

# Efficacy and safety of ipratropium bromide/salbutamol sulphate administered in a hydrofluoroalkane metered-dose inhaler for the treatment of COPD

Amal Bhattacharya<sup>1</sup>Salil Bhargava<sup>2</sup>Virendra Singh<sup>3</sup>Deepak Talwar<sup>4</sup>Jagdeep Whig<sup>5</sup>Juliet Rebello<sup>6</sup>Shrinivas Purandare<sup>6</sup>Jaideep Gogtay<sup>6</sup><sup>1</sup>Department of Medicine, MP Shah Medical College, Jamnagar, Gujarat,<sup>2</sup>Tuberculosis and Chest Diseases, MGM Medical College, Indore,<sup>3</sup>Pulmonary Division, SMS Hospital, Jaipur, Rajasthan,<sup>4</sup>Respiratory Diseases, Metro Hospital and Heart Institute, Noida, Uttar Pradesh,<sup>5</sup>Department of Medicine, Dayanand Medical College & Hospital, Ludhiana, Punjab,<sup>6</sup>Clinical Research Department, Cipla Ltd, Mumbai, Maharashtra, India

**Background:** The use of chlorofluorocarbons (CFCs) has contributed to the depletion of the stratospheric ozone layer resulting in serious health concerns. Ipratropium bromide/salbutamol sulphate CFC-pressurized metered-dose inhalers (IB/SAL-CFC pMDI) have been in widespread use for many years without any apparent ill consequences. This combination has now been reformulated using the hydrofluoroalkane (HFA) propellant. This study sought to establish the clinical noninferiority of a new HFA-containing IB/SAL pMDI to the conventional IB/SAL-CFC pMDI in subjects with mild/moderate COPD.

**Methods:** This was a randomized, double-blind, parallel-group, multicenter study in two consecutive periods: a 14-day run-in period followed by a 85-day treatment period. Eligible mild-to-moderate stable COPD subjects aged 40–75 years were enrolled into the study and entered the run-in period during which subjects withdrew all the bronchodilators, except for salbutamol as rescue medication. Subjects were randomized to 85 days treatment with either IB/SAL-HFA or IB/SAL-CFC, 20 µg qid.

**Results:** Of the 290 randomized patients, 249 completed the study. The primary efficacy variable was the change in forced expiratory volume in one second from predose to 60 minutes after dosing on day 85. At the end of the treatment period, the adjusted mean change in forced expiratory volume in one second at 60 minutes was 123 mL in the IB/SAL-HFA pMDI group and 115 mL in the IB/SAL-CFC pMDI group. Because the lower limit of the 95% confidence interval for the between-group difference (–62 mL) was well within the noninferiority margin (–100 mL), the HFA formulation was deemed clinically noninferior to the CFC formulation. This finding was supported by secondary efficacy assessments. Both formulations of IB/SAL were well tolerated during the prolonged multiple dosing.

**Conclusion:** It is concluded that IB/SAL-HFA pMDI provides effective bronchodilation of similar degree to that achieved with IB/SAL-CFC pMDI. Therefore, IB/SAL-HFA pMDI is a valuable alternative to IB/SAL-CFC pMDI.

**Keywords:** ipratropium/salbutamol, pressurized metered-dose inhaler, noninferiority, FEV<sub>1</sub>, hydrofluoroalkane, COPD

## Introduction

COPD is mainly associated with smoking, with up to 20% of all smokers developing the disease. COPD progresses with age, leading to disability and early death. According to the Annual World Health Report of the World Health Organization (WHO), ~600 million people suffer from COPD, with ~3 million dying from the disease each year.<sup>1</sup> The combination of anticholinergics with  $\beta_2$ -agonists is recommended for the management of COPD. In addition to bronchodilation, they improve dyspnea scores,

Correspondence: Juliet Rebello  
Clinical Research Department, Cipla Ltd, Fourth floor, North Block, R&D Centre, Vikhroli (W), Mumbai 400083, Maharashtra, India  
Tel +91 22 2575 6420  
Email juliet@cipla.com



exercise tolerance, promote sleep quality, decrease COPD exacerbations, and improve quality of life.<sup>1-3</sup> While regular use of long-acting combination bronchodilators is preferred in COPD subjects with persistent symptoms, a combination of a short-acting  $\beta_2$ -agonist (SABA) and antimuscarinic receptor antagonist (SAMA) may be an option in patients with stable, mild-to-moderate COPD.

