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Real-world evaluation of the clinical safety and efficacy of fluticasone/formoterol FDC via the Revolizer® in patients with persistent asthma in India

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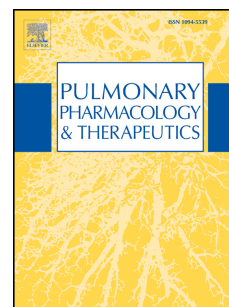
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Title: Real World Evaluation of the Clinical Safety and Efficacy of Fluticasone/Formoterol FDC via Revolizer[®] in Patients with Persistent Asthma in India

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Declaration of Interest

Abhijit Vaidya, Meena Lopez, Dr Rashmi Hegde and Dr Jaideep Gogtay are employees of Cipla Ltd. Other authors have no declarations of interest.

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Title: Real-World Evaluation of the Clinical Safety and Efficacy of Fluticasone/Formoterol FDC *via* the Revolizer® In Patients with Persistent Asthma in India

Abstract

The combination of inhaled corticosteroids (ICS) and long-acting beta₂-agonists (LABAs) is widely used for the management of asthma. This prospective, open-label, non-comparative, observational, 24-week multicentre study is the first real-world study from India to compare the efficacy and safety of fixed-dose combination of fluticasone/formoterol (Maxiflo® 100/6 mcg or 250/6 mcg) capsules *via* the Revolizer® device in patients with persistent asthma. The primary efficacy analyses included mean change in Asthma Control Test (ACT™) at 4, 8, 16 and 24 weeks. Secondary efficacy analyses included mean change in morning and evening peak expiratory flow rate (PEFR) at the end of 4, 8, 16 and 24 weeks, number of patients having symptom-free days and nights at the end of 4, 8, 16 and 24 weeks, the number and severity of exacerbations over 24 weeks and response to the Usability Preference Satisfaction Confidence questionnaire after 1 week. Overall, 385 (of 401; 96.01%) enrolled patients completed the study. The mean change in ACT™ score was 6.7±3.71 (95% CI: 6.32, 7.06; $p<0.0001$) at week 24. The ACT™ score at weeks 4, 8 and 16 showed progressive and statistically significant increase from baseline. A statistically significant improvement in morning and evening PEFR at weeks 4, 8, 16 and 24 was reported. The proportion of patients experiencing symptom-free days and nights continuously increased from baseline to week 24. A good safety profile over the 24-week period was observed. The Revolizer® device was preferred by 94.26% patients over their current device. Fluticasone propionate/formoterol fumarate FDC capsules administered *via* a single-dose dry powder inhaler ([DPI], (Revolizer®)) offers a novel, well-tolerated and effective treatment option for the long-term management of asthma.

Keywords: Asthma, fixed-dose combination, FDC, dry powder inhaler, DPI, peak expiratory flow rate, PEF, fluticasone/formoterol, airway inflammation

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Introduction

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation that affects people of all age groups ¹. As per the Global Asthma Network (GAN), asthma affects 334 million people worldwide and accounts for 383,000 deaths per year ^{2, 3}. It is the commonest chronic disorder among children with an estimated prevalence range of 3–38% ⁴ and the fourteenth most important disease in the world in terms of the extent and duration of disability⁵. As per data from the recent Global Burden of Disease (GBD) Study, the prevalence of asthma in India is approximately 38 million . Importantly, while India contributes to 11% (37.8 million asthma cases) of the global asthma burden, it accounts for 42% of all global asthma deaths. These disproportionate deaths due to asthma in India can largely be attributed to the deteriorating quality of air, lack of awareness, myths and social stigma associated with it, under-diagnosis and wrong diagnosis by physicians, poor use of inhalation therapy and non-adherence to the treatment⁶ .

Asthma is poorly controlled globally, especially in developing countries like India ⁷. Maintenance treatment with inhaled corticosteroids (ICS) and long-acting beta₂-adrenergic agonists (LABAs) is the mainstay for patients whose asthma is not controlled with a single ICS and a separate reliever inhaler used as rescue therapy. The ICS and LABA complement each other by acting on two different key components of asthma, inflammation and bronchoconstriction, respectively. Clinically, ICS/LABA therapy has been shown to result in a greater improvement in lung function, better symptom control, reduced rescue therapy use and lower incidence of exacerbations compared with higher doses of ICS alone⁸⁻¹¹ .

Fluticasone propionate/salmeterol and budesonide/formoterol are recognised and well-established ICS/LABA combinations used for patients with asthma¹²⁻¹⁶. Fluticasone propionate/formoterol fumarate is a relatively new ICS/LABA combination available in several countries in Europe, Asia and India. While fluticasone propionate has a potent and

sustained anti-inflammatory effect, formoterol has a rapid onset of action similar to salbutamol and has increasingly become the long-acting bronchodilator of choice. Studies have shown this combination to be comparable to its individual components when given separately, and to budesonide/formoterol when used through a pressurised metered dose inhaler (pMDI) ^{17, 18}.

