Respiratory Medicine (2004) **98**, 387–397

respiratoryMEDICINE

Improved delivery of ipratropium bromide/fenoterol from Respimat® Soft Mist™ Inhaler in patients with COPD

S.A. Kilfeather[a,*], H.H. Ponitz[b], E. Beck[c], P. Schmidt[d], A. Lee[e], I. Bowen[f], Ch. Hesse[g]

[a]*Aeirtec Research Unit, Aeirtec Ltd., Bioscience Building, Times Square, Newcastle Upon Tyne, UK*
[b]*Berlin, Germany*
[c]*Rüdersdorf, Germany*
[d]*Boehringer Ingelheim Austria GmbH, Vienna, Austria*
[e]*Boehringer Ingelheim Ltd, Bracknell, UK*
[f]*Lostwithiel, Cornwall, UK*
[g]*University of Graz, Austria*

Received 5 June 2003; accepted 28 December 2003

KEYWORDS
COPD;
Bronchodilators;
Fenoterol;
Ipratropium;
Respimat®;
Soft Mist™ Inhaler

Summary We performed a multicentre, randomised, double-blind (within-device), placebo- and active-controlled, parallel-group study to compare the efficacy and safety of ipratropium bromide plus fenoterol hydrobromide (IB/FEN; Berodual®) delivered via the novel, propellant-free Respimat® Soft Mist™ Inhaler (SMI) and from a chlorofluorocarbon (CFC)-metered-dose inhaler (MDI) in moderate-to-severe chronic obstructive pulmonary disease (COPD) patients.

After 2-weeks' run-in (CFC-MDI [IB 20 μg /FEN 50 μg per actuation] two actuations q.i.d. [MDI 40/100]), 892 patients were randomised to Respimat® SMI containing IB 10 μg/FEN 25 μg (Respimat® SMI 10/25), IB 20 μg/FEN 50 μg (Respimat® SMI 20/50) or placebo (one actuation q.i.d.), or a CFC-MDI containing IB 20 μg/FEN 50 μg (MDI 40/100) or placebo (two actuations q.i.d.) for 12 weeks.

Analysis of the primary endpoint (change in forced expiratory volume in 1 s [FEV_1] in the first 60 min after dosing [area under the curve; $AUC_{0-1\,h}$]) on day 85 showed that the efficacy of Respimat® SMI 20/50 (but not Respimat® SMI 10/25) was not inferior to that of MDI 40/100. The safety profile of Respimat® SMI was comparable to CFC-MDI. Switching from MDI 40/100 to Respimat® SMI was well tolerated. Respimat® SMI enables a 50% reduction of the nominal inhaled dose of IB/FEN in COPD patients while offering similar therapeutic efficacy and safety to the CFC-MDI.

Introduction

Globally, chronic obstructive pulmonary disease (COPD) is estimated to have been the cause of 2.66 million deaths in all WHO regions in 1999[1] COPD is also the ''fastest growing cause of death in the world's advanced economies''.[2]

*Corresponding author. Tel.: +44-191-241-6630; fax: +44-191-243-8201.
E-mail address: skilfeather@aeirtec.co.uk (S.A. Kilfeather).

0954-6111/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.rmed.2003.12.007

Although COPD is characterised by airflow obstruction which is largely non-reversible, bronchodilators are widely recommended to prevent or reduce symptoms in patients with the disease, and inhalation is the preferred route of administration of these agents.[3–6] In stable COPD, the combination of a short-acting β-agonist and the anticholinergic ipratropium bromide (IB) achieves greater and more sustained improvements in forced expiratory volume in 1 s (FEV_1) than either agent alone.[5] Furthermore, the combination of the β_2-agonist fenoterol hydrobromide (FEN) with IB has been shown to provide effective bronchodilation in COPD.[7] The fixed combination of IB and FEN (Berodual®; Boehringer Ingelheim GmbH) has been available as a metered-dose inhaler (MDI) for the treatment of COPD in a number of countries for many years.

Although MDIs are the most commonly used devices for inhaled drug administration in respiratory diseases, many patients use them incorrectly.[8,9] In one study of COPD patients, 40% performed some essential inhaler manoeuvres incorrectly;[10] if inhaler technique is poor, significant amounts of medication may fail to reach the lungs and hence disease control will be suboptimal. This may result in the prescribing of higher doses and additional drugs, thereby increasing drug costs. Thus, there are medical and economic needs for improved inhaler devices.

Respimat® Soft Mist™ inhaler (SMI) is a novel, propellant-free multidose inhaler with a unique delivery mechanism that uses the energy released from a tensioned spring to force a pre-defined metered volume of drug solution through an innovative nozzle array (the uniblock); these components are illustrated in Fig. 1. This mechanism produces a very fine aerosol for inhalation (the soft mist). Respimat® SMI is easy to use, with the patient simply having to twist the base of the device 180°, press the dose-release button, and inhale the soft mist. The medication is provided as a solution in a cartridge that is inserted into the device before first use. Each cartridge contains 120 actuations. Respimat® SMI generates a slow-moving cloud with a fine particle fraction of 66%;[11–13] this value is approximately 2.5 times that for MDIs.[12] These characteristics together with a relatively long duration of dose release (approximately 1.2 s)[13] significantly reduce oropharyngeal and increase lung deposition compared with chlorofluorocarbon- (CFC) and hydrofluoroalkane-(HFA) MDIs[14–16] and may also reduce the need for hand–lung co-ordination.

