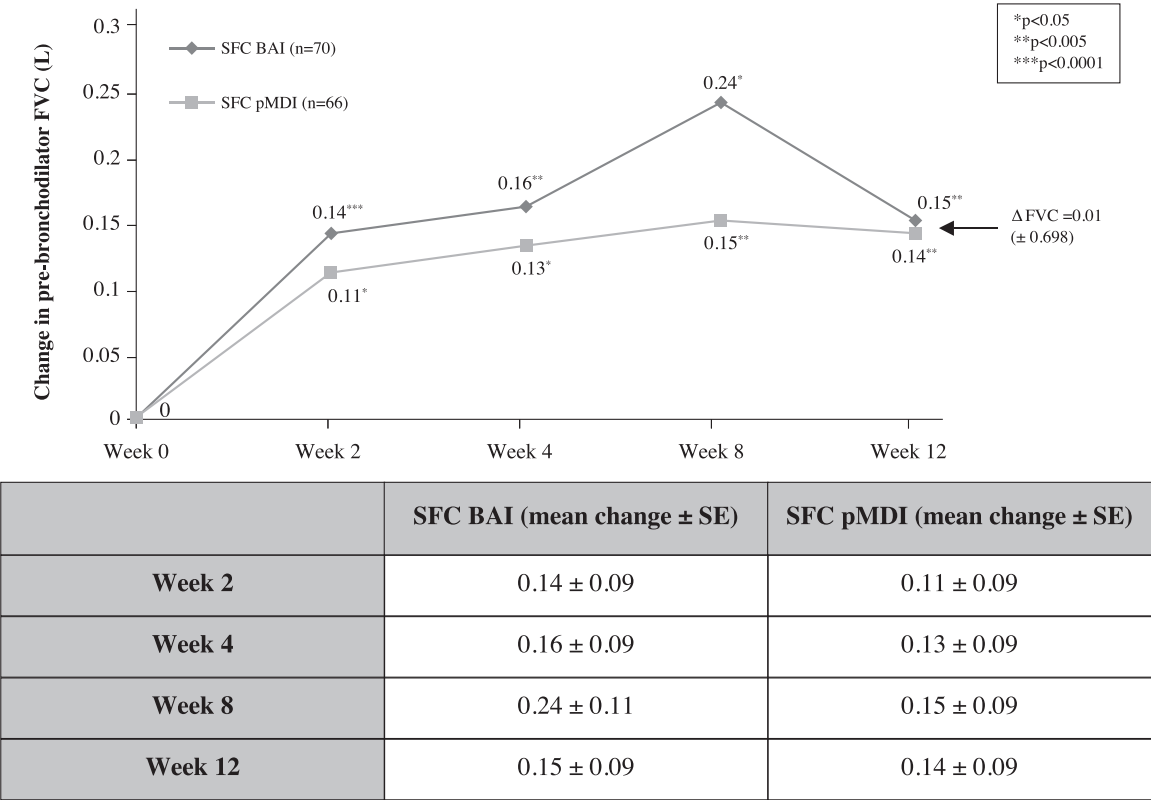


Figure 6. Mean change (± SE) in pre-bronchodilator FVC (L) at 2, 4, 8, and 12 weeks compared to baseline.