Dry powder inhalers (DPIs) are a more convenient alternative to MDIs ^{13, 14}. The presence of certain features such as not needing to coordinate actuation with inhalation, absence of chlorofluorocarbon propellants and requiring fewer user steps often make the DPI a good choice over the MDI ¹⁹. Moreover, DPIs may be more cost effective than pMDIs ²⁰. The Revolizer[®] is a unit-dose, capsule-based DPI that employs a simple inhalation technique and enables patients to confirm dose delivery as one can hear, taste and see the drug ²¹. Fluticasone/formoterol FDC capsules administered using the Revolizer[®] are available in India as Maxiflo[®] Rotacaps. However, real-world data regarding the efficacy and safety of this combination (administered using the Revolizer[®]) in patients with asthma is lacking. This is the first real-world study to assess the efficacy and safety of fluticasone propionate/formoterol fumarate FDC capsules when given *via* the Revolizer[®] in adult patients with persistent asthma in India.

Methodology

Study Design

This prospective, open-label, non-comparative, real-world observational, 24-week (October 2014 to November 2015), multicentre study was conducted at 15 centres in India. An Institutional Ethics Committee permission was obtained from all the centres. All the patients provided written informed consent prior to study enrolment. The study was conducted in accordance with the ethical principles of the current Declaration of Helsinki and was

consistent with the International Council on Harmonization (ICH) Good Clinical Practice (GCP) and applicable local regulatory requirements.^{10, 22}. The study is registered at the Clinical Trial Registry of India (CTRI/2014/11/005164).

Patient Population

The study included adult patients (age above 18 years) of either gender who were diagnosed with persistent asthma (as per the revised GINA 2012 guideline)²³ and were either already taking fluticasone propionate/formoterol fumarate combination capsules (100/6 mcg or 250/6 mcg) through the Revolizer[®] or were uncontrolled on other treatments taken through the Revolizer[®] and required a change in their treatment to fluticasone propionate/formoterol fumarate FDC as per the treating physician's discretion. Patients also had to be able to use a peak flow meter (Breathe-o-meter[®]) and Revolizer[®] correctly.

The study excluded patients with any chronic respiratory disease other than asthma, who had a known or suspected hypersensitivity to the combination or any other constituent of fluticasone propionate/formoterol fumarate FDC capsules, or who were on any medication likely to have a drug interaction with fluticasone propionate/formoterol fumarate FDC, those scheduled to receive any other investigational drug during the course of the study, or who received any investigational drug in the last 30 days prior to the screening visit. Patients with a smoking history of ≥ 10 pack-years and women who were pregnant, lactating or planning to become pregnant were also excluded.

Data Collection

At the first visit, patients were assessed for demographic details, physical and systemic examination, medical and surgical history, and vital signs. Those recruited in the study had a documented spirogram demonstrating reversibility and a chest X-ray done within the past 6 months showing no other chronic respiratory illness. The screening visit was considered as the baseline visit (day 0). The study patients were followed up for a duration of 24 weeks that

included six study visits with a window period of ± 2 days for each visit (except screening visit or baseline) (**Figure 1**).

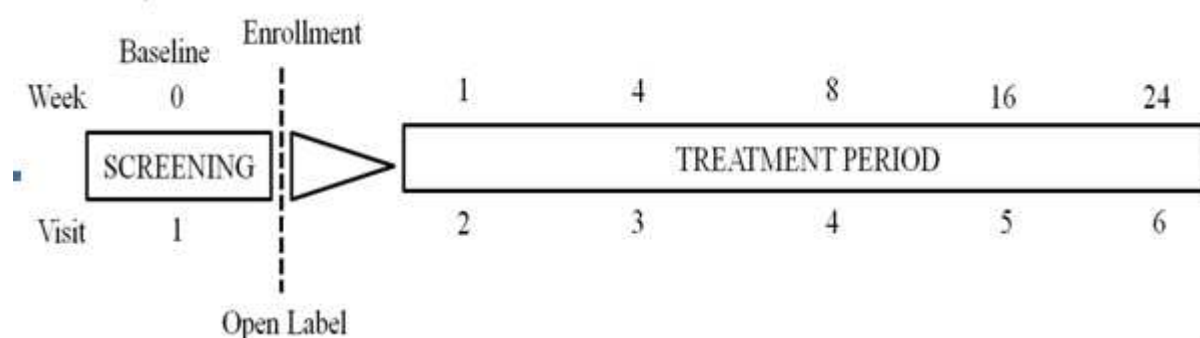


Figure 1: Study Design

***Procedures/activities done at all visits:**

Visit 1: Informed consent, Inclusion / Exclusion Criteria, Demographics, Personal and Medical history, Physical and Systemic examination, Dispense Breath-o-meter, Administer ACT Questionnaire; Visit 1 to Visit 6: Vitals, Previous and Concomitant medication, AE and SAE Monitoring and Reporting, Review and retrieve patient diary page, Visit 2: UPSC Questionnaire, Visit 3 to Visit 6: Administer ACT Questionnaire, Visit 6: Retrieve Breath-o-meter