The aim of this study was to show whether the more efficient delivery of a bronchodilator via Respimat® SMI seen in deposition studies is borne out in a large-scale clinical trial, so allowing a smaller dosage to be given via Respimat® SMI to achieve the same efficacy seen with CFC-MDI. This was done by comparing the efficacy and safety in COPD patients of IB/FEN delivered from Respimat® SMI (at a dosage of 10 μg IB/25 μg FEN per actuation or 20/50 μg per actuation; one actuation q.i.d.) and a CFC-MDI at a dosage of 40/100 μg (taken as two actuations of 20/50 μg each) q.i.d. The 40/100 μg q.i.d. MDI dosage was chosen because it has been established as the standard therapeutic dosage for maintenance therapy of COPD in practice. Smaller dosages were chosen for the two Respimat® SMI groups (one-quarter and one-half of the usual therapeutic dosage) on the strength of the results from dose-ranging and dose–response studies of

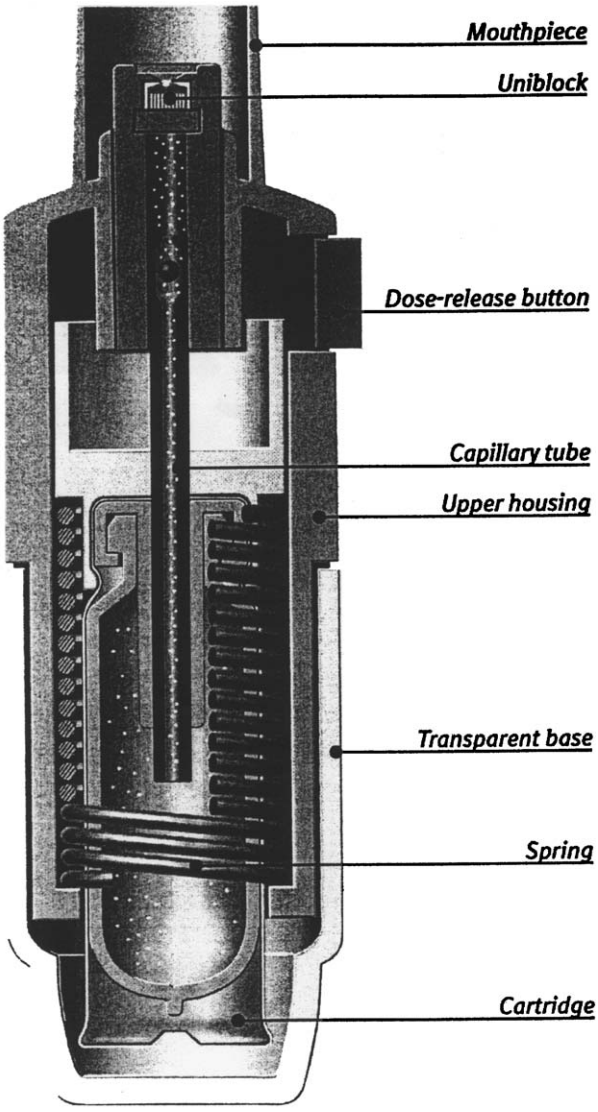

Figure 1 Sectional diagram of Respimat® SMI™, showing the main components of the device.

IB/FEN in asthma patients[17,18] and in corresponding studies of IB alone in COPD patients.[19,20]

Patients and methods

Patients

Patients aged $\geqslant$40 years were eligible for inclusion if they had a diagnosis of COPD, as indicated by $FEV_1 \leqslant 65\%$ of predicted normal[21] and FEV_1/FVC (forced vital capacity) $\leqslant 70\%$ at screening, and a smoking history of >10 pack-years. Exclusion criteria included: a history of clinically significant diseases other than COPD; recent upper or lower respiratory tract infection (RTI); history of asthma, allergic rhinitis or atopy, or blood eosinophil count $>600/mm^3$. The use of β-adrenergic and anticholinergic bronchodilators (short or long-acting) as concomitant medication was not allowed during the study, except as rescue medication (salbutamol only). Other drugs that were not allowed during the study were β-blockers, oral corticosteroids at a dosage of >10 mg prednisolone/day or its equivalent (except for the treatment of COPD exacerbations), antihistamines, anti-leukotrienes, sodium cromoglycate, nedocromil sodium, and chronic oxygen therapy.

Theophylline was permitted, as were stable doses of inhaled and low-dose oral corticosteroids. Appropriate washout periods for bronchodilators were used before pulmonary function tests.

Study design

This multicentre, randomised, double-blind (within-device), parallel group, placebo- and active-controlled study was conducted in 92 centres in the UK, Germany and Austria between February 1998 and April 1999. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The local Ethics Committee or Institutional Review Board for each centre approved the protocol and all patients gave written informed consent.

During the 2-week run-in period, all patients received Berodual® CFC-MDI (IB 20 μg/FEN 50 μg per actuation) two actuations q.i.d. Patients who experienced a COPD exacerbation during this period were not eligible for inclusion into the study. The remaining patients were randomised to one of five treatments for 12 weeks:

- Respimat® SMI IB 10 μg/FEN 25 μg, one actuation q.i.d.,
- Respimat® SMI IB 20 μg/FEN 50 μg, one actuation q.i.d.,
- CFC-MDI IB 20 μg/FEN 50 μg per actuation, two actuations q.i.d. (MDI 40/100),
- Respimat® SMI placebo, one actuation q.i.d., or,
- CFC-MDI placebo, two actuations q.i.d.