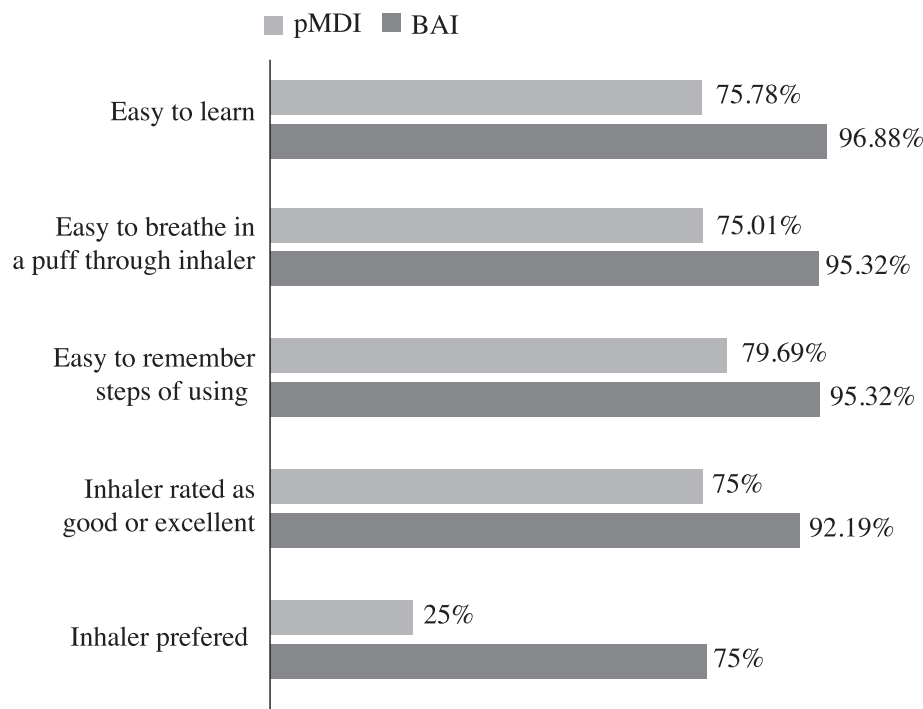


Figure 7. Usability assessment.

Safety assessment

About 12.50% ($n = 9$) and 11.27% ($n = 8$) patients reported at least one adverse event in the SFC BAI and the pMDI group, respectively. Of these, drug-related adverse event was reported in two patients, one in either group. More frequently seen adverse events ($>$ than 2% of patients) were anemia, pyrexia, and cough. Serious adverse event (7–8 episodes of vomiting and 2–3 episodes of loose motions requiring hospitalization) was reported in only one patient in the SFC BAI group; however, this was not related to the study drug.

Discussion

This is the first study evaluating the safety and the efficacy of SFC given through BAI as compared with the standard pMDI over a period of 12 weeks. The SFC BAI produced similar therapeutic response in terms of lung function and symptoms as that of the pMDI. Moreover, the BAI showed statistically significant superior bronchodilator responses when evaluated using FEV₁ and PEFR over the treatment period, compared with baseline, and was reported to be the preferred device of choice by 75% of the study patients because of ease of use.

A BAI is a simple to use, convenient, cost-effective, and patient-friendly inhaler. The BAI has clear advantages over a DPI in terms of ease of use, inhaler technique and patient preference. It is a vital inhaler for patients and can be used by all patients irrespective of their age and disease severity [18].

A combination of LABA/ICS has a well-established role in the long-term management of moderate-to-severe persistent asthma. SFC is widely used and prescribed for the management of patients with asthma, as well as for COPD. A number of studies have shown that inhaled SFC improves lung function, quality of life, reduces exacerbations, and provides better asthma control [14–16].

SFC has been conventionally available in the pMDI and DPI devices. However, for the first time, SFC has been formulated in the BAI. Hence, there was a need to evaluate the efficacy and safety of SFC in the BAI device.

The study assessed both the treatment groups over a sufficiently long period of 12 weeks to evaluate objectively the BAI device and also compare it with the pMDI.

The aim of the 2-week run-in-period, in which all the patients took a uniform dose of ICS, was to bring all the patients to a similar baseline level. Both the groups were well matched in terms of baseline characteristics, demographics, and severity of asthma.

This study showed that SFC BAI significantly improved morning and evening PEFR, FEV₁, FVC, day-time, and night time symptom scores and reduced the usage of rescue medication compared to baseline. These improvements were found to be comparable with SFC pMDI. In a study conducted by Lenney et al. [19], patients preferred BAI over pMDI, pMDI+spacer, and DPIs. Our study, which evaluated patient preference for BAI and pMDI, using a validated questionnaire showed that around 75% patients preferred the BAI. This high patient preference for the BAI would potentially result in high adherence to the therapy and may ultimately help in achieving better disease control.

Despite advanced pharmacotherapy, innovative devices, and guidelines on asthma management, the prevalence and incidence of uncontrolled asthma is a growing concern. A large number of patients have uncontrolled asthma despite taking prescribed therapy. A European survey showed that asthma is frequently poorly controlled and that levels of control do not meet the goals of the GINA guidelines [20]. Another study has shown that around 55% patients on standard asthma medications have uncontrolled asthma [21]. Patients with inadequately controlled severe persistent asthma are at a

particularly high risk of exacerbations, hospitalization and death, and often have severely impaired quality of life [20].

The reasons for this poor control of asthma are under-diagnosis, non-adherence with medication, sub-optimal levels of ICS, and improper use of inhaler. Poor inhalation technique results in marked decrease in the amount of drug deposited in the lung (up to 50%) leading to sub-optimal asthma control [22,23]. This may be because the inhalers are difficult and complex to operate. Consequently, patients find it challenging to learn and use these inhalers.