The Asthma Control Test (ACTTM) questionnaire was administered to each patient at every visit (except week 1). The ACTTM has been assessed for reliability and validity for assessing asthma control in earlier studies²⁴⁻²⁶. The ACTTM scores range from 5 to 25; wherein a score of 20–25 refers to ‘well-controlled asthma’, 16–20 to ‘not well-controlled’ and 5–15 to ‘very poorly controlled asthma’²⁷. The patients were also provided a peak flow meter for home monitoring of peak expiratory flow rate (PEFR) in the morning and evening. Patients were provided training to record their PEFR reading (morning and evening) daily in a patient diary throughout the study before taking the study drug with a window period of ± 1 hour. The daytime and night-time symptoms were also recorded by the patient in the diary in terms of

the daytime scores (0–4) and night-time scores (0–3), respectively. Exacerbation experienced by any patient during the study was classified as mild (15% decrease in morning PEFr, a 20% decrease in FEV₁, and/or increase in reliever medication use), moderate (events that required additional controller treatment to prevent progression to severe exacerbation) and severe (administration of systemic corticosteroid, and/or a 30% decrease in PEFr values on at least 2 consecutive days and hospitalisation). Patients were allowed to take any medication, if required, for the treatment of exacerbation, and this was documented in the e-case report forms (e-CRF). Patients were also asked to fill a Usability Preference Satisfaction Confidence (UPSC) 2014 questionnaire for the Revolizer® at week 1. It is a questionnaire adapted from previous studies assessing the usability of an inhaler device^{21, 28}. All the adverse events (AEs) and serious AEs (SAEs) were monitored throughout the study period.

Dosage and Mode of Administration of Treatment

Patients received either 100/6 mcg or 250/6 mcg dose of fluticasone propionate/formoterol fumarate FDC (Maxiflo®, Cipla Ltd.) Rotacaps through the Revolizer® (Cipla Ltd.) as prescribed by the investigator. The decision on the selection of the dose was based on disease severity and symptoms, as per the discretion of the investigator. Those who were already taking any dose of fluticasone propionate/formoterol fumarate for at least 1 month were assessed by their physicians for administration of the correct dose based on their disease severity and symptoms. Patients were instructed to inhale fluticasone propionate/formoterol fumarate immediately after recording the PEFr reading. The investigator had the liberty to change the dose of fluticasone propionate/formoterol fumarate during the study period based on the condition of the participating patient. Any change in the dose of fluticasone propionate/formoterol fumarate or change in the treatment was documented in the e-CRF.

Efficacy Evaluation

Primary Efficacy Analysis

The mean change in ACT™ was assessed at 4, 8, 16 and 24 weeks from baseline.

Secondary Efficacy Analyses

These included the mean change in morning and evening PEF at the end of 4, 8, 16 and 24 weeks as compared to baseline; the number and severity of exacerbations over the 24-week treatment period; the number of patients with symptom-free days and nights at 4, 8, 16 and 24 weeks and patient response to the UPSC 2014 questionnaire for the Revolizer® after 1 week of the study initiation.

Safety

All drug-related or non-related AEs and SAEs were documented during the study period.

Statistical Analysis

All efficacy variables were analysed for the intention-to-treat (ITT) population, defined as all patients who enrolled in the study, had no major protocol deviations and received at least one dose of the study drug. All safety variables were analysed for the safety population, defined as all patients who signed the informed consent and had received at least one dose of the study drug.

Baseline characteristics were analysed using descriptive statistics. The demographic details, anthropometric measurements, biochemical and other baseline data were presented descriptively. Unless and otherwise stated, all the continuous variables such as age, height, weight was represented by n, mean, standard deviation, standard error and range. All the categorical variables were presented as counts and percentages.

The Wilcoxon matched-paired test was used to analyse change in the ACT™ score from baseline to subsequent visits, since the data was non-normally distributed. The mean change

in morning and evening PEF from baseline to end of study visit was analysed using a paired t-test and the mean change from baseline to subsequent visits was analysed using repeated measures of ANOVA. The proportion of symptom-free days and nights were analysed using Clopper-Pearson exact method. Simple descriptive statistics were used to analyse the UPSC device questionnaire responses. Safety data were reported using frequency and percentages. All the statistical analysis was performed using SAS software version 9.3.

Results

Baseline and Demographic Characteristics

Overall, the ITT and safety population was the same and included 401 patients. Of the 401 patients (202 men and 199 women; mean age $\pm$ SD= 41.1 $\pm$ 14.36 years) enrolled, 385 (96.01%) patients completed the study (**Figure 2**).