Patients were randomised in blocks of eight in a 2:2:2:1:1 ratio. Treatment was open-label for devices and double-blind for the IB/FEN dose, i.e. active and placebo CFC-MDIs were of identical appearance and active and placebo Respimat® SMI devices were of identical appearance. A double-dummy technique was not used because inhalation of excipients from both devices would have made it impossible to assess any switch effect or the incidence of adverse events (AEs) caused by the excipients of either device. Patients were trained in the use of both inhaler devices at the screening visit before the run-in period. Salbutamol CFC-MDI 100 μg per actuation prn was used as rescue medication.

Assessments

Schedule of assessments

The study consisted of five clinic visits: a screening visit (Visit 1) followed by a 2-week run-in, and then Visits 2–5 on days 1, 29, 57 and 85. At Visit 1, demographic data were recorded and patients provided a medical history (previous 5 years) and underwent a physical examination (including blood pressure and pulse rate), pulmonary function tests (baseline FEV_1 and FVC and testing for reversibility to 200 μg salbutamol via CFC-MDI), electrocardiogram (ECG), clinical laboratory parameters, and training in the use of study inhalers. At Visits 2–5, FEV_1, FVC, pulse rate and blood pressure were recorded pre-dose and 5, 15, 30, 60 min post-dose. At Visit 2, pulmonary function testing started between 7.00 and 10.00 a.m., and at subsequent visits, testing started within 30 min of the actual start time at Visit 2, to minimise the influence of diurnal pulmonary variation. All AEs that occurred during the study were recorded. Laboratory tests, physical examination and ECG were repeated on day 85. Patients completed a daily diary card on which they recorded morning and evening peak expiratory flow rate (PEFR), study and rescue medication use and COPD symptom scores.

Efficacy parameters

The primary efficacy endpoint was the change from pre-dose in FEV_1 in the first 60 min after dosing, calculated as the area under the FEV_1-time curve between 0 and 1 h ($AUC_{0-1\,h}$) on day 85.

The secondary efficacy endpoints were: change in FEV_1 ($AUC_{0-1\,h}$) on days 1, 29 and 57; total FEV_1 calculated as the AUC between 0 and 1 h ($TAUC_{0-1\,h}$) on day 85; the peak FEV_1 achieved in the first 60 min after dosing on days 1 and 85 (measured as the change from the pre-dose value); FVC on all test-days (days 1, 29, 57 and 85), and the weekly mean values of (a) pre-dose morning and evening PEFR, (b) total daily inhaled rescue medication, and (c) day and night-time symptom scores. Symptoms were scored on a scale from 0 (no symptoms) to 4. For night-time symptom score, 4 represented waking $\geqslant$4 times per night, and for the daytime score, it represented symptoms that prevented the patient attending work and engaging in all normal activities.

Safety

Safety variables recorded included: AEs; blood pressure and pulse rate on test-days; 12-lead ECG, clinical laboratory parameters (haematology, biochemistry and urinalysis), and physical examination at screening and at the end of the study. The effect of switching from CFC-MDI to Respimat® SMI was assessed by comparing morning and evening PEFR, respiratory symptoms, rescue medication use and respiratory AEs in the first 2 weeks of randomised treatment with the corresponding values during the last week of the run-in (or, in the case of respiratory AEs, during both weeks of the run-in).

Statistical analysis

Statistical analyses were specified in the trial protocol before the study began. The primary efficacy objective was to demonstrate that at least one of the two doses of IB/FEN via Respimat® SMI gave a bronchodilatory response that was non-inferior to (i.e. equivalent to or better than) that obtained from IB/FEN via CFC-MDI. To do this, the null hypothesis was that each dose of IB/FEN via Respimat® SMI was therapeutically inferior to that delivered by CFC-MDI (as measured by the change in FEV_1 in the first 60 min after dosing ($AUC_{0-1\,h}$) on day 85) by a margin of at least 0.05 L. The alternative hypothesis, i.e. that IB/FEN Respimat® SMI was not inferior to IB/FEN CFC-MDI (using the same 0.05 L margin) would be proven if the lower 95% confidence limit (CL) for the mean difference (Respimat® SMI minus CFC-MDI) lay above -0.05 L at the 2.5% level (used rather than 5%, as each dose via Respimat® SMI was compared separately to the CFC-MDI).

A sample of 182 patients per active treatment group would give a power of approximately 80% to conclude that either IB/FEN dose delivered via Respimat® SMI was not inferior to IB/FEN delivered via the MDI at the 2.5% level of significance, allowing for two primary endpoint comparisons, given that the formulations were equal. Placebo groups were to include half as many patients as active treatment groups, giving a total of 728 patients.

The primary endpoint was evaluated by analysis of covariance (ANCOVA), including the factors country and treatment with baseline at Visit 2 (day 1) as covariate.

