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# Long-Term Efficacy and Safety of Ipratropium Bromide plus Fenoterol via Respimat® Soft Mist™ Inhaler (SMI) versus a Pressurised Metered-Dose Inhaler in Asthma

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## Abstract

**Objective:** Respimat® Soft Mist™ Inhaler (SMI) is a novel, propellant-free device that significantly increases lung deposition compared with pressurised metered-dose inhalers (pMDIs). The aim of this study was to compare the efficacy and safety of ipratropium bromide/fenoterol hydrobromide (IB/FEN; Berodual®) delivered via Respimat® SMI and via a chlorofluorocarbon (CFC)-driven pMDI (CFC-MDI) in patients with asthma.

**Design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group study.

**Patients:** 631 patients (18–65 years old) with stable asthma.

**Interventions:** After a 2-week run-in period (IB/FEN 20μg/50μg via CFC-MDI, two actuations four times a day), patients were randomised to 12 weeks' treatment with one of five treatments: IB/FEN 10μg/25μg, 20μg/50μg or placebo via Respimat® SMI (one actuation four times a day), or IB/FEN 20μg/50μg or placebo via CFC-MDI (two actuations four times a day). The main efficacy measure was lung function (assessed on days 1, 29, 57 and 85); safety was assessed by monitoring adverse events.

**Results:** Bronchodilator responses to IB/FEN were much greater than those to placebo (mean peak increases in forced expiratory volume in 1 second [$FEV_1$] on day 85: 0.498–0.521L, active treatment; 0.215 and 0.240L, placebo). According to the primary endpoint, i.e. the average change in $FEV_1$ from test-day baseline over the 6 hours after dosing on day 85, neither IB/FEN dosage via Respimat® SMI was inferior to IB/FEN via pMDI ($p < 0.001$). Non-inferiority of the two Respimat® SMI dosages was supported by analyses of other lung function measures, e.g. average change in $FEV_1$ from test-day baseline over the 6 hours

after dosing on the other 3 test days, and peak $FEV_1$ on all test days. Overall, the safety profile of IB/FEN via Respimat® SMI was comparable to that via CFC-MDI.

**Conclusion:** IB/FEN from Respimat® SMI is as effective and safe as from CFC-MDI and enables a 2- to 4-fold daily dose reduction of IB/FEN.

Pressurised metered-dose inhalers (pMDIs) are the most common devices for inhaled respiratory drugs. They are portable and relatively inexpensive.[1] Although they are seemingly easy to use, a large proportion of patients exhibit inadequate inhaler technique and incorrect use may result in poor therapeutic benefit.[2] Furthermore, with most pMDIs a high proportion of drug is lost through oropharyngeal impaction, with most devices delivering only a fraction of the nominal dose (≤30%) to the lungs.[3] Consequently, there is a need for improved inhaler devices for the treatment of respiratory disease.

Respimat® Soft Mist™ Inhaler (SMI)[1] [Boehringer Ingelheim GmbH, Ingelheim, Germany], is a novel, propellant-free inhaler with an easy to use "twist, press and breathe" procedure. Unlike other inhalers, it has a unique delivery mechanism, which uses the energy released from a tensioned spring to generate a slow-moving cloud – the Soft Mist™. Previous studies have shown that the Soft Mist™ has a high fine particle fraction, is much slower and lasts much longer than the aerosol clouds from chlorofluorocarbon (CFC) and hydrofluoroalkane (HFA) pMDIs.[4-6] These characteristics significantly reduce oropharyngeal and increase lung deposition compared with pMDIs.[5,7-9] For example, Respimat® SMI delivered 39.2% of fenoterol to the lungs compared with 11% delivered by a pMDI, while oropharyngeal deposition was 37.1% versus 71.7%, respectively.[9] Moreover, initial phase II studies have indicated the efficacy of reduced dosages of bronchodilator therapies[10-12] when delivered by Respimat® SMI compared with CFC-MDI.

The fixed combination of ipratropium bromide (IB) and fenoterol hydrobromide (FEN) [Berodual®, Boehringer-Ingelheim GmbH, Ingelheim, Germany], which has been available as a CFC-MDI for the treatment of asthma in a number of countries for many years, has shown a significant bronchodilating effect in patients with asthma[13] and achieved similar improvements in pulmonary function to salbutamol.[14] In accordance with the Montreal Protocol, the CFC-MDI version of IB/FEN has now been replaced with a pMDI containing HFA as the propellant. This product is used as an on-demand bronchodilator for patients with asthma and as maintenance therapy for patients with chronic obstructive pulmonary disease (COPD); the established dosage is IB 40μg/FEN 100μg (taken as two actuations of IB/FEN 20μg/50μg) when needed.