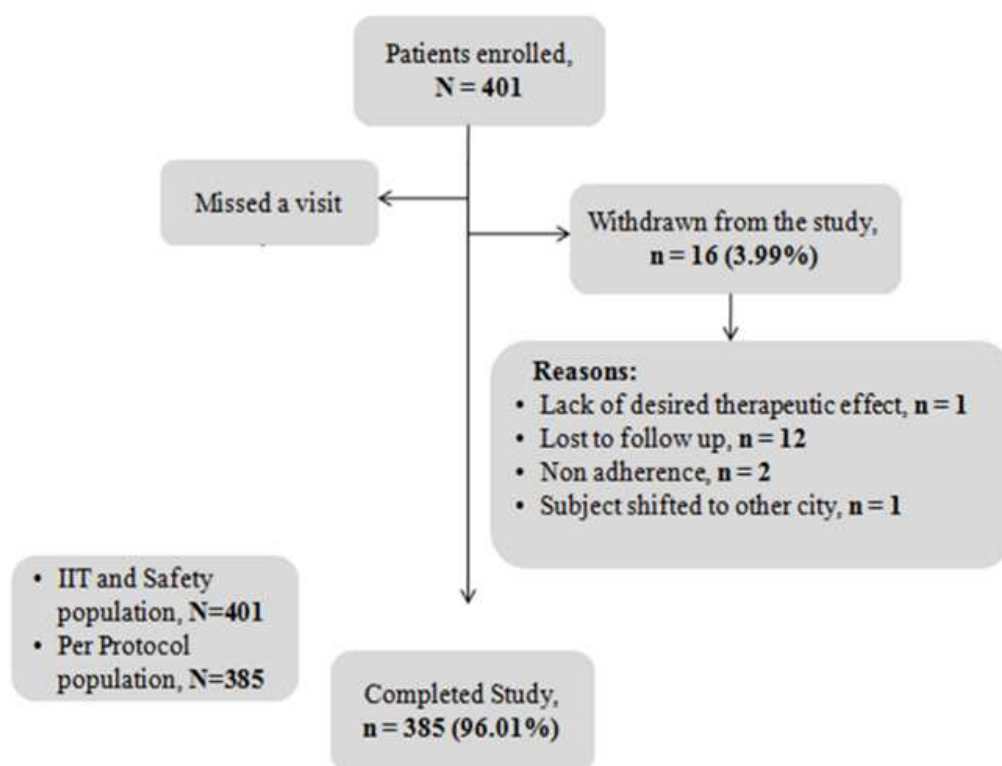


Figure 2: Patient disposition

The demographic and clinical details of the patients are outlined in **Table 1**. Sixty percent patients had uncontrolled asthma. Overall, 63 (15.71%) and 338 (84.29%) patients received fluticasone propionate/formoterol fumarate capsules 100/6 mcg and 250/6 mcg, respectively.

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Table 1: Demographic and Baseline Characteristics

Characteristic	Total
Age (years)	41.1±14.36
Gender, n (%)	
<i>Men</i>	202 (50.37)
<i>Women</i>	199 (49.63)
Weight (kg)	61.8±14.89
Height (cm)	159.7±9.28
Severity of Asthma, n (%)	
<i>Mild</i>	140 (34.91)
<i>Moderate</i>	192 (47.88)
<i>Severe</i>	69 (17.21)
Family History of Asthma; n (%)	126 (31.42)
Smoking history (Pack years)	4.8±2.00
Smokers, n (%)	20 (4.99)
Mean ACT score (Mean ± SD)	14.9±3.26
Morning PEFr (Mean ± SD, L/min)	271.7 ±101.58
Evening PEFr (Mean ± SD, L/min)	270.0 ±100.96
Asthma uncontrolled population (%)	59.8
Asthma partially controlled population (%)	31.6
Asthma controlled population (%)	8.4
Prior medications reported	
<i>ICS</i>	3 (0.74)
<i>ICS plus LABA</i>	18 (4.5)
<i>SABA</i>	2 (0.5)

<i>LTRA</i>	1 (0.25)
<i>LTRA plus antihistamine</i>	1 (0.25)
<i>PDE-5 inhibitor</i>	2 (0.5)

*The values are expressed as mean $\pm$ SD unless otherwise specified. ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; SABA: short-acting beta2-agonist; LTRA: leukotriene receptor antagonist, PDE: phosphodiesterase

Primary Efficacy Analysis (ITT and Safety Population)

Mean change in ACTTM

The mean ACTTM score increased from 14.9 $\pm$ 3.26 (95% confidence interval [CI]: 14.58, 15.22) at baseline to 21.6 $\pm$ 2.75 (95% CI: 21.28, 21.83) at week 24, resulting in a mean change in ACTTM score of 6.7 (95% CI: 6.32, 7.06; $p<0.0001$) (**Figure 3a**). The mean change in ACTTM scores from baseline to each subsequent visit (week 4, week 8, week 16 and week 24) was also statistically significant ($p<0.0001$) (**Figure 3a**).

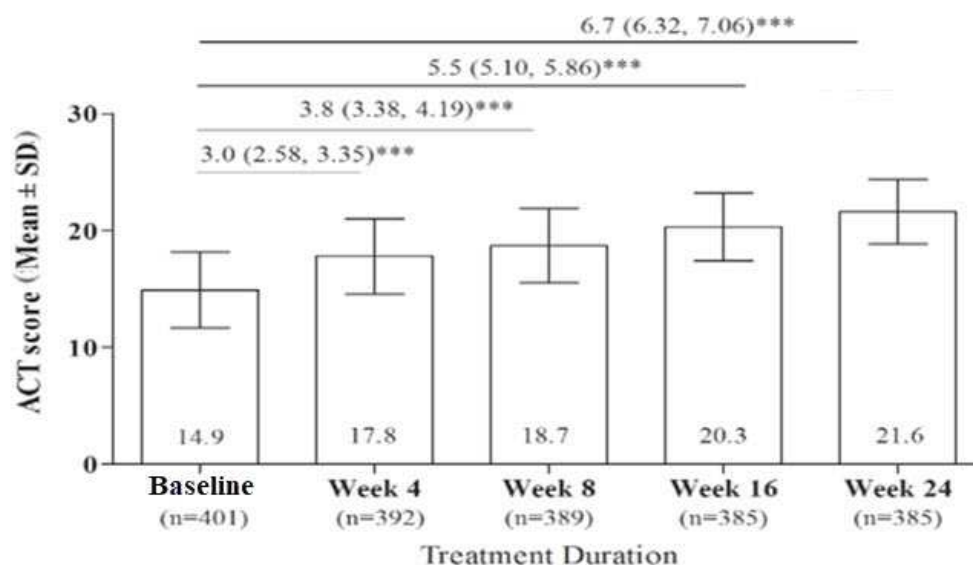
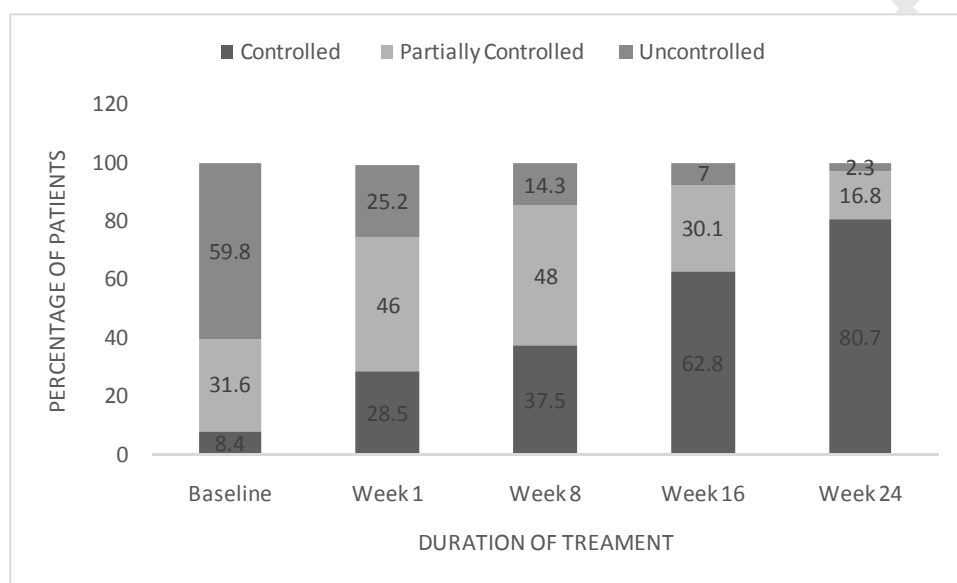