Data from patients who received at least one dose of randomised treatment, and for whom the pre-dose FEV_1 preceding the first dose of randomised treatment and at least one post-dose FEV_1 was available, constituted the clinic spirometry intention-to-treat (ITT) population; the clinic spirometry per-protocol (PP) population excluded those patients with major protocol violations or protocol deviations that potentially obscured treatment response. Primary and secondary efficacy analyses of all spirometry data were performed on the clinic spirometry PP population, and confirmatory analyses done on the clinic spirometry ITT population. Patients without major protocol violations and who had at least 4 days morning (or evening) PEFR data for both run-in and randomised treatment periods constituted the diary morning (or evening) PEFR PP population. All randomised and treated patients (the safety population) were included in AE summaries.

Results

Patients

Of 1117 patients enrolled, 225 were not entered (mainly because of failure to fulfil inclusion/exclusion criteria). The remaining 892 patients were randomised to treatment (safety population; Table 1). As two randomised patients had missing pre-dose pulmonary function test data on day 1, the clinic spirometry ITT population consisted of 890 patients. A total of 54 patients from this population had serious protocol violations, which were mainly those affecting Visit 2 (concomitant medication violations, exacerbations of COPD, or upper or lower RTIs) and elevated eosinophil counts. The remaining patients ($n = 836$) constituted the clinic spirometry PP population. The

Table 1 Patient disposition.

Population	Respimat® SMI 10/25	Respimat® SMI 20/50	MDI 40/100	Respimat® SMI placebo	MDI placebo	Total
Enrolled						1117
Entered and treated (safety population)	217	224	220	114	117	892
Clinic spirometry ITT	216	224	220	114	116	890
Clinic spirometry PP	202	208	209	106	111	836
Prematurely discontinued (%)	36 (16.6)	41 (18.3)	39 (17.7)	23 (20.2)	19 (16.2)	158 (17.7)

SMI: Soft Mist™ Inhaler; MDI: metered-dose inhaler; ITT: intention-to-treat; PP: per-protocol.

diary morning PEFR PP population contained 790 patients and its evening counterpart 786. In total, 158 (17.7%) patients discontinued the trial prematurely, due to: AEs ($n = 112$), administrative reasons ($n = 37$); non-compliance with protocol ($n = 12$), loss to follow-up ($n = 9$), withdrawal of consent ($n = 16$) or other reasons ($n = 9$). The proportion of withdrawals was comparable across treatment groups.

Baseline and demographic characteristics were generally comparable across treatment groups (Tables 2 and 3). The median duration of COPD was 8 years and all patients were either current or ex-smokers. Pulmonary function measurements were also comparable across groups with the exception of a slight imbalance in reversibility to salbutamol at screening: increase in FEV_1 30 min after salbutamol 200 μg was greater in the MDI 40/100 group than in other groups. Overall, the mean FEV_1 was 1.16 L, with a mean % of predicted normal FEV_1 of 41% and mean FEV_1/FVC ratio of 56%. The range of severity of airflow limitation, using the GOLD classification[5] is shown in Table 3. Pulmonary therapies taken during the 6 weeks before the run-in were also comparable across treatment groups, except that slightly fewer Respimat® SMI 10/25 and Respimat® SMI 20/50 patients were on inhaled corticosteroids while slightly more Respimat® SMI 20/50 patients were receiving oral corticosteroids (14% vs. overall mean of 11%). During randomised treatment the use of inhaled corticosteroids and oral xanthines remained fairly stable; however, the use of oral corticosteroids increased due to the treatment of COPD exacerbations, which were an exclusion criterion during the run-in period and before study enrolment. Baseline characteristics for the clinic spirometry PP population were similar to the clinic spirometry ITT population.

Efficacy

Primary endpoint

Analysis of the primary endpoint (change from pre-dose in FEV_1 [$AUC_{0-1\,h}$] in the first 60 min after dosing on day 85) in the clinic spirometry PP population showed that the difference between the mean values for Respimat® SMI 20/50 and MDI 40/100 was only 0.001 L (lower 2.5% CL −0.0323 L). As the lower CL for this difference was greater than −0.05 L, Respimat® SMI 20/50 was shown to be non-inferior to MDI 40/100 ($P = 0.0013$). Non-inferiority was not demonstrated for Respimat® SMI 10/25 vs. MDI 40/100, as the treatment difference was −0.020 L with a lower 2.5% CL of −0.053 L. These results are shown graphically in Fig. 2. The supportive analysis of the primary endpoint on the clinic spirometry ITT population produced comparable results.

Time–response curves for change in FEV_1 in the first 60 min after dosing on day 85 showed that the responses to IB/FEN in the three active treatment groups were similar, and superior to the responses in the two placebo groups (Fig. 3).

Secondary endpoints

The results for the change in FEV_1 in the first 60 min after dosing on day 1 ($AUC_{0-1\,h}$) mirrored those of the analysis of the primary endpoint on day 85; non-inferiority to MDI 40/100 was demonstrated for Respimat® SMI 20/50, but not for Respimat® SMI 10/25. For days 29 and 57, however, non-inferiority to MDI could not be shown for either Respimat® SMI dose.

Results for the remaining secondary endpoints, namely FEV_1 ($TAUC_{0-1\,h}$) on day 85, peak FEV_1 achieved in the first 60 min after dosing on days 1 and 85 (measured as the change from the pre-dose

Table 2 Demographic and baseline characteristics of all randomised patients (safety population; mean values unless otherwise indicated).