In several studies, it has been reported that patients find breath actuated inhaler devices easier to use than other inhalation devices [24,25]. In the present study, almost 97% of the patients found the BAI easy to learn and 95% found it easy to remember. According to the study investigators, this can be related to the simplicity of using the BAI device. Our study showed that 95% patients found it was easy to breathe in the medication through the BAI while 92% patients rated BAI as a good or excellent device. SFC is the first LABA/ICS combination formulated in the BAI device, and this is the first study to evaluate this novel device in comparison with the conventional pMDI.

There is a need for further studies that objectively evaluate the BAI and also there is a need for developing more drug options including combination medications in this device.

Conclusion

This was the first study to demonstrate that SFC when given with BAI was comparable in terms of efficacy and safety to pMDI in patients with moderate-to-severe asthma. BAI was the preferred inhaler by patients when assessed at the end of 12 weeks.

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Declaration of interest

Dr. Jaideep Gogtay is a permanent employee of Cipla Ltd. Other authors have no conflict of interest. The study was funded by Cipla Ltd.

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				Least Square Mean of change from baseline			p-value
Visit	Treatment	n	Mean ± SD	Estimate	Standard Error	95% Confidence Intervals	1 vs. 2*
Visit 4 (Week 2)	pMDI (N = 75)	66	18.5 ± 30.67	18.60	3.78	(11.11, 26.09)	0.2250
	BAI (N = 75)	70	25.1 ± 31.37	25.03	3.68	(17.76, 32.30)	.
Visit 5 (Week 4)	pMDI (N = 75)	66	24.8 ± 38.08	24.72	5.14	(14.54, 34.90)	0.3656
	BAI (N = 75)	70	31.2 ± 44.84	31.23	5.00	(21.35, 41.11)	.
Visit 6 (Week 8)	pMDI (N = 75)	66	35.8 ± 50.43	35.74	6.35	(23.19, 48.30)	0.7642
	BAI (N = 75)	70	38.4 ± 52.36	38.40	6.16	(26.21, 50.60)	.
Visit 7 (Week 12)	pMDI (N = 75)	66	48.8 ± 70.49	48.76	8.69	(31.57, 65.94)	0.8558
	BAI (N = 75)	70	50.9 ± 70.41	50.96	8.44	(34.27, 67.65)	.
Abbreviations: LOCF = Last observation carried forward; N = number of subjects in specified treatment; n = number of subjects having non-missing values at baseline and specified visits. * p-values calculated with ANCOVA model: change from baseline = baseline + treatment with Bonferroni method.							

**Online Supplement 1: Analysis of change from baseline in pre-dose morning
PEFR recorded over the 2, 4, 8 & 12 weeks treatment period
ITT population (LOCF Method)**

			Least Square Mean of change from baseline			p-value
Treatment	n	Mean ± SD	Estimate	Standard Error	95% Confidence Intervals	1 vs. 2*
pMDI (N = 75)	66	48.8 ± 70.49	48.76	8.69	(31.57, 65.94)	0.8558
BAI (N = 75)	70	50.9 ± 70.41	50.96	8.44	(34.27, 67.65)	.
Abbreviations: LOCF = Last observation carried forward; N = number of subjects in specified treatment; n = number of subjects having non-missing values at baseline and specified visits. * p-values calculated with ANCOVA model: change from baseline = baseline + treatment with Bonferroni method.						

**Online Supplement 2: Analysis of change from baseline in pre-dose morning
PEFR at the end of 12 weeks from baseline
ITT Population (LOCF Method)**

				Least Square Mean of change from baseline			p-value
Visit	Treatment	n	Mean ± SD	Estimate	Standard Error	95% Confidence Intervals	1 vs. 2*
Visit 4 (Week 2)	pMDI (N = 75)	66	16.8 ± 26.72	16.72	3.62	(9.56, 23.89)	0.0449
	BAI (N = 75)	70	26.9 ± 32.00	26.94	3.52	(19.99, 33.89)	.
Visit 5 (Week 4)	pMDI (N = 75)	66	21.8 ± 37.61	21.85	5.06	(11.84, 31.85)	0.1246
	BAI (N = 75)	70	32.8 ± 43.92	32.74	4.91	(23.03, 42.45)	.
Visit 6 (Week 8)	pMDI (N = 75)	66	34.4 ± 51.63	34.42	6.30	(21.95, 46.89)	0.4173
	BAI (N = 75)	70	41.6 ± 50.78	41.57	6.12	(29.46, 53.67)	.
Visit 7 (Week 12)	pMDI (N = 75)	66	47.5 ± 71.64	47.59	8.57	(30.64, 64.55)	0.5117
	BAI (N = 75)	70	55.5 ± 68.07	55.46	8.32	(38.99, 71.92)	.
Abbreviations: LOCF = Last observation carried forward; N = number of subjects in specified treatment; n = number of subjects having non-missing values at baseline and specified visits. * p-values calculated with ANCOVA model: change from baseline = baseline + treatment with Bonferroni Method.							