Figure 3a: ACT score over 24 weeks

*** $p < 0.0001$; the values written between the bar and mean change from baseline (95 % Confidence Interval)

The proportion of patients achieving asthma control increased from 8.4% at baseline to 80.78% at week 24 while the proportion of patients with uncontrolled asthma (as per ACTTM) decreased from 59.8% at baseline to 2.3% at week 24 (**Figure 3b**).

**Figure 3b: Effect of Fluticasone/Formoterol FDC on asthma control over 24 weeks****Secondary Efficacy Analysis***Mean Change in Morning and Evening PEFr Values from Baseline to Week 24*

The mean morning and evening PEFr significantly improved ($p < 0.0001$) from baseline to the subsequent visits (week 4, week 8, week 16 and week 24) (**Figure 3c**). At week 24, the mean increase from baseline in morning and evening PEFr was 45.44 ± 65.90 L/min ($p < 0.001$) and 46.14 ± 65.51 L/min ($p < 0.001$), respectively.

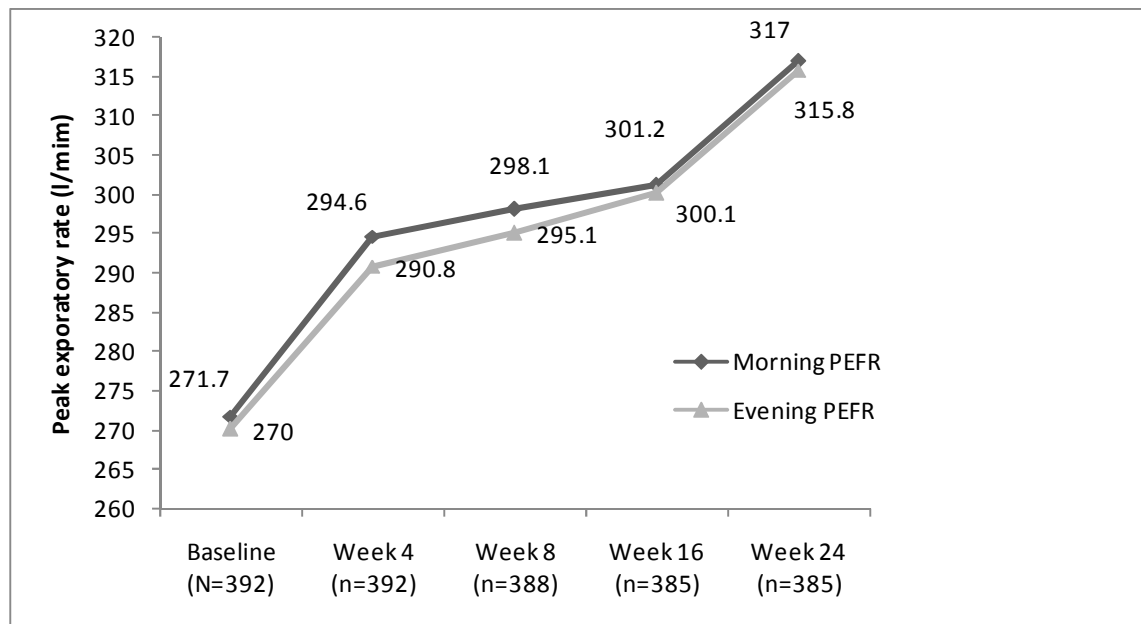


Figure 3c: Effect of Fluticasone/Formoterol FDC on morning and evening PEFR over 24 weeks

Exacerbations

Only one patient was reported to have an exacerbation, which was severe in nature.