The aim of this study was to prove the principle that since delivery of bronchodilator via Respimat® SMI is more efficient, less drug needs to be given to achieve the same efficacy than if it were given via CFC-MDI. The method by which we did this was to compare the efficacy and safety of 12 weeks' treatment with IB/FEN delivered from Respimat® SMI versus a conventional CFC-MDI in patients with asthma. The reason for giving the drug on a fixed regimen (i.e. four times daily) was to assess more fully the tolerability and safety profile of IB/FEN in the new Respimat® SMI formulation; this decision was taken after consultation with regulatory agencies to whom the data has since been submitted to support applications for a product licence for IB/FEN in Respimat® SMI. In previous dose-ranging and dose-response studies in asthma patients,[12,15] the bronchodilator effect of IB/FEN via Respimat® SMI was equivalent to that produced by a dose two or four times larger delivered via CFC-MDI. The dosages selected for this study, therefore, were IB/FEN 10μg/25μg and 20μg/50μg four times daily from Respimat® SMI, and IB/FEN 40μg/

**1** The use of tradenames is for product identification purposes only and does not imply endorsement.

100μg four times daily from a CFC-MDI. A placebo group was also included, to assess the safety profile of the Respimat® SMI formulation itself.

## Patients and Methods

### Study Participants

Adult patients (18–65 years old) with stable asthma,[16] a forced expiratory volume in 1 second ($FEV_1$) of 40–80% of predicted,[17] and reversible airway obstruction (increase in $FEV_1$ of ≥200mL and ≥12% from baseline 30 min after inhaling two actuations of salbutamol 100μg from a pMDI) were eligible for inclusion. Patients had to be non- or ex-smokers (≥1 year before enrolment) with a smoking history of <10 pack-years. They also had to have had no hospital admissions for an exacerbation and stable dosages of all pulmonary medications in the previous 4 weeks.

Exclusion criteria included: a history of clinically significant diseases other than asthma; severe bronchial asthma with frequent nocturnal attacks or acute exacerbations induced by recurrent bronchial infections several times per year; and recent respiratory tract infection. Patients using β-blockers or oral corticosteroids at variable dosages or a dosage greater than the equivalent of prednisone 10 mg/day were excluded, as were women who were pregnant, breast feeding or of childbearing potential and not using an acceptable method of contraception.

Usual maintenance treatment, such as stable dosages of inhaled corticosteroids, leukotriene modifiers, inhaled cromoglycate/nedocromil and theophylline preparations were permitted. Appropriate washout periods were used before pulmonary function tests. Long-acting $\beta_2$-agonists were not permitted.

### Study Design

This multicentre, randomised, double-blind (within-device), parallel-group study was conducted in Belgium, The Netherlands and South Africa, in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Local ethics committees approved the protocol and all patients gave written informed consent.

During the 2-week run-in period all patients received IB/FEN CFC-MDI (20μg/50μg per actuation) two actuations four times daily. Patients needing more than eight actuations of salbutamol rescue medication on ≥3 consecutive days during run-in were excluded from randomisation. The remaining patients received one of five treatments for 12 weeks:

- Respimat® SMI IB 10μg/FEN 25μg one actuation four times daily (Respimat® SMI 10/25)
- Respimat® SMI IB 20μg/FEN 50μg one actuation four times daily (Respimat® SMI 20/50)
- CFC-MDI IB 20μg/FEN 50μg per actuation, two actuations four times daily (pMDI 40/100)
- Respimat® SMI placebo, one actuation four times daily (Respimat® SMI PLA)
- CFC-MDI placebo, two actuations four times daily (pMDI PLA).

Randomisation was performed in blocks of eight patients stratified by centre. The allocation of patients to each of the five groups was done in a ratio of 2 : 2 : 2 : 1 : 1, so that the number in each active treatment group was twice that in each placebo group. Treatment was double-blind with respect to drug dose but not to device, i.e. active and placebo CFC-MDIs were identical in appearance, as were active and placebo Respimat® SMI devices. Blinding the study with respect to device by adopting a double-dummy design was not done, because the inhalation of excipients from both devices would have made it impossible to assess any "switch effect" (see Assessments: Safety section) from CFC-MDI to Respimat® SMI or to assess the incidence of adverse events (AEs) caused by each device. Rescue medication was salbutamol CFC-MDI (100μg per actuation), two actuations as needed. Spacer use with the study or rescue medication was not permitted.

### Assessments

#### *Efficacy*

The primary efficacy endpoint was the average change in $FEV_1$ from test-day baseline on day 85,

calculated as the area under the $FEV_1$-time curve between 0 and 6h ($AUC_{0–6h}$). The $AUC_{0–6h}$ was divided by 6 to allow the result to be expressed in litres.

Secondary endpoints assessed were:

- the average change in $FEV_1$ from test-day baseline assessed in the same way as described above, but on days 1, 29 and 57
- peak increase in $FEV_1$ (from test-day baseline)
- time to peak increase in $FEV_1$
- onset and duration of therapeutic response (i.e. an increase of ≥15% in $FEV_1$ over test-day baseline)
- forced vital capacity (FVC) on days 1, 29, 57 and 85
- weekly mean values of (a) pre-dose morning and evening peak expiratory flow rate (PEFR), (b) total inhaled rescue medication, and (c) day- and night-time symptom scores.