The SABA/SAMA combination of ipratropium bromide/salbutamol sulphate (IB/SAL) delivered by chlorofluorocarbon (CFC)-pressurized metered-dose inhaler (pMDI) has been in widespread use for many years without apparent ill consequences.<sup>4</sup> Use of CFCs in domestic, commercial, and other products has contributed to the depletion of the stratospheric ozone layer, resulting in serious health concerns. Alternatives to CFCs for use in pMDIs are the hydrofluoroalkanes (HFAs). These compounds do not contain chlorine and, therefore, have limited ozone-depleting potential. HFAs have safety profiles comparable to CFCs and are, therefore, considered as suitable alternatives to the CFCs to be used in the formulation of medicinal products.<sup>5</sup>

Interestingly, although dry powder inhalers (DPIs) offer a highly effective CFC-free alternative, they may not provide the most optimal means of drug delivery for all COPD patients, particularly those with more severe disease. Studies have shown that the lung deposition of drugs administered via a DPI is reduced, especially in the peripheral lungs, at lower inspiratory flow rates.<sup>6-8</sup> Furthermore, not all powder devices are equally acceptable to patients. These factors have led some experts to recommend that, during the transition from old inhalers to new ones, patients currently using a CFC pMDI should be switched to a CFC-free pMDI rather than a DPI, the latter only being considered if clinically indicated.<sup>9</sup>

Therefore, this study sought to establish the clinical noninferiority of a new HFA-containing IB/SAL pMDI to the conventional IB/SAL-CFC pMDI in subjects with mild-to-moderate COPD.

## Methods

### Patients

Patients were of either sex, aged 40–75 years, with a confirmed diagnosis of COPD according to the Global Initiative for Obstructive Lung Disease criteria.<sup>1</sup> Patients were either newly diagnosed or who required regular bronchodilator treatment for COPD. The study included both current smokers and ex-smokers with a forced expiratory volume in one second ( $FEV_1$ )  $\geq 50\%$  of predicted value and a prebronchodilator  $FEV_1$ /forced vital capacity (FVC)

ratio  $< 70\%$ . All the patients were able to use the pMDI without a spacer and were able to perform the required pulmonary function tests. Female patients who were of childbearing potential and willing to use effective contraceptive measures were also included.

The specific exclusion criteria were as follows: current diagnosis of asthma; acute exacerbations and/or use of oral corticosteroids within the past 4 weeks; abnormal clinically significant electrocardiography (ECG); long-term oxygen therapy; and any significant medical disorder that would place the patient at risk, interfere with evaluations, or influence study participation.

All the patients provided written, informed consent in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice.

### Study design

This randomized, double-blind, double-dummy, parallel-group, multicenter study (study code: CP/04/03) was approved by the institutional review boards/Independent Ethics Committee for each of the 25 investigative sites in India. The study was conducted in two consecutive periods: a 14-day run-in period followed by a 85-day treatment period.

All the subjects signed an informed consent before initiation of any study procedures. Eligible patients were enrolled into the study and entered the run-in period during which patients stopped using other bronchodilators, except for salbutamol as rescue medication. However, inhaled steroids and theophyllines were allowed at a constant dose throughout the study. All the patients recorded symptom scores, rescue medication ( $\beta_2$ -agonist) use, and self-reported side effects in their diaries throughout the study.

Patients who fulfilled the enrollment criteria (ie, reported no change in treatment and no COPD-related hospital visits during the run-in period and had a prebronchodilator  $FEV_1 \geq 50\%$  and  $FEV_1/FVC < 70\%$  of predicted value and whose prebronchodilator  $FEV_1$  was within a range of  $\pm 15\%$  of the value at the screening visit) at the end of the run-in period were randomized to a 85-day treatment phase with either IB/SAL-HFA pMDI (test product) or IB/SAL-CFC pMDI (comparator) in a 1:1 ratio. Since the test and comparator product devices differed in appearance, patients also received a placebo pMDI with the appearance of the alternative product.