**Online Supplement 3: Analysis of change from baseline in pre-dose evening
PEFR recorded over the 2, 4, 8 & 12 weeks treatment period
ITT Population (LOCF Method)**

				Least Square Mean of change from baseline			p-value
Visit	Treatment	n	Mean ± SD	Estimate	Standard Error	95% Confidence Intervals	1 vs. 2*
Visit 4 (Week 2)	pMDI (N = 75)	66	0.1 ± 0.22	0.08	1.65	(-3.18, 3.33)	0.3266
	BAI (N = 75)	70	2.4 ± 18.57	2.34	1.60	(-0.83, 5.50)	.
Visit 5 (Week 4)	pMDI (N = 75)	66	0.1 ± 0.23	0.09	0.03	(0.03, 0.15)	0.0542
	BAI (N = 75)	70	0.2 ± 0.26	0.17	0.03	(0.12, 0.23)	.
Visit 6 (Week 8)	pMDI (N = 75)	66	0.1 ± 0.26	0.14	0.03	(0.08, 0.20)	0.2013
	BAI (N = 75)	70	0.2 ± 0.24	0.19	0.03	(0.13, 0.25)	.
Visit 7 (Week 12)	pMDI (N = 75)	66	0.1 ± 0.27	0.14	0.03	(0.08, 0.21)	0.2181
	BAI (N = 75)	70	0.2 ± 0.27	0.20	0.03	(0.14, 0.26)	.
Abbreviations: LOCF = Last observation carried forward; N = number of subjects in specified treatment; n = number of subjects having non-missing values at baseline and specified visits. * p-values calculated with ANCOVA model: change from baseline = baseline + treatment with Bonferroni method.							

**Online Supplement 4: Analysis of change from baseline in FEV1 (L) at the end of
2, 4, 8 & 12 weeks treatment period
ITT Population (LOCF Method)**

				Least Square Mean of change from baseline			p-value
Visit	Treatment	n	Mean ± SD	Estimate	Standard Error	95% Confidence Intervals	1 vs. 2*
Visit 4 (Week 2)	pMDI (N = 75)	66	0.1 ± 0.38	0.11	0.04	(0.03, 0.19)	0.6979
	BAI (N = 75)	70	0.1 ± 0.28	0.14	0.04	(0.06, 0.21)	.
Visit 5 (Week 4)	pMDI (N = 75)	66	0.1 ± 0.41	0.14	0.04	(0.05, 0.23)	0.8520
	BAI (N = 75)	70	0.2 ± 0.34	0.15	0.04	(0.06, 0.24)	.
Visit 6 (Week 8)	pMDI (N = 75)	66	0.1 ± 0.40	0.16	0.08	(0.00, 0.31)	0.4920
	BAI (N = 75)	70	0.2 ± 0.80	0.23	0.08	(0.08, 0.38)	.
Visit 7 (Week 12)	pMDI (N = 75)	66	0.1 ± 0.39	0.14	0.04	(0.06, 0.23)	0.9705
	BAI (N = 75)	70	0.2 ± 0.34	0.15	0.04	(0.06, 0.23)	.
Abbreviations: LOCF = Last observation carried forward; N = number of subjects in specified treatment; n = number of subjects having non-missing values at baseline and specified visits. * p-values calculated with ANCOVA model: change from baseline = baseline + treatment with Bonferroni method.							