Characteristic	Respimat® SMI 10/25 ($n=217$)	Respimat® SMI 20/50 ($n=224$)	MDI 40/100 ($n=220$)	Respimat® SMI placebo ($n=114$)	MDI placebo ($n=117$)	Total ($n=892$)
Sex M/F (N)	151/66	163/61	161/59	85/29	76/41	636/256
Age*, years (range)	63.1 (38–87)	62.7 (29–83)	62.8 (37–83)	64.9 (28–84)	64.4 (40–88)	63.3 (28–88)
Smoking history (%)						
Ex-smoker	54	55	57	59	56	56
Smoker	47	46	43	41	44	44
Pack years (range)	39.3 (10–200)	36.0 (10–96)	37.4 (10–114)	36.0 (8–102)	36.4 (10–99)	37.2 (8–200)
Median duration of COPD, years (range)†	9.0 (0–48)	9.0 (0–50)	7.0 (0–36)	9.5 (1–50)	8.0 (1–50)	8.0 (0–50)
FEV_1, (L) (SD)	1.16 (0.42)	1.17 (0.44)	1.15 (0.46)	1.14 (0.39)	1.14 (0.43)	1.16 (0.43)
% Predicted FEV_1 (SD)	42 (13)	41 (13)	40 (13)	41 (13)	42 (13)	41 (13)
FEV_1 increase at 30 min (%) (SD)	15 (16)	16 (21)	20 (20)	14 (15)	16 (18)	17 (19)
Number (n and %) of patients with FEV_1 reversibility of $\geqslant 15\%$§	90 (41)	93 (42)	111 (51)	44 (39)	53 (46)	391 (44)
FEV_1/FVC (%) (SD)	55 (11)	56 (11)	55 (11)	56 (12)	56 (11)	56 (11)
Pulmonary therapies taken during the 6 weeks before run-in (% patients)						
Inhaled glucocorticoids	63	64	72	75	69	68
Oral glucocorticoids	9	14	10	12	11	11
Short-acting inhaled β-agonists	50	52	53	52	54	52
Long-acting inhaled β-agonists	13	16	18	21	21	17
Anticholinergics	17	12	14	11	13	14
β-agonist/anticholinergic combination	37	33	37	35	27	35
Oral xanthines	38	39	33	38	33	36

SMI: Soft Mist™ Inhaler; MDI: metered-dose inhaler; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SD: standard deviation.

*Inclusion of patients below the age of 40 years was a protocol violation.

†0 represents <6 months' duration.

§Post-bronchodilator FEV_1 missing for five patients.

Table 3 Categorisation of all randomised patients (safety population, $n = 892$) according to extent of airflow limitation (baseline FEV_1 as % predicted) using the GOLD classification (5).

	Number of patients in each stage (%)				
	Respimat® SMI 10/25 ($n = 217$)	Respimat® SMI 20/50 ($n = 224$)	MDI 40/100 ($n = 220$)	Respimat® SMI placebo ($n = 114$)	MDI placebo ($n = 117$)
Mild (Stage I)	2 (0.9)	2 (0.9)	1 (0.5)	2 (1.8)	0 (0)
Moderate (Stage IIa)	86 (39.6)	86 (38.4)	88 (40.0)	41 (36.0)	52 (44.4)
Moderate (Stage IIb)	102 (47.0)	104 (46.4)	96 (43.6)	53 (46.5)	52 (44.4)
Severe (Stage III)	27 (12.4)	31 (13.8)	33 (15.0)	17 (14.9)	12 (10.3)
Unclassified	0 (0)	1 (0.5)	2 (0.9)	1 (0.9)	1 (0.9)

FEV_1: forced expiratory volume in 1 s; MDI: metered-dose inhaler; SMI: Soft Mist™ Inhaler.

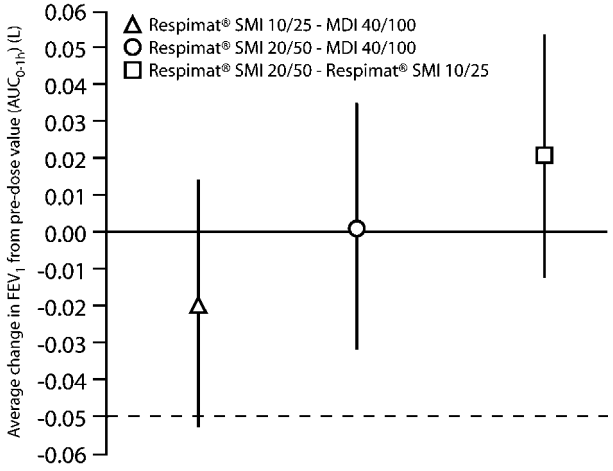

Figure 2 Difference between treatments in bronchodilator response to ipratropium bromide/fenoterol (change in forced expiratory volume in 1 s (FEV_1) from pre-dose value expressed as area under the curve ($AUC_{0-1\,h}$)) during the first 60 min after dosing on day 85 in adults with chronic obstructive pulmonary disease (COPD). Differences shown (mean and 95% confidence intervals) are those between each Respimat® Soft Mist™ Inhaler (SMI) group and the metered-dose inhaler (MDI) group, and between the two Respimat® SMI groups, and are adjusted for country and treatment baseline (pre-dose on day 1). Data shown are from clinic spirometry per-protocol population ($n = 619$, active treatments only).