Day- and night-time asthma symptoms were scored on a scale from 0 to 4. On both scales, 0 represented no symptoms. For daytime symptoms, a score of 4 represented symptoms that prevented the patient attending work and engaging in all normal activities, and for night-time symptoms, 4 represented "woke up most of the night" (more than three times).

#### *Safety*

Safety variables recorded were: AEs, blood pressure, pulse rate, 12-lead ECG, clinical laboratory parameters (haematology, biochemistry and urinalysis), and physical examination. Adverse events and other observations that could possibly indicate administration-related bronchoconstriction, such as a fall of ≥15% in $FEV_1$ from test-day baseline, or wheeze and cough shortly after inhalation of study treatment, were recorded separately. The effect of switching from a CFC-MDI to Respimat® SMI was assessed by comparing PEFR, respiratory symptoms, use of rescue medication and respiratory AEs during the first two weeks of randomised treatment with the corresponding values during the 2-week run-in.

#### *Schedule of Assessments*

The study comprised a screening visit (visit 1) at the start of the 2-week run-in and visits 2–5 on treatment days 1, 29, 57 and 85. At visit 1, the following were recorded: demographic data, medical history, physical examination (including blood pressure and pulse rate), ECG, haematological, blood biochemistry and urinalysis investigations, and plasma theophylline levels. Patients were trained to use study inhalers and were also tested for reversibility to salbutamol. At visits 2–5, pulmonary function was tested ($FEV_1$ and FVC measured pre-dose and 5, 15, 30, 60, 90, 120, 180, 240, 300 and 360 min post-dose), and AEs, pulse rate and blood pressure were measured. Theophylline levels were measured if screening levels were >5 μg/mL. Spirometric testing on each test-day started between 7am and 10am. Laboratory tests, physical examination and ECG were repeated on day 85. Patients completed a daily diary card recording morning and evening pre-dose PEFR, study and rescue medication use and asthma symptom scores. Diary cards were reviewed at each visit to determine compliance, changes in concomitant medication and AEs.

### Statistical Analysis

The null hypothesis was that each IB/FEN dose delivered via Respimat® SMI is therapeutically inferior to that delivered by CFC-MDI by at least 0.1L in average $FEV_1$ ($AUC_{0–6h}$) after 12 weeks' treatment. To reject the null hypothesis, i.e. to show that IB/FEN via Respimat® SMI was not inferior to IB/FEN via CFC-MDI by at least 0.1 L, the lower 95% confidence limit for the mean difference (Respimat® SMI - CFC-MDI) would have to lie above –0.1 L at the 2.5% significance level (used rather than 5% as each Respimat® SMI dose was compared separately to CFC-MDI). The choice of 0.1L as the limit value to show inferiority was based on responses observed to IB/FEN via Respimat® SMI and pMDI in previous clinical trials (unpublished data). A sample size of 528 (132 per active treatment and 66 per placebo group) was sufficient to give 80% power to test each null hypothesis of inferiority.

The primary endpoint was evaluated by analysis of covariance (ANCOVA), using country and treatment baseline as the covariates. Secondary analyses were explanatory or confirmatory.

Data from patients for whom the baseline $FEV_1$ preceding the first dose of randomised treatment and at least one post-dose $FEV_1$ were available constituted the intention-to-treat (ITT) population; the per-protocol (PP) population excluded patients with major protocol violations or protocol deviations that potentially obscured treatment response. Primary and secondary efficacy analyses were performed on the PP population; the primary analysis was repeated for the ITT population. All patients in the ITT population were included in the AE summaries.

## Results

Of 866 patients enrolled, 235 were screening failures (most inclusion/exclusion criteria failures). Thus, 631 patients were randomised and received at least one dose of study medication (ITT population). The clinic spirometry PP population consisted of the ITT population minus 49 patients with 70 protocol violations, which were primarily concomitant medication violations (n = 23), and pre-trial or run-in exacerbations (n = 16). In total, 55 (8.7%) patients failed to complete the study: AEs (n = 31), administrative (n = 12, i.e. protocol non-compliance n = 5, lost to follow-up n = 2, withdrawal of consent n = 5) or other reasons (n = 12).

Baseline demographic and pulmonary function characteristics were comparable across treatment groups (table I). Median duration of asthma was 17 years. Average $FEV_1$ was 2.17L or 66% of predicted and the mean $FEV_1$ increase following salbutamol 200μg was 0.53L, or 26% of baseline $FEV_1$. Pulmonary therapies taken within 6 weeks of run-in were comparable between groups. During treatment the use of inhaled corticosteroids, inhaled cromoglycate or nedocromil, and oral xanthines remained relatively stable. Baseline characteristics of the PP population were similar to the ITT dataset.