Proportion of Patients with Symptom-free Days and Symptom-free Nights

A continuous increase in the proportion of patients experiencing symptom-free days and nights was observed from baseline to week 24. The proportion of patients having symptom-free days were 51.9%, 63.1%, 65.8%, 67.6% and 70.8% at week 1, week 4, week 8, week 16 and week 24, respectively; while the proportion of patients with symptom-free nights were 55.9%, 65.8%, 69.6%, 70.3% and 71.6%, respectively (**Figure 4**). The daytime (baseline: 0.7 ± 0.87 ; week 24: 0.6 ± 1.19) and night-time symptom scores (baseline: 0.6 ± 0.75 ; week 24: 0.5 ± 0.89) showed a significant reduction ($p < 0.0001$) at week 24 from baseline.

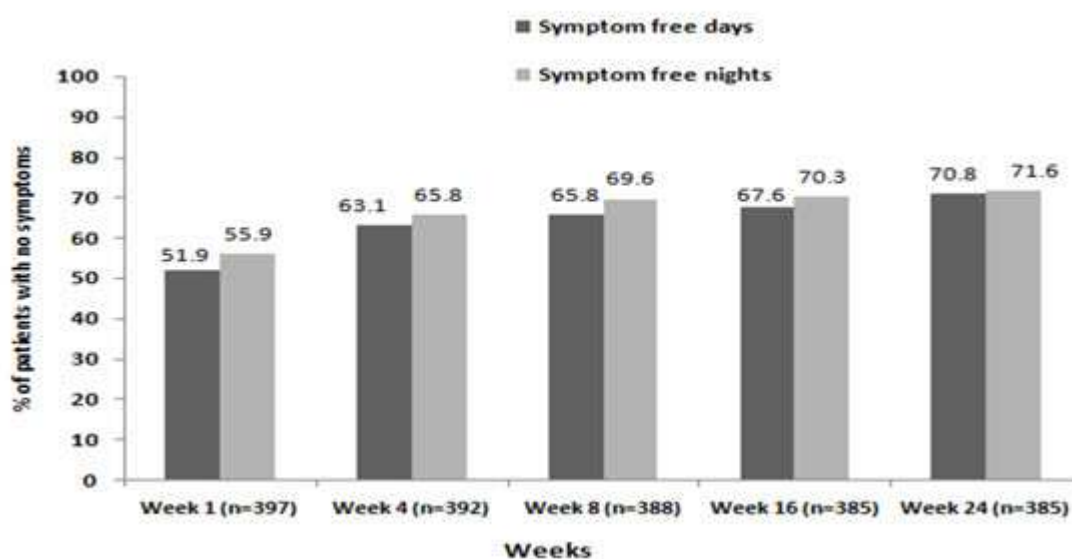


Figure 4: Proportion of symptom-free days and nights over 24 weeks

Concomitant Medications

Overall, 22 (5.5%) patients were taking additional leukotriene receptor antagonists (LTRAs) for asthma, 1 (0.2%) patient was taking additional LTRA and theophylline, 12 (3.0%) patients were taking additional theophylline, and 25 (6.2%) patients were taking additional LTRA plus an antihistamine.

UPSC Questionnaire

Analysis of the responses to the UPSC questionnaire showed that the Revolizer[®] was easy to learn and operate. Overall, 394 patients (98.2%) found the Revolizer[®] very easy or easy to use and an equal number of patients responded that it was either very easy or easy to remember how to use it. Patients also found the Revolizer[®] aesthetically appealing. The shape and colour of the inhaler was reported as very good by 129 (32.2%) patients and good by 252 (62.8%) patients. Overall, 205 (51.1%) patients were very satisfied and 186 (46.4%) patients were fairly satisfied with the inhaler. There were 344 (85.8%) patients who said "yes" when asked specifically about whether the Revolizer[®] can be used quickly in case of emergency/asthma attacks (if required). Overall, 95.8% patients responded that they would

continue using the Revolizer[®] and 94.3% patients reported a preference for the Revolizer[®] over their current device. **Table 2** outlines the summary of the responses of the patients to the UPSC Questionnaire at week 1.

Table 2: Patient Responses to UPSC Questionnaire

	Very Comfortable / Very Easy n (%)	Comfortable/ Easy n (%)	Uncomfortable/ Difficult n (%)
USABILITY ASSESSMENT			
Overall, was the inhaler easy to use?	128 (31.9)	266 (66.3)	1 (0.2)
Is the mouthpiece of the inhaler comfortable to hold between your lips?	131 (32.7)	257 (64.1)	7 (1.7)
How easy was it to learn, how to use the inhaler?	154 (38.4)	237 (59.1)	4 (1.0)
Was It comfortable inhaling the medicine through the inhaler?	148 (36.9)	241 (60.1)	6 (1.5)
How comfortable is the inhaler to carry?	149 (37.2)	240 (59.9)	6 (1.5)
Was it easy to keep the inhaler clean?	159 (39.7)	229 (57.1)	7 (1.7)
Were you comfortable using the inhaler in public places?	197 (49.1)	162 (40.4)	36 (9.0)
CONFIDENCE ASSESSMENT			
	Very Easy/ Very Confident n (%)	Easy/ Somewhat Confident n (%)	Difficult/ Not confident n (%)

Was it easy to remember how to use the inhaler?	157 (39.2)	237 (59.1)	1 (0.2)
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After using the inhaler, were you confident that you have taken a dose?	251 (62.6)	143 (35.7)	1 (0.2)
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After you have used the inhaler, are you confident that you used it correctly?	259 (64.6)	132 (32.9)	4 (1.0)
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PREFERENCE ASSESSMENT	Very Good	Good	Average
	n (%)	n (%)	n (%)

