REVIEW ARTICLE

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A Review of Ipratropium Bromide/ Fenoterol Hydrobromide (Berodual®) Delivered Via Respimat® Soft Mist™ Inhaler in Patients with Asthma and Chronic Obstructive Pulmonary Disease

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) can be effectively treated by the use of bronchodilator therapies delivered by inhalation. Berodual® is a fixed combination of the anticholinergic agent ipratropium bromide (IB) and the β_2-adrenergic agonist fenoterol hydrobromide (FEN). IB/FEN has been available for the treatment of asthma and COPD in a pressurised metered dose inhaler (MDI) [pMDI] formulation for many years.

The pMDI is the most widely used device for the delivery of inhaled medications, such as IB/FEN. However, most conventional pMDIs contain chlorofluorocarbon (CFC) propellants, which are currently being withdrawn because of their detrimental effects on the environment. This has resulted in alternative methods of drug delivery being developed. Respimat® Soft Mist™ Inhaler (SMI) is a new generation, propellant-free inhaler that generates a fine, slow-moving cloud (the

Soft Mist™) which can be easily inhaled. Scintigraphic studies have shown that this improves deposition of drugs in the lung and results in less oropharyngeal deposition than the CFC-MDI.

A clinical development programme has been conducted to compare the efficacy and safety of IB/FEN delivered via Respimat® SMI with that of IB/FEN via CFC-MDI in the treatment of patients with asthma or COPD. Five clinical studies (two phase II and three phase III) investigated dosages of IB/FEN 5/12.5μg to 320/800μg via Respimat® SMI in single and multiple dose administration regimens. Four of the trials were conducted in patients with asthma (three in adults and one in children), while one phase III trial was conducted in patients with COPD. In phase III, 2058 patients participated, with a total of 1112 patients treated with IB/FEN via Respimat® SMI. In the phase III studies, each dose from Respimat® SMI was given in one actuation compared with two actuations with the CFC-MDI. In the paediatric asthma phase III study, all CFC-MDI doses were delivered via a spacer device.

The results of the trials demonstrated that IB/FEN via Respimat® SMI allows a reduction in the nominal dose of IB/FEN, while offering similar therapeutic efficacy and safety to a CFC-MDI. In children, Respimat® SMI obviates the need for a spacer.

Bronchodilators are an important component of treatment for patients with asthma or chronic obstructive pulmonary disease (COPD). In common with other drugs used in the treatment of these diseases, delivery via the inhaled route is preferred and is supported by international guidelines.[1-5] The inhaled route has a number of advantages over other routes of administration, the primary one being the direct delivery of the drug to the site of action, thus enabling lower dosages to be used. Furthermore, the onset of action of the drug is usually faster than when given via other routes of administration and systemic adverse effects are generally reduced.[6]

The efficacy of inhaled drugs depends upon both the site of deposition and the amount of drug delivered. These, in turn, are influenced by many factors, including the patient, the disease, the characteristics of the aerosol and the mode of inhalation. The efficacy of inhalation therapy will be markedly influenced by the type of delivery device used[6] and the ability of the patient to use the device properly (inhaler technique). Of the range of inhaler devices available, the conventional chlorofluorocarbon (CFC) pressurised metered dose inhaler (MDI) [CFC-MDI] is the most widely used.[7,8] Pressurised MDIs (pMDIs) are patient-friendly and have a high market appeal. Unfortunately, they also have serious disadvantages, the most important of which is that only a small proportion of inhaled drug from a pMDI actually reaches the lung.[9,10] The very rapid expulsion of the aerosol from the pMDI makes it difficult for patients to coordinate inhalation with actuation, although coordination is easier when the pMDI is used with a spacer. Furthermore, pMDIs containing CFCs as propellants cause environmental damage and, for this reason, they are being withdrawn and replaced by pMDIs based on alternative propellants such as hydrofluoroalkanes. Consequently, recent emphasis in inhalation device technology has been on developing environmentally friendly devices with improved delivery characteristics. Dry powder inhalers (DPIs) are breath-actuated devices that may improve lung deposition of drugs and, for many patients, are easier to use than pMDIs. However, delivery of drug into the airways from some DPIs depends on the ability of a patient to

generate the necessary inspiratory flow.[6] Respimat® [1] Soft Mist™ Inhaler (SMI) is a novel, propellant-free inhaler developed to improve the lung deposition of inhaled drug compared with that achieved with pMDIs or DPIs.