Patients were followed up at regular intervals (day 7, 21, 42, 63, and 85) after randomization to assess safety and efficacy.

## Assessments

The overall median time to a peak response in  $FEV_1$  for the IB/SAL combination is 60 minutes after the study drug administration.<sup>10</sup> Hence, the primary efficacy variable was the change in  $FEV_1$  from predose to 60 minutes after dosing over 85 days after randomization. Other efficacy parameters included: change in  $FEV_1$  and FVC from predose to 60 minutes after dosing, daytime and nighttime symptom scores, total daily inhaled rescue medication at regular intervals (day 7, 21, 42, 63, and 85) after randomization, and change in St George's Respiratory Questionnaire (SGRQ) score at the end of the 85-day treatment period.

Spirometric measurements were performed in the clinic at each visit at approximately the same time of the day for each patient, ie, within 1 hour of the time, it was performed at the screening visit, to eliminate the influence of diurnal variation in bronchial resistance. Prior to each clinic visit, patients were instructed to withhold the morning dose of the study drug, any short-acting theophylline in use for 24 hours, any long-acting theophylline in use for 48 hours, and any rescue medication (salbutamol) in use for at least 6 hours.

The patients assessed and graded symptom scores daily and recorded the results in their diary card, according to the following scoring system:

### Breathlessness

The score for breathlessness was rated as follows: 0= not breathless at rest or on exertion; 1= not breathless at rest, but breathless on moderate exertion (eg, walking quickly); 2= not breathless at rest, but breathless on mild exertion (eg, walking on level); 3= not breathless at rest, but breathless on minimal exertion (eg, getting dressed); and 4= breathless at rest.

### Cough, wheeze, and sputum

The score for cough, wheeze, and sputum was rated as follows: 0= none (no symptoms); 1= mild (symptom was minimally troublesome, ie, not sufficient to interfere with normal activity or sleep); 2= moderate (symptom was sufficiently troublesome to interfere with normal daily activity or sleep); and 3= severe (symptom was so severe as to prevent normal daily activity or sleep).

The SGRQ is a questionnaire that is designed to measure "health-related quality of life", ie, the impact of chest disease on daily life and well-being. Validated SGRQs were not available in all Indian languages. Therefore, the questionnaire was completed by literate patients who were able to read and understand Tamil, Malayalam, Hindi, or English.

The patients completed the SGRQ, under supervision, at baseline and at the end of the treatment period or at the time of withdrawal. The questionnaires were completed at the clinic, not at home.

## Safety

Safety was investigated by assessing the nature, incidence and severity of any adverse events (AEs) reported by the patient. Additionally, ECG, tremor, clinical laboratory values including serum potassium and blood glucose levels and vital signs (blood pressure and pulse rate) were recorded at the beginning and the end of the study period.

## Statistical analysis

A sample size of 222 evaluable patients (111 per treatment group) was calculated to give the study a power of ~80% to test IB/SAL-HFA pMDI for noninferiority against IB/SAL-CFC pMDI. This calculation assumed a noninferiority margin of 100 mL for  $FEV_1$ , a SD of 300 mL, the mean change for both the treatment groups to be the same, and an alpha of 0.05 (one-sided). Allowing for a dropout rate of 30%, it was planned that 290 patients would be randomized in this study.