Median treatment compliance from diary card data was 100%. Two of the five patients who were excluded from the per-protocol dataset for protocol non-compliance had poor treatment compliance (they took zero to two actuations per day over long periods during the 12-week treatment phase).

### Efficacy

#### *Primary Endpoint*

In the PP population, analysis of change in $FEV_1$ ($AUC_{0–6h}$) on day 85 demonstrated that the difference between the adjusted means for Respimat® SMI 20/50 and pMDI 40/100 was 0.016L (lower 2.5% CI −0.0416L; non-inferiority $p < 0.001$). For Respimat® SMI 10/25 and pMDI 40/100, the difference was −0.011L (lower 2.5% CI −0.0699L; non-inferiority $p < 0.002$) [figure 1]. The lower limit of the CI for the treatment difference between pMDI 40/100 and both Respimat® SMI doses being above −0.1L indicates that both Respimat® SMI 10/25 and 20/50 were therapeutically non-inferior to pMDI 40/100. The supportive analysis of the primary endpoint on the clinic spirometry ITT dataset gave comparable results. All active treatment groups displayed similar time-response curves for $FEV_1$ with a rapid onset of action and a peak effect after ~1h (figure 2 and table II).

#### *Secondary Endpoints*

Analysis of change in $FEV_1$ ($AUC_{0–6h}$) on days 1, 29 and 57 mirrored those of the primary analysis on day 85; the values achieved in the three active treatment groups on day 1 were maintained on the other three test-days (figure 3). Respimat® SMI 10/25 and 20/50 were shown to be non-inferior to pMDI 40/100 on all test-days ($p < 0.001$).

There was a negligible difference between the two Respimat® SMI groups and the pMDI 40/100 group in peak $FEV_1$ values achieved (table III); indeed, statistical analyses on all test-days showed both Respimat® SMI doses to be non-inferior to pMDI 40/100 ($p < 0.005$). The peak bronchodilator effect of placebo on all test-days was much less than that of IB/FEN (table III); this peak was also reached consistently later than with IB/FEN (table II). A therapeutic response (increase of 15% in $FEV_1$ from the test-day baseline) could only be measured in the IB/FEN groups; onset and duration were broadly

**Table I.** Demographic and baseline characteristics of intention-to-treat population (mean values unless otherwise indicated)

| Parameter | Respimat® SMI 10μg/25μg (n = 152) | Respimat® SMI 20μg/50μg (n = 161) | pMDI 40μg/100μg (n = 159) | Respimat® SMI placebo (n = 79) | pMDI placebo (n = 80) | Total (n = 631) |
|---|---|---|---|---|---|---|
| Sex [M/F (n)] | 79/73 | 76/85 | 71/88 | 36/43 | 37/43 | 299/332 |
| Age [y (range)] | 42.1 (18–67) | 41.9 (17–70) | 41.6 (19–68) | 41.3 (18–68) | 42.2 (20–66) | 41.8 (17–70) |
| Smoking history (%) | | | | | | |
| never smoked | 53.3 | 56.5 | 56.6 | 58.2 | 60.0 | 56.4 |
| ex-smoker | 46.7 | 43.5 | 43.4 | 41.8 | 38.8 | 43.4 |
| smoker | 0 | 0 | 0 | 0 | 1.3 | 0.2 |
| pack-years (range) | 5.7 (0.4–30) | 6.5 (0.1–36) | 6.0 (0.3–25) | 6.4 (0.5–32) | 6.2 (0.5–10) | 6.1 (0.1–36) |
| Median duration of asthma [y (range)] | 17.0 (0.5–60) | 16.0 (0.08–65) | 16.2 (0.17–65) | 17.3 (0.17–60) | 18.3 (0.08–61) | 17.0 (0.08–65) |
| $FEV_1$ [L] (SD) | 2.20 (0.66) | 2.19 (0.64) | 2.13 (0.61) | 2.11 (0.60) | 2.19 (0.65) | 2.17 (0.63) |
| % predicted $FEV_1$ (SD) | 65 (11) | 66 (11) | 66 (12) | 64 (12) | 66 (11) | 66 (11) |
| $FEV_1$ reversibility [L] (SD) | 0.53 (0.23) | 0.53 (0.28) | 0.52 (0.27) | 0.55 (0.29) | 0.54 (0.28) | 0.53 (0.27) |
| $FEV_1$ reversibility [%] (SD) | 26 (12) | 25 (12) | 26 (13) | 27 (14) | 26 (16) | 26 (13) |
| Pulmonary therapies taken within 6 weeks of run-in (%): | | | | | | |
| inhaled corticosteroids | 84 | 87 | 84 | 90 | 86 | 86 |
| inhaled β-agonists | | | | | | |
| long-acting | 24 | 28 | 35 | 23 | 23 | 28 |
| short-acting | 89 | 81 | 82 | 76 | 83 | 83 |
| oral xanthines | 7 | 9 | 13 | 9 | 13 | 10 |
| others[a] | 0–8 | <1–12 | 0–9 | 0–9 | 0–8 | <1–8 |

a Inhaled anticholinergics, inhaled β-agonists plus inhaled anticholinergics, inhaled cromoglycate and inhaled nedocromil, oral corticosteroids, oral β-agonists, oral antihistamines, leukotriene antagonists.