The purpose of this article is to review the clinical performance of Respimat® SMI in delivering a combination of two bronchodilators, ipratropium bromide (IB) and fenoterol hydrobromide (FEN) [Berodual®; Boehringer-Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany], in adult patients with asthma or COPD, and in children with asthma. Comparisons of efficacy and safety are made with conventional CFC-MDIs containing the same combination. This is a review of five studies (two phase II and three phase III) performed as part of the clinical development programme for IB/FEN via Respimat® SMI. Berodual® Respimat® was launched in Germany in January 2004.

1. Synopsis of Clinical Studies

An international clinical development programme was conducted for IB/FEN delivered via Respimat® SMI, with clinical trials carried out in Germany, the UK, The Netherlands, Belgium, South Africa, Austria and France.

Five clinical studies have been completed: two in phase II and three in phase III. In phase II, dose-ranging and cumulative dose studies were conducted in adult patients with asthma;[8,11] the phase III programme consisted of two trials in asthma patients (one in adults and one in children)[12,13] and one in patients with COPD.[14] All trials compared a range of dosages of IB/FEN via Respimat® SMI with conventional doses of IB/FEN via CFC-MDI, using the same IB:FEN dose ratio in Respimat® SMI (2 : 5) as in the CFC-MDI.

1.1 Clinical Efficacy

1.1.1 Asthma

Phase II Studies

In the dose-ranging study, 62 eligible patients were randomised to receive five out of the following eight possible single dose treatments according to a crossover design: IB/FEN doses of 5/12.5, 10/25, 20/50, 40/100 or 80/200μg delivered via Respimat® SMI; IB/FEN doses of 20/50 or 40/100μg delivered using a conventional CFC-MDI; and placebo.[11] Pulmonary function was evaluated by measuring the change in forced expiratory volume in 1 second (FEV_1) from baseline at regular intervals during the 6 hours following administration of the test drug. The primary endpoint was the average increase in FEV_1 from baseline over the 6-hour period after dose administration, expressed as the area under the concentration-time curve (FEV_1AUC_{6h}). A log-linear dose-response relationship was demonstrated for the five doses delivered via Respimat® SMI (figure 1). Comparison between devices did not demon-

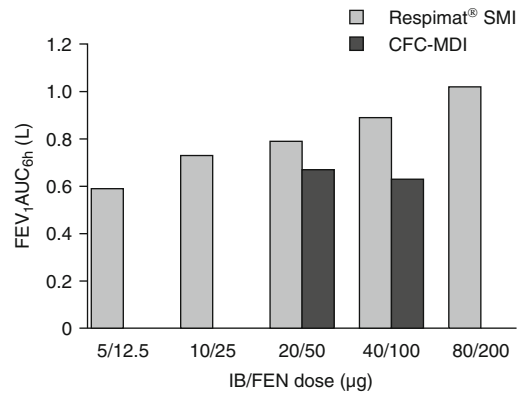

Fig. 1. Dose response of mean increase in forced expiratory volume in 1 second (FEV_1) over a 6-hour period after dose administration (FEV_1AUC_{6h}) in 47 patients with asthma who received a single dose of ipratropium bromide/fenoterol hydrobromide (IB/FEN) via Respimat® Soft Mist™ Inhaler (SMI; five dose levels) or chlorofluorocarbon metered-dose inhaler (CFC-MDI; two dose levels). Difference between largest and smallest dose via Respimat® SMI was significant (0.42L, 95% CI 0.25, 0.59L; p = 0.0001).[11] **AUC_{6h}** = area under the concentration-time curve from 0 to 6 hours.