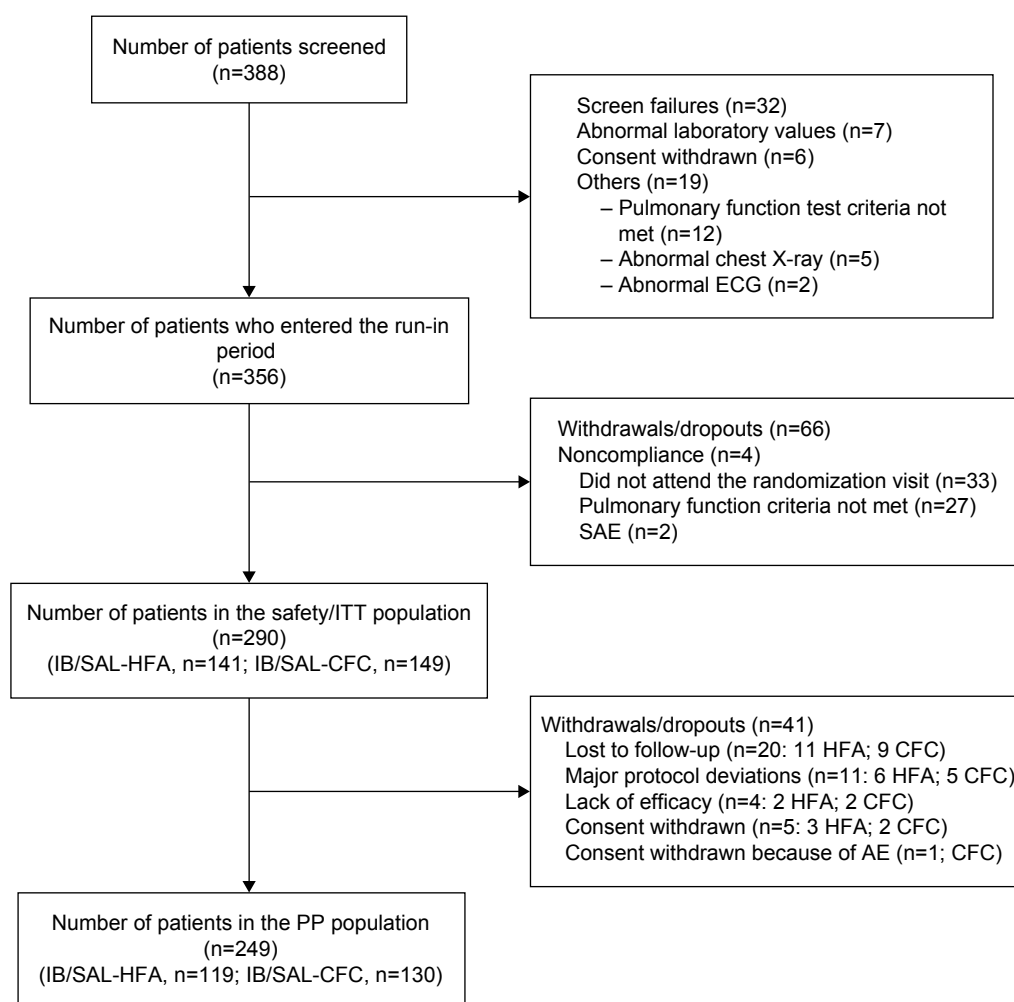
Statistical analyses were performed after all of the patients had ended their participation in the study and the database was locked. Patients withdrawn before randomization were not assessed for outcome variables or safety. Continuous variables were summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum), while categorical variables were summarized as the number (and percentage) of patients in each category. The primary endpoint was calculated by analysis of covariance, including factors center and treatment with baseline as covariate. It was determined that the noninferiority of the HFA inhaler would be established if the lower limit of the 95% confidence interval (CI) for the change in  $FEV_1$  at 60 minutes after dosing was superior to -100 L/min.

All the patients in whom at least one posttreatment value was available were included in the intention-to-treat (ITT) population. All the patients who completed the scheduled treatment period of 85 days as per the protocol without major protocol deviations constituted the per protocol (PP) analysis population.

## Results

### Patient disposition and baseline characteristics

A total of 388 patients were screened for the study (Figure 1). Thirty-two of the patients who were screened did not enter



**Figure 1** Summary of patient disposition.

**Abbreviations:** AE, adverse event; CFC, chlorofluorocarbon; ECG, electrocardiography; HFA, hydrofluoroalkane; IB/SAL, ipratropium bromide/salbutamol sulphate; ITT, intention-to-treat; PP, per protocol; SAE, serious adverse event.

the run-in period: 26 had clinical reasons for being unsuitable for the study and six withdrew their consent. Therefore, 356 patients entered the run-in period. Eighty-two percent of the patients who entered the run-period were randomized and included in the ITT/safety population: 141 patients in the HFA group and 149 patients in the CFC group. A total of 249 patients completed the 85-day treatment period and were included in the PP population (119 patients in the HFA group and 130 patients in the CFC group).