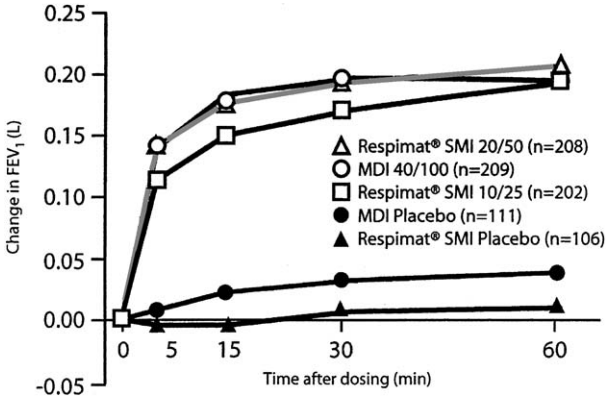

Figure 3 Change in forced expiratory volume in 1 s (FEV_1) from pre-dose value in first 60 min after dosing on day 85, adjusted for country and treatment baseline (pre-dose on day 1). Data shown are from clinic spirometry per-protocol population ($n = 836$). SMI, Soft Mist™ Inhaler; MDI, metered-dose inhaler.

value) and FVC on all test-days, confirmed the analysis of the primary endpoint. All FEV_1 and FVC analyses showed a trend to higher bronchodilator response for Respimat® SMI 20/50 compared with Respimat® SMI 10/25, with consistently higher point estimates for the higher Respimat® SMI dose.

There were small improvements in morning and evening PEFR during the study for most treatment groups except for evening PEFR in the two placebo groups (Figs. 4 and 5). There was little difference between groups for either daytime or night-time symptom scores or rescue medication use.

Safety and tolerability

The safety profile of Respimat® SMI 10/25 and Respimat® SMI 20/50 was comparable to that of MDI 40/100. The most commonly reported AEs were associated with the respiratory system (Table 4). COPD exacerbation was the most common event in all groups and was slightly more frequent in the Respimat® SMI 20/50 group (27%) than in other groups (18–21%). Dyspnoea was less frequent in the Respimat® SMI groups (7.8% and 7.6%) than in the other groups (9.4–12.3%). Coughing was reported less frequently in the Respimat® SMI 20/50 group than in the Respimat® SMI 10/25 and MDI 40/100

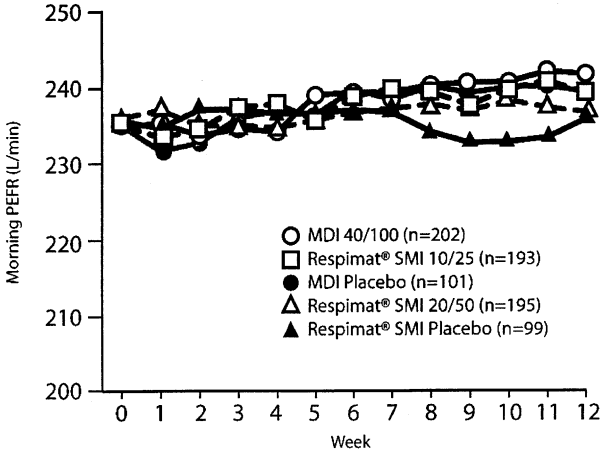

Figure 4 Mean weekly morning pre-dose peak expiratory flow rates (PEFR) adjusted for country and treatment baseline (run-in week). Run-in week is the last week before the first dose of randomised treatment; data shown are from diary morning PEFR per-protocol population ($n = 790$). MDI = metered-dose inhaler; SMI = Soft Mist™ Inhaler.

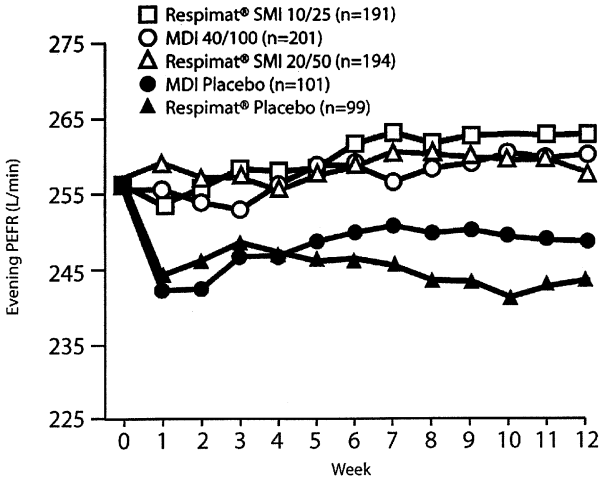

Figure 5 Mean weekly evening pre-dose peak expiratory flow rates (PEFR) adjusted for country and treatment baseline (run-in week). Run-in week is the last week before the first dose of randomised treatment; data shown are from diary evening PEFR per-protocol population ($n = 786$). SMI = Soft Mist™ Inhaler; MDI = metered-dose inhaler.

groups. There were fairly similar incidences of upper RTI and urinary tract infections across the treatment groups. Incidences of all other AEs were low across all groups (<3%).

A total of 112 (13%) patients discontinued randomised treatment because of AEs; worsening of COPD was reported by 82 patients, worsening of other pre-existing disease by 6, and other AEs by 24. The number of patients who discontinued treatment because of AEs was similar across treatment groups (range 10.0–15.8%).