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

strate therapeutic equivalence between any IB/FEN dose administered via Respimat® SMI and the conventional dose via CFC-MDI (40/100µg). Indeed, the mean FEV_1AUC_{6h} for four of five Respimat® SMI doses was greater than that obtained with the 40/100µg dose from the CFC-MDI, and for three of these doses (20/50, 40/100 and 80/200µg via Respimat® SMI) this difference was statistically significant at $\alpha = 0.1$ (two-sided). The mean FEV_1AUC_{6h} for the smallest Respimat® SMI dose (5/12.5µg) was slightly less than the CFC-MDI value, but this difference was not statistically significant. These results indicated that IB/FEN could be given at a considerably lower dose (at least four times less) when delivered via Respimat® SMI than by CFC-MDI, without compromising efficacy in single dose studies.

Kunkel et al.[8] set out to establish the cumulative dose of IB/FEN via Respimat® SMI that would produce bronchodilator activity equivalent to that of a cumulative dose of 320/800µg delivered by a conventional CFC-MDI. In a randomised, four-way crossover design, 43 patients with asthma received cumulative doses of IB/FEN over a 200-minute period from each of four devices in turn. The primary endpoint of the study was the average increase in FEV_1 from baseline between 45 and 245 minutes after the first inhalation. Cumulative doses of 160/400 and 320/400µg via Respimat® SMI produced bronchodilation equivalent to that achieved with a cumulative dose of 320/800µg via CFC-MDI; equivalence comparisons are shown in figure 2. When comparing identical cumulative doses from each device (i.e. IB/FEN 320/800µg), the bronchodilatory response to IB/FEN was significantly greater with Respimat® SMI than the CFC-MDI. The authors concluded that IB/FEN via Respimat® SMI was as effective as the CFC-MDI, but at half the cumulative dose.[8]

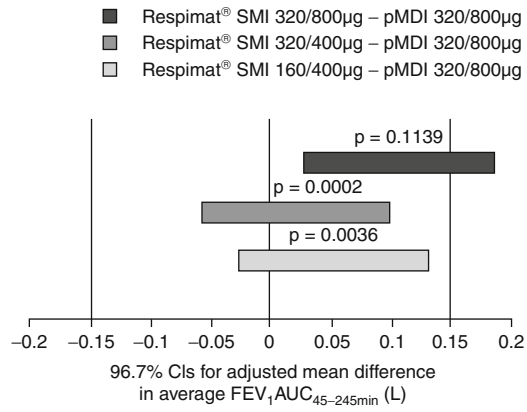

Fig. 2. Differences in bronchodilator responses to cumulative doses of ipratropium bromide/fenoterol hydrobromide (IB/FEN) delivered via Respimat® Soft Mist™ Inhaler (SMI) or conventional pressurised metered-dose inhaler (pMDI) in 43 asthma patients. Bronchodilation was measured as adjusted mean increase from baseline in forced expiratory volume in 1 second (FEV_1) between 45 and 245 minutes after the start of dose administration ($FEV_1AUC_{45–245min}$). Results shown are 96.7% CIs around the adjusted mean differences in $FEV_1AUC_{45–245min}$ between three different doses of IB/FEN via Respimat® SMI and IB/FEN 320/800µg via pMDI (reproduced from Kunkel et al.,[8] with permission from S. Karger AG, Basel).

Phase III Studies

On the basis of the results of these phase II studies, two dosages of IB/FEN Respimat® SMI were used for the two phase III trials in patients with asthma: 10/25 and 20/50µg given three or four times a day, depending on the study protocol. In both these trials (and the one in patients with COPD, see section 1.1.2), each dose from Respimat® SMI was always administered as a single actuation, whereas each dose from the CFC-MDI was administered as two actuations. In the phase III trials, 1166 patients with asthma were recruited (631 adults and 535 children). Of these patients, 671 (313 adults and 358 children) received IB/FEN via Respimat® SMI.

Vincken et al.[12] aimed to demonstrate that at least one of the two dosages of IB/FEN (10/25 and 20/50µg; one actuation four times daily) delivered via Respimat® SMI would produce a bronchodilator effect that was non-inferior to that produced by the conventional dose of IB/FEN (two actuations of 20/50µg [40/100µg] four times daily) administered via CFC-MDI.[12] Following randomisation, 631 adult patients with asthma were treated for 12 weeks with one of the aforementioned treatments or with placebo administered via Respimat® SMI or CFC-MDI.