Demographic and disease characteristics at screening were similar across both the treatment groups (Table 1).

The screening spirometry results indicated mild-to-moderate airflow obstruction with a mean baseline FEV<sub>1</sub> of 65% of predicted. All patients had a documented history of COPD with mild-to-moderate symptoms. Patients had a significant smoking history which was comparable across both the treatment periods. The baseline characteristics of

the PP population were comparable with those of the ITT population.

## Efficacy

In the PP population, the estimated mean difference for the primary endpoint was 0.018 L and the lower 95% CI was −0.062 L. Similar results were observed in the ITT population, the estimated difference between the treatment groups was 0.066 L and the lower limit of the 95% CI was −0.033 L. As the lower limit in both analyses was superior to the noninferiority margin of −100 mL, it was concluded that the efficacy of IB/SAL-HFA pMDI was noninferior to that of the IB/SAL-CFC pMDI.

The mean changes in FEV<sub>1</sub> from predose values on all of the test days are illustrated in Figure 2. The results of this clinical trial demonstrated that treatment with both the test and reference product provided a clinically relevant

**Table 1** Baseline and demographic characteristics (ITT population)

Variable	IB/SAL HFA MDI (n=141)	IB/SAL CFC MDI (n=149)
Sex		
Male (%)	138 (98)	148 (99)
Female (%)	3 (2.13)	1 (0.67)
Age (years), mean (SD)	55.2 (9.9)	56.3 (9.5)
Weight (kg), mean (SD)	58.0 (11.1)	58.8 (12.1)
Height (cm), mean (SD)	163 (7)	164 (7)
Duration of COPD (years)		
Mean (SD)	4.2 (3.6)	4.7 (4.1)
Most common symptoms n (%)		
Breathlessness	135 (96)	141 (95)
Cough	123 (87)	130 (87)
Smoking status (cigarettes) n (%)		
Former smoker	23 (16)	25 (17)
Current smoker	26 (18)	17 (11)
Smoking status (beedis) *n (%)		
Former smoker	26 (18)	30 (20)
Current smoker	65 (46)	77 (52)
Spirometry*		
FEV <sub>1</sub> (L), mean (SD)	1.73 (0.55)	1.75 (0.50)
FEV <sub>1</sub> % predicted, mean (SD)	65 (15)	65 (13)

**Notes:** \*Beedis are small, thin, hand-rolled cigarettes. They comprise tobacco wrapped in a tendu or temburni leaf (plants native to Asia) and may be secured with a colorful string at one or both ends. \* $P > 0.05$  for all comparisons.

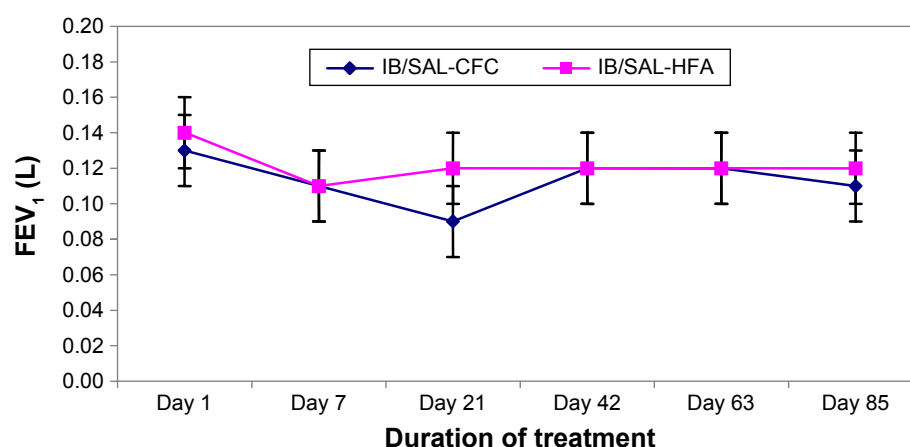
**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in one second; ITT, intention-to-treat; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; IB/SAL, ipratropium/salbutamol.

improvement in 1-hour postdose FEV<sub>1</sub> throughout the treatment period. The improvement in 1 hour postdose FEV<sub>1</sub> was observed on day 1 and continued throughout the 85-day treatment period in both the treatment groups with no evidence of tolerance (Table 2).