**F** = female; **$FEV_1$** = forced expiratory volume in 1 second; **M** = male; **pMDI** = pressurised metered-dose inhaler; **SMI** = Soft Mist™ Inhaler.

similar in these three groups (table II). FVC time profiles showed similar trends to those for $FEV_1$ (data not shown).

Diary data showed that morning and evening PEFRs were stable throughout the study in all groups. All groups showed a small increase in rescue medication use during the study compared with baseline (end of the run-in period); this increase was slightly greater with placebo than with active treatment. Night-time symptom scores were slightly lower at the end of the study than at baseline but there was very little difference between treatments. This pattern was repeated for daytime symptoms, although from week 5 until the end of the study, the scores were consistently a little higher in the pMDI PLA group than the other groups.

For those patients who switched from using CFC-MDI during the 2-week run-in to Respimat® SMI in the first 2 weeks of randomised treatment, comparison of morning and evening PEFR and rescue medication use between these two periods did not demonstrate any switch effect.

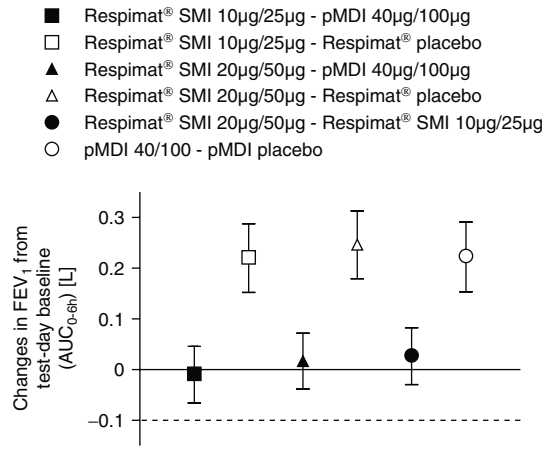


**Fig. 1.** Difference between treatments in bronchodilator response to ipratropium bromide/fenoterol (change in forced expiratory volume in 1 second [$FEV_1$] from test-day baseline on day 85, calculated as the area under the $FEV_1$-time curve between 0 and 6h [$AUC_{0–6h}$]) in adults with asthma. Differences shown (mean and 95% confidence intervals) are those between each Respimat® Soft Mist™ Inhaler (SMI) group and the pressurised metered-dose inhaler (pMDI) group, and are adjusted for country and treatment baseline (pre-dose $FEV_1$ on day 1). Data shown are from the per-protocol population (n = 436, active treatments only). Non-inferiority is proven if the lower confidence limit lies above −0.1L (the value indicated by the horizontal dotted line).

## Safety and Tolerability

The safety profiles of Respimat® SMI 10/25 and 20/50 were comparable to those of pMDI 40/100, Respimat® SMI PLA and pMDI PLA. Overall, the incidence of AEs was slightly higher with Respi-

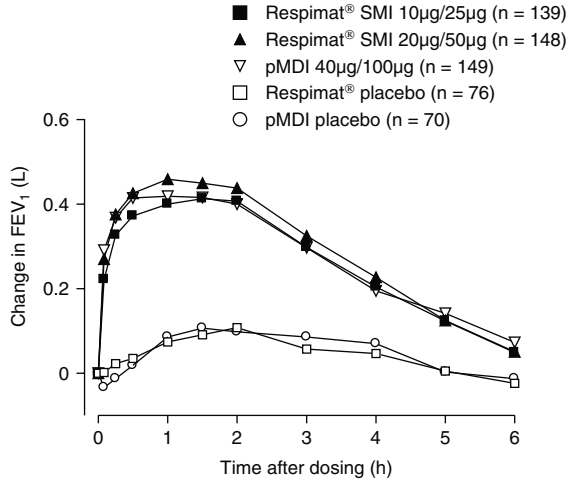


**Fig. 2.** Change in forced expiratory volume in 1 second ($FEV_1$) from test-day baseline over the first 6 hours after dosing with ipratropium bromide/fenoterol or placebo, delivered via Respimat® Soft Mist™ Inhaler (SMI) or pressurised metered-dose inhaler (pMDI) on day 85 in adults with asthma. Data shown are mean values adjusted for country and treatment baseline (pre-dose on day 1) for the per-protocol population (n = 582).