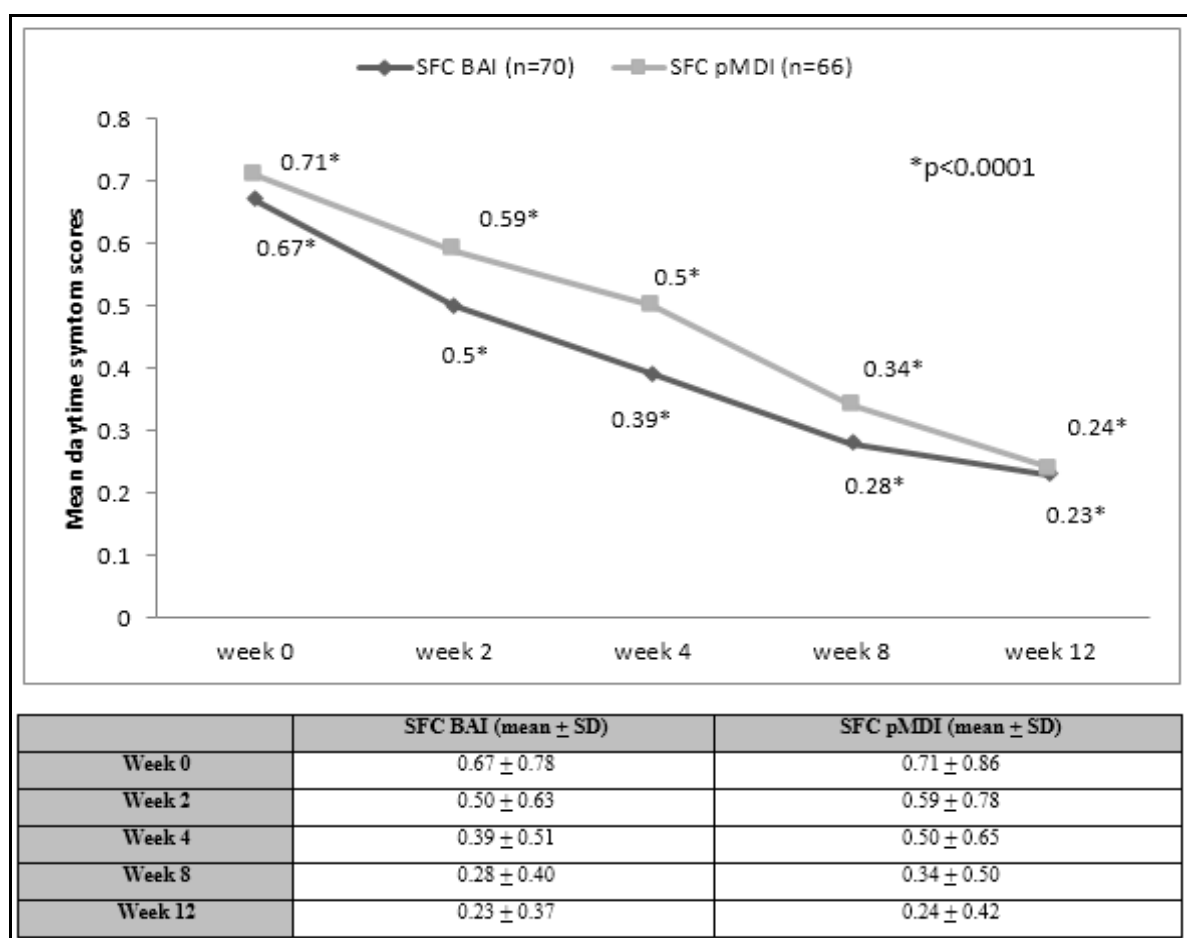
**Online Supplement 5: Analysis of change from baseline in FVC (L) at the end of 2, 4, 8 & 12 weeks treatment period
ITT Population (LOCF Method)**

Treatment groups	Baseline	Week 2	Week 4	Week 8	Week 12
SFC BAI	12.40 ± 1.78	7.24 ± 1.24	4.93 ± 0.80	5.54 ± 1.41	4.69 ± 1.54
Mean Change	--	-5.16	-7.47	-6.86	-7.71
p-value	--	<0.001	<0.001	0.0004	0.0004
SFC <u>pMDI</u>	13.35 ± 1.88	9.30 ± 1.56	7.20 ± 1.42	7.09 ± 1.52	4.48 ± 1.33
Mean Change	--	-4.05	-6.15	-6.26	-8.47
p-value	--	0.0001	0.0004	0.0020	<0.0001