Results from the secondary efficacy assessments, FVC, symptom scores, and SGRQ confirmed the findings of the primary efficacy assessment. There were no statistically significant differences in changes in FVC post 1 hour after dosing between the two treatment groups at each clinic visit. The mean scores for cough, sputum, wheeze, and

breathlessness were  $<1$  throughout the study in both the treatment groups. There were no significant differences between the two groups in rescue medication use ( $P=0.5046$  vs IB/SAL-CFC on day 85). The median use of rescue medication was 14 puffs in the IB/SAL-HFA group and 16 puffs in the IB/SAL-CFC group at baseline, which decreased to zero puffs in both the groups at the end of the treatment period.

Treatment with both the IB/SAL formulations also resulted in SGRQ scores lower at the end of the 85-day treatment period as compared with baseline. In the HFA group ( $n=35$ ), mean (SD) total SGRQ scores were 51.0 (22.5) at

**Figure 2** Mean change in FEV<sub>1</sub> over the 85-day treatment period.

**Abbreviations:** CFC, chlorofluorocarbon; FEV<sub>1</sub>, forced expiratory volume in one second; HFA, hydrofluoroalkane; IB/SAL, ipratropium bromide/salbutamol sulphate.



**Table 2** Statistical analyses for the mean change in FEV<sub>1</sub> at 60 minutes for IB/SAL-HFA pMDI vs IB/SAL-CFC pMDI after dosing on day 1 and day 85 (PP population)

	Treatment	N	Mean change in FEV <sub>1</sub> (L) at 60 minutes from baseline	Mean difference (HFA vs CFC; 95% CI)
Day 1	IB/SAL-HFA	119	0.141	0.009 (−0.094, 0.112)
	IB/SAL-CFC	130	0.128	
Day 85	IB/SAL-HFA	119	0.123	0.018 (−0.062, 0.099)
	IB/SAL-CFC	130	0.115	

**Abbreviations:** CFC, chlorofluorocarbon; CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in one second; HFA, hydrofluoroalkane; IB/SAL, ipratropium bromide/salbutamol sulphate.

baseline and 36.9 (23.8) at day 85, respectively. In the CFC group (n=29), the total scores were 54.7 (29.1) and 33.3 (18.4) at baseline and day 85, respectively. The subscores (symptom score, activity score, and impacts score) gave similar findings to the total scores.

## Safety

A total of 73 AEs were reported by 33 (23%) patients in the HFA group, and 54 AEs were reported by 24 (16%) patients in the CFC group. The most common AEs during the treatment period were headache (19 AEs in the HFA group and nine AEs in the CFC group), followed by productive cough (seven AEs in the HFA group and two AEs in the CFC group), and nasopharyngitis (four AEs in each group). Two serious AEs occurred during the study, both in patients prior to randomization; hence, neither serious AE was related to the study medication. In addition, there were two exacerbations of COPD during the treatment period, one in each treatment group. The findings of the other safety assessments were similar in the two groups.

There were no deaths during the study. There were no differences between the groups or changes overall in mean laboratory values, including potassium and glucose, throughout the study. There were no clinically relevant differences between the two groups on physical examination, or in the assessment of vital signs. No unexpected cardiovascular effects were observed with either formulation of IB/SAL.

There were no clinically relevant differences between the groups in the reporting of tremor. Those episodes of tremor that did occur were mostly mild, and there were no episodes of severe tremor. Therefore, there was no evidence of an influence of the propellant in the pMDI on any propensity of the active ingredients to cause tremor.