How do you like the shape and color of the inhaler?	129 (32.2)	252 (62.8)	14 (3.5)
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Do you prefer the inhaler (Revolizer [®]) over your current device? (Yes/No)	378 (94.3)	17 (4.2)	
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SATISFACTION ASSESSMENT	Very Good/ Very Satisfied	Good/ Fairly Satisfied	Average/ Not Very Satisfied
	n (%)	n (%)	n (%)

Overall how did you find the inhaler?	165 (41.1)	213 (53.1)	17 (4.2)
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How does it feel to hold the inhaler?	129 (32.2)	240 (59.9)	26 (6.5)
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Overall, are you satisfied with the inhaler?	205 (51.1)	186 (46.4)	4 (1.0)
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How easy was it to open the Revolizer [®] and prepare it for inhalation?	143 (35.7)	247 (61.6)	5 (1.2)
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SPECIFIC QUESTIONS	Yes	Somewhat	No
	n (%)	n (%)	n (%)

Was using the Revolizer [®] comfortable in terms of size and weight?	139 (34.7)	252 (62.8)	4 (1.0)
Was it easy to see the medication through the Revolizer [®] ?	151 (37.7)	238 (59.4)	6 (1.5)
Did the rattling sound of the rotacap while inhaling through the Revolizer [®] give you an audio feedback of the dose taken?	210 (52.4)	162 (40.4)	23 (5.7)
Can the Revolizer [®] be used quickly in case of emergency/asthma attacks (if required)?	344 (85.8)		26 (6.5)
Would you like to continue using the Revolizer [®] ?	384 (95.8)		11 (2.7)
Any problems / difficulties you faced with the Revolizer [®] (if any)	4 (1.0)		

Safety Evaluation

No deaths were reported during the study. Overall, 27 (6.7%) patients had AEs regardless of the study drug relationship. An SAE was reported for one subject as severe asthma symptoms leading to hospitalisation, but it was considered unlikely to be related to the study medication by both the investigator and the sponsor. The patient recovered and was discharged from the hospital. All vital signs were within the normal range throughout the study duration. The details of AEs reported during the study are presented in **Table 3**.

Table 3: Number of patients with adverse events (Adverse events in ≥ 2) (safety population, N=401)

Adverse events	No. of patients
Abdominal pain	2
Pain	2
Headache	3
Upper respiratory tract infection	5
Worsening of asthma	2
Cough	4
Allergic rhinitis	2
Oropharyngeal pain	2
Pyrexia	2

*A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment; A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Discussion

This is the first real-world study from India to evaluate the efficacy and safety of fluticasone propionate/formoterol fumarate (100/6 mcg or 250/6 mcg) in adult patients with persistent asthma over a period of 24 weeks. Our study results showed a mean change in ACTTM score of 6.7 (95% CI: 6.32, 7.06; $p < 0.0001$) at week 24 from baseline. The proportion of patients achieving asthma control increased about 10-fold from 8.4% at baseline to 80.78% at week 24. There was a statistically significant improvement reported in PEF_R (evening and

morning) at week 24 from baseline. Overall, only 15% of patients required additional concomitant medications for asthma during the study period. Majority of the patients found the Revolizer[®] easy to operate and understand; and were satisfied with the device. The study also found that fluticasone propionate/formoterol fumarate was safe and well tolerated.

Since the establishment of the GINA guidelines in 1993, which were based on disease severity, there has been a paradigm shift in the management of asthma. Various clinical trials reported that asthma control was achievable in most patients regardless of the level of severity^{5, 29, 30}. This shifted the focus of clinicians and researchers from management based on disease severity towards control-driven management^{31, 32}. However, asthma control in the real world remains an elusive goal for many patients around the globe and in India^{33, 34}. A survey conducted by the Asia Pacific Asthma Insight and Management (AP-AIM) in North America, Europe, the Asia-Pacific region and Latin America reported that none of the patients in India (n=400) had guideline-defined asthma control. Additionally, India was linked with the highest exacerbation frequency, the highest numbers of overnight hospitalisations, and the largest proportion of respondents who admitted that they had to miss work or school because of asthma^{35, 36}.

The guidelines recommend the use of ICS/LABA combination for patients who do not achieve optimal asthma control on ICS monotherapy³⁵. In the late 90s, two meta-analyses compared fluticasone with budesonide and showed that the use of fluticasone was associated with better outcomes than budesonide. Fluticasone scored better in all the asthma parameters and was deemed cost-effective in both the meta-analysis^{32, 37}. When used as a combination therapy, fluticasone propionate/formoterol fumarate has demonstrated comparable efficacy and tolerability profile to the established budesonide/formoterol fumarate and fluticasone propionate/salmeterol combinations³⁸⁻⁴⁰. A randomised controlled trial (RCT), which

compared the efficacy and safety of formulations containing budesonide/formoterol fumarate, fluticasone propionate alone, and the single-capsule combination of fluticasone propionate/formoterol fumarate on lung function in 243 patients with mild-to-moderate persistent asthma, showed that the proportions of patients with controlled asthma in the fluticasone propionate/formoterol fumarate, budesonide/formoterol and fluticasone groups increased from 59%, 60% and 66%, respectively, at baseline, to 83%, 63%, and 68%, respectively, at the end of the study with the difference tending to be significant ($p=0.08$) in the fluticasone propionate/formoterol fumarate group ⁴¹. Our real-world study findings are consistent with the previously conducted controlled studies; the proportion of patients achieving asthma control in our study increased from 8.4% at baseline to ~81% at week 24. We used the ACTTM tool, which is an accurate and preferred tool for assessing asthma control in clinical practice ^{42, 43}. A continuous significant improvement in the mean ACTTM score was observed in our study from baseline to subsequent visits (week 4, week 8, week 16 and week 24). Further, the improvement in mean score for ACTTM was 6.7 at week 24, which is far above the minimal clinically important difference (MCID) of 3 – a threshold above which the outcome score is considered as clinically meaningful, both by physicians and patients ^{44, 45}.