A total of 63 (7.1%) patients reported serious adverse events (SAEs) during randomised treatment. The most frequent SAE was COPD exacerbation ($n = 24$), which occurred more often in active treatment groups (Respimat® SMI 10/25, 2.3%; Respimat® SMI 20/50, 4.9%; MDI 40/100, 2.7%) than placebo groups (0.9% in both). Three patients in the Respimat® SMI 20/50 group and one in the MDI 40/100 group developed pneumonia. All other SAEs occurred in no more than one or two patients per treatment group. Five patients who developed SAEs died, but none of these events were considered to be related to the trial drug.

There were no clinically relevant differences across treatment groups regarding effects on vital signs or changes in laboratory parameters, ECG and physical examinations. There were no spontaneous reports of paradoxical or administration-related bronchoconstriction during the study.

The comparison of the first 2 weeks of randomised treatment with the last week of the run-in period showed the absence of any switch effect for either active Respimat® SMI treatment as measured by morning and evening PEFR and symptom scores. However, an increase in rescue medication use was observed during the first 2 weeks of randomised treatment compared with the last week of the run-in, across all treatment groups. On average, patients in the Respimat® SMI 10/25 and Respimat® SMI 20/50 groups used slightly less rescue medication than the other groups. There was a significant increase in the incidence of all respiratory AEs (mainly COPD exacerbations, bronchitis and dyspnoea) during the first 2 weeks of randomised treatment compared with the 2 run-in weeks in all treatment groups, except Respimat® SMI 10/25.

Discussion

The aim of the present study was to compare the efficacy and safety of IB/FEN (Berodual®) delivered from Respimat® SMI and a CFC-MDI in COPD patients. The efficacy of both Respimat® SMI 10/25 and Respimat® SMI 20/50 were superior to placebo, and Respimat® SMI 20/50 was non-inferior to MDI 40/100. Thus, since the safety and tolerability of Respimat® SMI 20/50 and Respimat® SMI 10/25 were shown to be very similar to that of MDI 40/100, delivery via Respimat® SMI enables a 50% reduction in the nominal dose of IB/FEN in this patient population compared with the MDI. This is

Table 4 Number of patients reporting adverse events (AEs) (%) during randomised treatment with ipratropium bromide plus fenoterol via Respimat® SMI™ or CFC-MDI or matching placebos in the safety population ($n = 892$). The "most common AEs" are defined as those reported by >3% of patients in at least one group and events are described by WHO preferred term.

Number of patients (and % of total) reporting at least one adverse event	Respimat® SMI 10/25 ($n = 217$)	Respimat® SMI 20/50 ($n = 224$)	MDI 40/100 ($n = 220$)	Respimat® SMI placebo ($n = 114$)	MDI placebo ($n = 117$)
Total with any adverse event	122 (56)	125 (56)	115 (52)	57 (50)	57 (49)
Most common AEs:					
COPD exacerbation	44 (20.3)	60 (26.8)	46 (20.9)	22 (19.3)	21 (17.9)
Dyspnoea	17 (7.8)	17 (7.6)	24 (10.9)	14 (12.3)	11 (9.4)
URTI	15 (6.9)	13 (5.8)	9 (4.1)	7 (6.1)	3 (2.6)
Coughing	12 (5.5)	7 (3.1)	13 (5.9)	4 (3.5)	3 (2.6)
UTI	7 (3.2)	5 (2.2)	2 (0.9)	3 (2.6)	3 (2.6)

CFC: chlorofluorocarbon; MDI: metered-dose inhaler; FEV_1: forced expiratory volume in 1 s; URTI: upper respiratory tract infection; UTI: urinary tract infection.

consistent with the results of deposition studies which have shown that the proportion of drug deposited in the lung after inhalation from Respimat® SMI is much greater than that delivered from a MDI.[14–16]

The analysis of the primary endpoint on day 85 showed that the efficacy of Respimat® SMI 20/50 (but not Respimat® SMI 10/25) was not inferior to that of MDI 40/100. Except for the change in FEV_1 ($AUC_{0–1\,h}$) on days 29 and 57, analyses of secondary endpoints supported the non-inferiority of the Respimat® SMI 20/50 dose compared with the MDI 40/100 group. The pre-specified analyses of the primary endpoint used a very strict definition of non-inferiority, i.e. the lower 95% CL for the difference between treatments had to be above −0.05 L. However, had a slightly less strict inferiority margin been used, i.e. −0.06 L, then Respimat® SMI 20/50 would have been shown to be non-inferior to MDI 40/100 on all four test-days, as the mean differences between treatments were all above −0.05 L. Furthermore, a trend towards a higher bronchodilator response for Respimat® SMI 20/50 compared with Respimat® SMI 10/25 was observed with consistently higher point estimates for the higher Respimat® SMI dose. These observations appear to make the Respimat® SMI 20/50 dose a rational choice.