The AE profile for IB/SAL-HFA pMDI was similar to that of IB/SAL-CFC pMDI.

The safety profile of both the formulations of IB/SAL in this study was consistent with what would be expected with the administration of a SABA and an anticholinergic agent.

## Discussion

Combinations of  $\beta_2$ -agonists and anticholinergics are the preferred first-choice treatment for COPD. Though long-acting  $\beta_2$ -agonists and long-acting anticholinergic agents are widely used (though sometimes not available in the same device), the combination of ipratropium and salbutamol via a pMDI is likely to be preferred primarily due to its quick onset of action and immediate symptomatic relief in COPD patients.

The main objective of this study was to demonstrate the multiple-dose clinical noninferiority of an IB/SAL-HFA-formulated pMDI and an IB/SAL-CFC-formulated pMDI over a 85-day treatment period in adult patients with mild-to-moderate COPD.

The two treatment groups were well balanced for all demographic characteristics. However, all, except four patients were male. The COPD prevalence varies from 3% to 8% among Indian males and ~2.5%–4.5% among Indian females.<sup>11</sup> In India, COPD also seems to be underdiagnosed in women by physicians. Furthermore, for sociocultural reasons, female subjects may be reluctant to participate in clinical studies.<sup>12</sup> Recent data suggest that there are differences between the sexes in the pathophysiology of the disease and in the response to therapy with COPD medications.<sup>13</sup> Hence, the low number of women in the study population is a limitation of this study. However, because this study evaluated the noninferiority of two similar formulations of IB/SAL, it is not likely that the findings in women would differ.

Interestingly, most subjects in the study were using beedis rather than cigarettes. Beedis have higher concentrations of nicotine, tar, and carbon monoxide than conventional cigarettes. Thus, beedi smoking may be more likely to cause clinical and functional impairment of lungs as compared with cigarette smoking.<sup>14</sup> This may also account for the fact that the mean age of the enrolled subjects was lower than that reported in published studies.<sup>15</sup>

We found that the mean change in FEV<sub>1</sub> from predose to 60 minutes after dosing at the end of the 85-day treatment

period in the IB/SAL-HFA pMDI group and in the IB/SAL-CFC pMDI group were similar with an estimated difference between groups equal to 18 mL with a lower limit of 95% CI equal to -62 mL. Therefore, we concluded that IB/SAL-HFA pMDI was noninferior to IB/SAL-CFC pMDI since the lower limit of the 95% CI of the estimated difference for FEV<sub>1</sub> was superior to -100 mL (noninferiority margin).

The secondary efficacy variables supported the findings of the primary variable. In most published studies with a large sample size, the change from baseline in SGRQ ranges from 5 to 6 units.<sup>16</sup> However, a larger change from baseline in the SGRQ scores was observed in this study. Since the sample size, who completed the SGRQ in this study, was less (n=64) and the observed variation in SGRQ scores was high, these findings must be interpreted cautiously. The most common AE was headache, which is a known AE of IB/SAL. The second most common AE was productive cough, which is a symptom of COPD, followed by cough and nasopharyngitis, which are more likely to be symptoms of a common cold than AEs of treatment. The incidence of AEs overall was low, and it may, therefore, be concluded that both treatments were safe and well tolerated.

In controlled clinical trials in COPD patients where most treatments are withdrawn except the study drug under evaluation, the adherence rates reported were ~62%.<sup>17</sup> However, in clinical practice since patients would require multiple medications to adequately manage COPD, patient adherence with therapy is likely to be poor with reported adherence rates as low as 40%.<sup>18</sup> The need to simplify medical regimens in COPD patients is, therefore, critical since many patients have significant comorbid illnesses that also require other pharmacologic therapies. A combination product containing two common classes of medications in a single inhaler would simplify therapy for many patients, improve adherence, and represent a valuable treatment option for many, considering the withdrawal of CFC products. The combination IB/SAL provided sustained symptom relief throughout the 85-day treatment period.