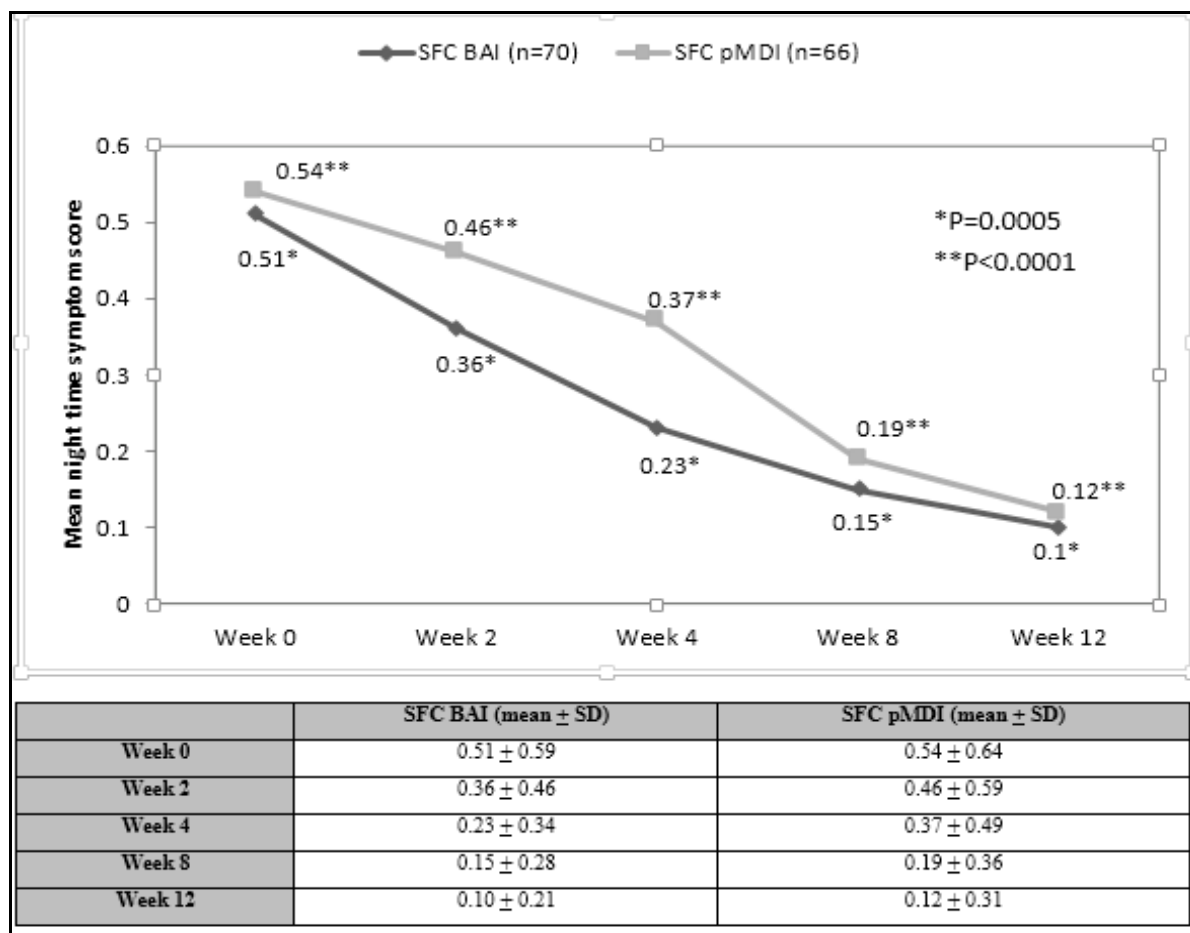
Online Supplement 6: Reduction in number (± SE) of puffs of rescue medication at 2, 4, 8 and 12 weeks from baseline

			Least Square Mean of change from baseline			p-value
Treatment	n	Mean ± SD	Estimate	Standard Error	95% Confidence Intervals	1 vs. 2*
pMDI (N = 75)	66	-0.8 ± 1.05	-0.73	0.05	(-0.83, -0.62)	0.9188
BAI (N = 75)	70	-0.7 ± 1.05	-0.73	0.05	(-0.84, -0.63)	.
Abbreviations: LOCF = Last observation carried forward; N = number of subjects in specified treatment; n = number of subjects having non-missing values at baseline and specified visits. * p-values calculated with ANCOVA model: change from baseline = baseline + treatment with Bonferroni method.						

**Online Supplement 7: Analysis of change from baseline in number of puffs of rescue medication at end of 12 weeks
ITT Population (LOCF Method)**



Online Supplement 8: Mean ($\pm$ SD) day time symptom scores at 0, 2, 4, 8 and 12 weeks



Online Supplement 9: Mean ($\pm$ SD) night time symptom scores at 0, 2, 4, 8 and 12 weeks