**Table II.** Effects of ipratropium bromide/fenoterol and placebo via Respimat® SMI and CFC-MDI

| Day | Respimat® SMI 10μg/25μg | Respimat® SMI 20μg/50μg | pMDI 40μg/100μg | Respimat® SMI placebo | pMDI placebo |
|---|---|---|---|---|---|
| Median time to peak response (min) | | | | | |
| day 1 | 60 | 90 | 60 | 90 | 90 |
| day 29 | 60 | 60 | 60 | 120 | 120 |
| day 57 | 60 | 60 | 60 | 120 | 90 |
| day 85 | | 60 | 60 | 120 | 90 |
| Median onset of therapeutic response (min) | | | | | |
| day 1 | 14 | 13 | 10 | | |
| day 29 | 18 | 11 | 14 | | |
| day 57 | 22 | 12 | 13 | | |
| day 85 | 18 | 11 | 10 | | |
| Median duration of therapeutic response (min) | | | | | |
| day 1 | 127 | 165 | 138 | | |
| day 29 | 154 | 169 | 108 | | |
| day 57 | 113 | 135 | 117 | | |
| day 85 | 124 | 155 | 124 | | |

**CFC** = chlorofluorocarbon; **pMDI** = pressurised metered-dose inhaler; **SMI** = Soft Mist™ Inhaler.

mat® SMI 10/25 (66.4%) and 20/50 (64.0%) than with pMDI 40/100 (58.5%), Respimat® SMI PLA (58.2%) and pMDI PLA (57.5%). The number of patients reporting any adverse events, and the incidence of the eight most commonly reported events, are shown in table IV.

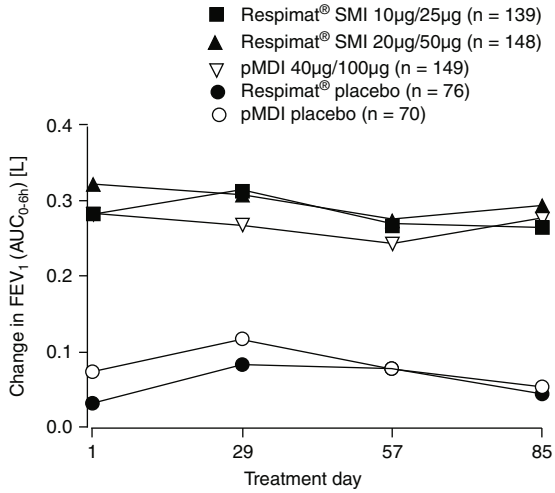


**Fig. 3.** Mean values of $AUC_{0\text{-}6h}$ on the four test-days. $AUC_{0\text{-}6h}$ expresses the average change in forced expiratory volume in 1 second ($FEV_1$) from test-day baseline during the 6 hours after dosing with ipratropium bromide/fenoterol via Respimat® Soft Mist™ Inhaler (SMI) or pressurised metered-dose inhaler (pMDI). Values are adjusted for country and treatment baseline (pre-dose on day 1) for the per-protocol population (n = 582).

Except for headaches and influenza-like symptoms, the most commonly reported AEs (>3% of patients) were associated with the respiratory system. The most common AE in the active treatment groups was asthma exacerbation, which was slightly more frequent in the Respimat® SMI 10/25 and 20/50 groups than in the active pMDI or placebo groups. The frequency of AEs considered to be treatment-related was generally low across all groups (from 3.8% of the pMDI PLA group to 9.3% of the Respimat® SMI 20/50 group). Most AEs were of mild or moderate intensity. A slightly higher incidence of severe AEs (primarily asthma exacerbations) was observed in the Respimat® SMI 20/50 group (11.2%) compared with the four other treatment groups (6.3–7.6%).

A total of 31 patients (4.9%) discontinued treatment because of AEs; for most patients (n = 24) this was because of worsening asthma (Respimat® SMI 10/25, 9; Respimat® SMI 20/50, 7; pMDI 40/100, 5; Respimat® SMI PLA, 1; pMDI PLA, 2); other patients had unexpected worsening of other pre-existing disease (n = 2), or other AEs (5). The incidence of discontinuations because of AEs was

slightly higher in the Respimat® SMI 10/25 (7.2%) and 20/50 groups (6.2%).

Serious AEs occurred in 18 patients (19 events): Respimat® SMI 10/25 (n = 10), Respimat® SMI 20/50 (5), pMDI 40/100 (2) and Respimat® SMI PLA (1). Events were primarily asthma exacerbations (n = 8); other events included: back pain (2), cholecystitis (2), influenza-like symptoms (2) and other events (5). No serious AEs were considered to be related to the study drug and there were no deaths.