We also observed a significant ($p<0.0001$) improvement in mean morning and evening PEFr from baseline to the subsequent visits (week 4, week 8, week 16 and week 24). This is in concordance with previous studies, wherein, fluticasone propionate/formoterol fumarate demonstrated significant improvements in PEFr that were comparable to budesonide/formoterol and fluticasone propionate/salmeterol ⁴⁶⁻⁴⁸. A prospective, active-controlled, clinical trial comparing the efficacy and safety of fluticasone propionate/formoterol fumarate with budesonide/formoterol reported statistically significant ($p<0.0001$) improvements in morning PEFr within both the study groups (48.07 L/min and

49.03 L/min, respectively) ⁴⁶. A Phase III trial reported the efficacy of fluticasone propionate/formoterol fumarate to be comparable to fluticasone propionate/salmeterol for 2-hour post-dose PEFr at week 12 (least square mean of the treatment difference of -10.0 L/min; 95% CI: -33.6, 13.7; assessed in the full analysis set population; $p=0.408$) ⁴⁷. Moreover, fluticasone propionate/formoterol fumarate can offer an advantage of improvement in the post-bronchodilator FEV₁ due to the fast onset of action of formoterol fumarate as compared with that of salmeterol. A previous 12-week study showed that fluticasone propionate/formoterol fumarate scored better in the initiation of bronchodilation that was significantly rapid in comparison to fluticasone propionate/salmeterol (overall hazard ratio: 1.64; 95% CI: 1.28, 2.10; $p<0.001$) during the entire 12-week study period ⁴⁷. The post-hoc analysis of the bronchodilatory effects reported that the odds of a patient achieving bronchodilatory effects within 5 minutes of receiving the dose were approximately 4-fold higher with fluticasone propionate/formoterol fumarate in comparison to fluticasone propionate/salmeterol on day 0 (odds ratio [OR] = 3.97; 95% CI: 1.96–8.03) ⁴⁸.

Our study based on a real-world setting also provided useful insights into the usage of the Revolizer[®]. Ninety-eight percent of the patients found the device very easy or easy to use. Moreover, about 86% of the patients responded that they could quickly use the Revolizer[®] in case of an emergency. These results are consistent with those of Rajan et al. who investigated the usability, confidence, satisfaction and device preference with the Revolizer[®] in healthy volunteers and patients with mild asthma or chronic obstructive pulmonary disease, wherein 85% of participants stated that the Revolizer[®] was easy to use ²¹. Overall, the fluticasone propionate/formoterol fumarate combination was safe and very well tolerated and the results were consistent with the previous studies conducted with this combination. Only 1 patient

had a severe exacerbation in the present study. None of the patients had an AE related to the study drug.

There is an increasing demand for real-world evidence from pragmatically designed studies as clinicians are keen to know the effectiveness and safety of a pharmaceutical product when taken by a wide range of population ⁴⁹. During an RCT, patients are carefully chosen based on specific eligibility criteria, frequently monitored and instructed on the use of inhalers and are, thus, usually adept at inhalation techniques, thereby generally leading to an optimal outcome. However, in a real-world setting, the use of inhaler devices in a heterogeneous population is largely characterised by poor inhaler technique and low treatment observance. Hence, this first real-world study on fluticasone propionate/formoterol fumarate FDC administered via the Revolizer[®] is of significant value.

Our study had certain limitations. Data on prior medications was not reported for the vast majority (93%) of patients; and it is likely that a significant number were receiving oral therapy of common anti-asthmatic drugs like salbutamol (SABA), theophylline (PDE inhibitor), and methylprednisolone (corticosteroid), which is a common practice in India and could be attributed to the poor awareness, myths and social stigma associated with inhalation therapy ^{6,50}. This could have contributed to the dramatic improvement in asthma control observed in our study. It is also possible that participation in the study, albeit in a real-world setting, resulted in improved adherence and improved inhaler technique. The open-label study design of the study limits the reliability of its interpretations as the drug was not compared with any control such as previously available treatment regimens. Also, the inhalation technique with Revolizer[®] inhaler was not assessed critically due to the real-world nature of the study.

To conclude, in this observational real-world study, fluticasone propionate/formoterol fumarate FDC administered through the Revolizer[®] device significantly improved asthma control, peak flow and quality of life of patients with persistent asthma. The results of the present study complement those reported earlier with fluticasone propionate/formoterol fumarate pMDI in RCTs. Thus, the combination of fluticasone propionate/formoterol fumarate given through the Revolizer[®] is an effective and well-tolerated treatment option for the long-term management of asthma

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Declaration of Interest

Abhijit Vaidya, Meena Lopez, Dr Rashmi Hegde and Dr Jaideep Gogtay are employees of Cipla Ltd.