The choice of dosage for the MDI treatment arm was made because 40/100 μg q.i.d. via CFC-MDI has been established as the optimal dosage of IB/FEN for maintenance therapy in COPD patients in clinical practice. 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. We have already mentioned that the aim of this study was to prove the principle that a patient can obtain the same bronchodilator efficacy as from the currently used MDI dosage by delivering a half or a quarter of this dosage via Respimat® SMI. It is possible that the findings of our study could have been strengthened if a second CFC-MDI arm (20/50 μg q.i.d.) had been included, in case the 40/100 μg q.i.d. dosage was on the plateau of the dose–response curve. However, the results of all the FEV_1 and FVC analyses in the current study showed a trend in favour of a higher bronchodilator response for IB/FEN 20/50 μg via Respimat® SMI than for IB/FEN 10/25 μg. Furthermore, the results of the study by Kunkel and colleagues in asthma patients[18] showed that when a cumulative dose of IB/FEN 320/800 μg was given via Respimat® SMI and MDI, the bronchodilator response was significantly greater via Respimat® SMI, and a dose of only half this size from Respimat® SMI (160/400 μg) gave equivalent bronchodilation to 320/800 μg via MDI.

The results of the present study confirm the results of initial dose-ranging studies that demonstrate that, when delivered by Respimat® SMI, IB in COPD patients,[19] FEN in asthma patients[22] and an IB/FEN combination in asthma patients[17] are just as efficacious as when delivered via CFC-MDI but at a smaller dose. Another cumulative dose–response study has also shown that Respimat® SMI improves the delivery of IB compared with MDIs in patients with COPD,[20] providing a significantly greater bronchodilator effect, at half the dose given via MDI, from 45 min after the first dose of the series to 45 min after the final dose. The efficacy results of the present study are also consistent with results of 12-week studies of Respimat® SMI containing

IB/FEN or IB alone in adults with COPD or asthma. In a study of IB/FEN in adult asthma patients, the change in FEV_1 ($AUC_{0-6\,h}$) from test-day baseline on day 85 demonstrated that both Respimat® SMI doses (20 μg IB/50 μg FEN and 10 μg IB/25 μg FEN) were non-inferior to the CFC-MDI 40 μg IB/100 μg FEN.[23] In a study of IB alone in COPD patients which used the same outcome measure, IB doses of 20 and 40 μg q.i.d. delivered by Respimat® SMI were also shown to be therapeutically non-inferior to IB 40 μg q.i.d. delivered via a conventional CFC-MDI.[24]

Overall, the safety profiles of both Respimat® SMI 20/50 and Respimat® SMI 10/25 are comparable to that of MDI 40/100. This confirms previous observations of comparable safety profiles for Respimat® SMI and CFC-MDIs for the delivery of IB in COPD patients.[20,24] In the current study, the incidences of AEs and withdrawals were similar between treatment groups. The higher incidence of COPD exacerbations in the Respimat® SMI 20/50 group is a surprising result which has not been found in any of the other studies in the Respimat® SMI clinical development programme. It was probably a chance occurrence, although one contributing factor may have been that a greater proportion of patients in this treatment group received oral corticosteroids before the study, implying that more of the patients in this group were prone to exacerbations.

Concern has been expressed over any possible adverse effects of changing the propellant or formulation in inhaler devices, the so-called 'switch effect'. A number of parameters were measured to assess any switch effects. A comparison of the first 2 weeks' randomised treatment vs. the two-week run-in period showed no switch effect for either of the active Respimat® SMI treatments as assessed by morning or evening PEFR or symptom scores. There was, however, an increase in respiratory AEs (COPD exacerbations, dyspnoea and bronchitis) compared with the run-in period across all treatment groups, except Respimat® SMI 10/25. There was also an increase in rescue medication use in all groups, although this was less pronounced in the Respimat® SMI 20/50 and Respimat® SMI 10/25 groups. The increase in respiratory AEs and the associated increase in rescue medication use may be explained by the fact that patients who developed COPD exacerbations were withdrawn from the study if these occurred during the run-in period, but not if they occurred after randomisation.

The inclusion and exclusion criteria used in this study were chosen to ensure as far as possible that the patients enrolled were a representative group of COPD patients. Patients had to be at least 40 years old, have a diagnosis of COPD ($FEV_1 \leqslant 65\%$ predicted and $FEV_1/FVC \leqslant 70\%$ at screening), and have a smoking history of >10 pack-years. Patients were excluded if they had a history of asthma, allergic rhinitis or atopy, a raised eosinophil count, or were on antihistamines, leukotriene modifiers or cromones. Reversibility of airflow obstruction was measured at baseline to better characterise the study population, but it was not used as an inclusion or exclusion criterion, and patients were not stratified at randomisation according the degree of reversibility. A little less than half of the patients had FEV_1 reversibility of 15% or more, suggesting an asthmatic component to their disease. If we had tested our hypothesis separately on the two subgroups of patients either side of the 15% reversibility threshold, we might have been able to show whether our results were affected by the presence of this asthmatic component. This was not done however, as the size of the subgroups would have given insufficient statistical power to detect a treatment difference at the chosen level of significance.

In conclusion, Respimat® SMI enables a 50% reduction of the nominal daily dose of IB/FEN in COPD patients while offering similar therapeutic efficacy and safety to the corresponding CFC-MDI. Furthermore, each individual dose was delivered from Respimat® SMI in just one actuation, rather than the two actuations needed with the CFC-MDI. Respimat® SMI thus has the potential to be a useful alternative to MDIs for the delivery of inhaled drugs to this patient population.

Acknowledgements

We thank all investigators in Austria, Germany and the UK who participated in the study. The study was sponsored by Boehringer Ingelheim.

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