The occurrence of a switch effect was also assessed by comparing the change in the incidence of respiratory AEs after patients switched from IB/FEN via CFC-MDI during the run-in to IB/FEN via Respimat® SMI. The incidence of such AEs (especially asthma exacerbations and bronchitis) during the first 14 days of randomised treatment in the two groups receiving IB/FEN via Respimat® SMI was up to twice as high as during the run-in period. However, this 2-fold increase was also seen in the pMDI 40/100 group (in whom no treatment switch had taken place). The incidence of respiratory AEs fell slightly in those who switched to Respimat® SMI PLA, and fell by 75% in those who switched to pMDI PLA. There were no clinically significant differences between groups with regard to vital signs, physical examination or laboratory parameters.

Administration-related bronchoconstriction was not evident in any of the patients taking IB/FEN, but aggravated bronchospasm within 30 minutes of inhalation of study treatment was spontaneously reported in a pMDI PLA recipient.

## Discussion

The aim of this study was to compare the efficacy and safety of IB/FEN delivered from Respimat® SMI with that from a conventional CFC-MDI in patients with asthma. The results showed that, despite a 2- to 4-fold reduction in the nominal dose, IB/FEN delivered from Respimat® SMI was as effective and well tolerated as when delivered from a conventional pMDI.

Since the average therapeutic dosage of IB/FEN via CFC-MDI is 40μg/100μg four times daily, this was chosen for the active control group. Based on the results from dose-ranging,[10,12] cumulative dose-response[15,18] and deposition studies,[8,9] the dosages chosen for the two Respimat® SMI treatment arms were a quarter and a half of the pMDI dosage. Indeed, Respimat® SMI allows effective treatment with only one actuation compared with two with the CFC-MDI. Although the currently marketed pMDI formulation of IB/FEN is used "as required" for the treatment of asthma, our study used a continuous administration regimen to evaluate the safety of the new formulation in more detail, given that in everyday practice some patients might use the product in this way if their symptoms became more severe. The use of this regimen is not intended as an endorsement of continuous therapy with IB/FEN for patients with asthma. However, because the bronchodilator response seen on day 1 was maintained after 12 weeks' continuous therapy with IB/FEN, there is no evidence that any tolerance to the effect of this combination of drugs occurs.

Results from the analysis of the primary efficacy endpoint clearly demonstrated that both Respimat® SMI 10/25 and 20/50 were therapeutically non-in-

**Table III.** Adjusted[a] mean peak increase in forced expiratory volume in 1 second from test-day baseline on all four test-days (L). Comparison of ipratropium bromide/fenoterol and placebo via Respimat® SMI and CFC-MDI

| Day | Respimat® SMI 10μg/25μg | Respimat® SMI 20μg/50μg | pMDI 40μg/100μg | Respimat® SMI placebo | pMDI placebo |
|---|---|---|---|---|---|
| 1 | 0.519 | 0.559 | 0.520 | 0.207 | 0.253 |
| 29 | 0.537 | 0.540 | 0.518 | 0.244 | 0.283 |
| 57 | 0.496 | 0.503 | 0.482 | 0.230 | 0.247 |
| 85 | 0.498 | 0.521 | 0.506 | 0.215 | 0.240 |

a Adjusted for pooled country and treatment baseline.

**CFC** = chlorofluorocarbon; **pMDI** = pressurised metered-dose inhaler; **SMI** = Soft Mist™ Inhaler.

**Table IV.** Number of patients reporting adverse events (AEs) during randomised treatment with ipratropium bromide (IB) plus fenoterol (FEN) via Respimat® Soft Mist™ Inhaler (SMI) or chlorofluorocarbon metered-dose inhaler (CFC-MDI) in adults with asthma (safety population; n = 631). The "most common AEs" were defined as those reported by >3% of patients in at least one treatment group. AEs were described by the WHO preferred term

| No. of patients (and % of total) reporting at least one AE | IB/FEN 10μg/25μg via Respimat® SMI (n = 152) | IB/FEN 20μg/50μg via Respimat® SMI (n = 161) | IB/FEN 40μg/100μg via CFC-MDI (n = 159) | Placebo via Respimat® SMI (n = 79) | Placebo via CFC-MDI (n = 80) |
|---|---|---|---|---|---|
| **Total with any adverse event** | **101 (66.4)** | **103 (64.0)** | **93 (58.5)** | **46 (58.2)** | **46 (57.5)** |
| Most common AEs | | | | | |
| asthma exacerbation | 31 (20.4) | 26 (16.1) | 19 (11.9) | 3 (3.8) | 10 (12.5) |
| upper respiratory tract infection | 17 (11.2) | 16 (9.9) | 13 (8.2) | 11 (13.9) | 11 (13.8) |
| headache | 11 (7.2) | 11 (6.8) | 17 (10.7) | 14 (17.7) | 13 (16.3) |
| influenza-like symptoms | 6 (3.9) | 8 (5.0) | 11 (6.9) | 5 (6.3) | 8 (10.0) |
| rhinitis | 10 (6.6) | 14 (8.7) | 8 (5.0) | 5 (6.3) | 1 (1.3) |
| bronchitis | 12 (7.9) | 8 (5.0) | 9 (5.7) | 5 (6.3) | 3 (3.8) |
| dyspnoea | 9 (5.9) | 9 (5.6) | 12 (7.5) | 2 (2.5) | 3 (3.8) |
| pharyngitis | 4 (2.6) | 4 (2.5) | 5 (3.1) | 6 (7.6) | 1 (1.3) |