## Conclusion

In conclusion, treatment with the combination IB/SAL four times a day over a period of 85 days provided a clinically relevant improvement in both symptoms and lung function in patients with COPD. The improvement in lung function and symptoms was similar between the test and reference product, indicating that IB/SAL-HFA pMDI is clinically noninferior to IB/SAL-CFC pMDI. This conclusion is supported by the

secondary efficacy variables. The benefits provided by the combination were not associated with any additional clinically significant AE. Both IB/SAL-HFA and IB/SAL-CFC pMDIs were safe and well tolerated.

## Acknowledgment

The authors thank Dr Vaibhav Gaur for his editorial assistance.

## Disclosure

J Rebello, S Purandare, and J Gogtay are employees of Cipla Ltd. The authors report no other conflicts of interest in this work.

## References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [homepage on the Internet]. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease [updated 2015]. Available from: <http://www.goldcopd.org>. Accessed September 9, 2015.
2. National Institute for Clinical Excellence. Chronic Obstructive Pulmonary Disease. Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care. Clinical Guideline 12. London: National Institute for Clinical Excellence; 2004.
3. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis*. 1987;136:225-244.
4. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. *Chest*. 1994; 105:1411-1419.
5. CPMP/391/97. Consolidation of CPMP Reviews of Alternatives to Chlorofluorocarbon Propellants. London: 1997.
6. Nielsen KG, Skov M, Klug B, Iversen M, Bisgaard H. Flow-dependent effect of formoterol dry-powder inhaled from the Aerolizer®. *Eur Respir J*. 1997;10:2105-2109.
7. Smith KJ, Chan H-K, Brown KF. Influence of flow rate on aerosol particle size distributions from pressurized and breath-actuated inhalers. *J Aerosol Med*. 1998;11:231-245.
8. Borgstrom L, Bondesson E, Moren F, Trofast E, Newman SP. Lung deposition of budesonide inhaled via turbuhaler: a comparison with terbutaline sulphate in normal subjects. *Eur Respir J*. 1994;7: 69-73.
9. Hartung TK, Allbutt H, Dewar M, Innes JA, Crompton GK. Moving from CFC aerosol to HFA aerosol or dry powder inhalers: what do patients think? *Respiration*. 2002;69:314-319.
10. ZuWallack R, De Salvo MC, Kaelin T, et al; Combivent Respimat Inhaler Study Group. Efficacy and safety of ipratropium bromide/albuterol delivered via Respimat inhaler versus MDI. *Respir Med*. 2010; 104:1179-1188.
11. Bhome A. COPD in India: iceberg or volcano? *J Thorac Dis*. 2012;4(3): 298-309.
12. Jain NK, Thakkar MS, Jain N, Rohan KA, Sharma M. Chronic obstructive pulmonary disease: does gender really matter? *Lung India*. 2011;28(4):258-262.
13. Lopez Varela MV, Montes de Oca M. Sex-related differences in COPD in five Latin American cities: the PLATINO study. *Eur Respir J*. 2010; 36:1034-1041.
14. Chabra SK, Rajpal S, Gupta S. Pattern of smoking in Delhi and comparison of chronic respiratory morbidity among beedi and cigarette smokers. *Indian J Chest Dis Allied Sci*. 2001;43:19-26.

15. James G, Donaldson G, Wedzicha JA, Nazareth I. Trends in management and outcome of COPD patients in primary care, 2000–2009, a retrospective cohort study. *NPJ Prim Care Respir Med.* 2014;24:14015.
16. Singh D, Ferguson GT, Bolitschek J, et al. Tiotropium and olodaterol shows clinically meaningful improvements in quality of life. *Respir Med.* 2015;109(10):1312–1319.
17. Charles MS, Blanchette CM, Silver H, Lavalley D, Dalal AA, Mapel D. Adherence to controller therapy for chronic obstructive pulmonary disease: a review. *Curr Med Res Opin.* 2010;26:2421–2429.
18. Restrepo R, Alvarez M, Wittnebel L, et al. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis.* 2008; 3:371–384.

## International Journal of COPD

Dovepress

### Publish your work in this journal

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management protocols.

Submit your manuscript here: <http://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal>

This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.