ferior to pMDI 40/100. This conclusion was supported by the results for the secondary efficacy parameters. These results build on those of dose-ranging studies in patients with asthma.[12,19] Thus, Maesen et al. found that fenoterol 12.5 and 25μg administered via Respimat® SMI were therapeutically equivalent to 100μg delivered via CFC-MDI.[19] Goldberg et al. showed that, although therapeutic equivalence could not be demonstrated statistically, the two single doses administered via Respimat® SMI that came closest to therapeutic equivalence to IB/FEN 40/100 via CFC-MDI were IB/FEN 5/12.5 and 10/25.[12]

The design of the study could have been improved by including a second (lower) dose level for the CFC-MDI, as the 40μg/100μg dosage might have been on the plateau of the dose-response curve, and half this dosage delivered from the CFC-MDI might have been equally effective. However, when comparing the delivery of a single dose of IB/FEN 40μg/100μg from the CFC-MDI with that from the new HFA-MDI in patients with asthma, Maesen and co-workers showed not only that the two devices were therapeutically equivalent, but that a dose-response relationship was evident from 20μg/50μg to 80μg/200μg via HFA-MDI.[20] In addition, in the study by Goldberg et al., a dose-response relationship ($FEV_1$ [$AUC_{0–6h}$]) was demonstrated across the range of IB/FEN doses delivered by Respimat® SMI up to a dose of 80μg/200μg.[12] The 40μg/100μg dosage level for the CFC-MDI treatment arm was chosen because this is the most commonly used bronchodilator dose in practice. The aim of our study was to confirm the trend established in earlier studies on IB and FEN (either alone or in combination), i.e. that a patient can obtain the same bronchodilator efficacy as from the pMDI 40μg/100μg dosage by delivering a half or a quarter of this dosage via Respimat® SMI.

Overall, the tolerability and safety profile of IB/FEN when delivered via Respimat® SMI was comparable to that when delivered via CFC-MDI. The safety profiles of IB and FEN (alone and in combination) delivered via Respimat® SMI in dose-ranging and cumulative-dose studies in asthma patients

are very similar to those seen when these drugs are delivered via pMDIs[11,15] and in longer-term studies in patients with COPD.[21,22] The incidence of all adverse events, and of asthma exacerbations, was higher in the Respimat® SMI active treatment groups, and this may have been responsible for the higher discontinuation rate in these groups. However, it is not possible to conclude that the differences in incidence seen in our study represent a real difference in tolerability between drug delivered via the new device and via CFC-MDI. Because of the small number of patients in this study, there was insufficient power to detect clinically significant differences between treatment groups in the overall incidence of AEs, and the incidence of specific AEs such as asthma exacerbation, or discontinuation rates; no such statistical analysis was therefore done. In two studies similar to ours, in which the effect of IB/FEN in these two devices was compared in patients with COPD and in children with asthma,[22,23] no differences in tolerability were shown. The Respimat® SMI formulation contains a stabilising agent (ethylene diamine tetra-acetic acid) and a preservative (benzalkonium chloride), which have been reported to cause bronchoconstriction when administered separately,[24-26] albeit at much larger doses than that contained in a single actuation from Respimat® SMI. In our study, no patient receiving active or placebo treatment via Respimat® SMI reported any event that indicated administration-related bronchoconstriction.

Concern has been expressed over possible adverse effects of changing the propellant/formulation in inhalers, the so-called 'switch' effect. A comparison of the first 2 weeks' randomised treatment versus run-in showed no reductions of morning or evening PEFR or increases in rescue medication use when patients were changed from a CFC-MDI to propellant-free Respimat® SMI. The increase in respiratory AEs in the two groups who received IB/FEN via Respimat® SMI cannot be explained by a switch effect, since the incidence also increased in those who were randomised to pMDI 40/100, and fell slightly in those who were randomised to placebo via Respimat® SMI. A possible reason for the increased incidence in the three active treatment groups is that according to the study protocol, patients who developed exacerbations during run-in were excluded from the randomised treatment period and also from the analysis of any switch effect.

## Conclusion

In conclusion, these results demonstrated that IB/FEN 10μg/25μg and 20μg/50μg administered four times daily via Respimat® SMI produced bronchodilator responses comparable to that achieved with 40μg/100μg four times daily via a CFC-MDI. Hence, Respimat® SMI enables a 2- to 4-fold reduction of the daily dosage of IB/FEN without loss of therapeutic efficacy and with a similar safety profile. Respimat® SMI may therefore be a useful alternative to pMDIs for the administration of inhaled drug therapy in asthma.

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