The primary efficacy endpoint was the average change from pre-dose in FEV_1 over the 6 hours after dose administration on test day 85, calculated as the AUC_{6h}.

Analysis of the primary endpoint in the per-protocol population of 582 patients (49 patients were excluded because of protocol violations) demonstrated that both IB/FEN 10/25 and 20/50μg four times daily via Respimat® SMI were non-inferior to IB/FEN 40/100μg four times daily via CFC-MDI (table I). Time-response curves for FEV_1 were similar in all active treatment groups, with the peak effect reached after approximately 1 hour. Analysis of secondary efficacy endpoints, such as the average change in FEV_1 from pre-dose on days 1, 29 and 57, gave results similar to those for the primary endpoint (on day 85) [figure 3a]. As previously identified in the study by Goldberg et al.,[11] a dose-response relationship for IB/FEN was observed, with a higher bronchodilator response to 20/50μg four times daily via Respimat® SMI than for 10/25μg four times daily. The authors concluded that delivery via Respimat® SMI instead of a CFC-MDI allows a 2- to 4-fold reduction in the nominal dosage of IB/FEN, while producing similar efficacy to the CFC-MDI.[12]

Similar findings have been reported in the phase III paediatric study, where the bronchodilator response to IB/FEN via Respimat® SMI was compared with that obtained with IB/FEN administered via CFC-MDI plus Aerochamber® in 535 children with asthma.[13] After a 2-week run-in period, during which all patients received IB/FEN via CFC-MDI plus Aerochamber® (40/100μg three times daily), patients were randomised to one of the following three treatments, each given three times daily for 4 weeks: IB/FEN 10/25μg via Respimat® SMI; IB/FEN 20/50μg via Respimat® SMI; or IB/FEN 40/100μg via CFC-MDI plus Aerochamber®. The primary endpoint was the average change in FEV_1, compared with pre-dose, in the first 60 minutes after dose administration on the final day (day 29) of the study period, calculated as the FEV_1AUC_{1h}. Efficacy was assessed in the per-protocol population of 461 patients.

After 4 weeks of treatment, IB/FEN via Respimat® SMI (both dosages) showed comparable efficacy to IB/FEN 40/100μg via pMDI plus Aerochamber® (table II). Time-response curves for FEV_1 on day 29 showed similar bronchodilation profiles for all three active treatment groups, with a rapid onset of action followed by further increases in FEV_1 up to the last timepoint of 1 hour. Changes in FEV_1 in the first hour after dose administration on days 1 and 15 were similar to those on day 29. Both dosages of IB/FEN via Respimat® SMI demonstrated non-inferiority to IB/FEN 40/100μg via CFC-MDI plus Aerochamber®. These results confirm that in children with asthma, the use of Respimat® SMI instead of CFC-MDI plus spacer enables the daily

Table I. Mean change in forced expiratory volume in 1 second (FEV_1) over a 6-hour period after dose administration (FEV_1AUC_{6h}) on day 85 in 582 asthma patients treated for 12 weeks with ipratropium bromide/fenoterol hydrobromide (IB/FEN) or placebo, delivered via Respimat® Soft Mist™ Inhaler (SMI) or pressurised metered dose inhaler (pMDI). All doses were given four times per day. Respimat® SMI treatments are non-inferior to pMDI if the lower 95% CI for the difference is greater than −0.1L[12]

	Respimat® SMI			pMDI	
	IB/FEN 10/25μg	IB/FEN 20/50μg	placebo	IB/FEN 40/100μg	placebo
Number of patients	139	148	76	149	70
Mean FEV_1AUC_{6h} (L) [±SE]	0.266 ± 0.023	0.293 ± 0.022	0.047 ± 0.029	0.276 ± 0.022	0.054 ± 0.030
Difference[a] (Respimat® SMI − pMDI) [L]					
mean	−0.011	0.016			
lower 95% CI	−0.070	−0.042			
p-value	0.002	<0.001			

a Adjusted for country and treatment baseline.

AUC_{6h} = area under the concentration-time curve from 0 to 6 hours; **SE** = standard error.

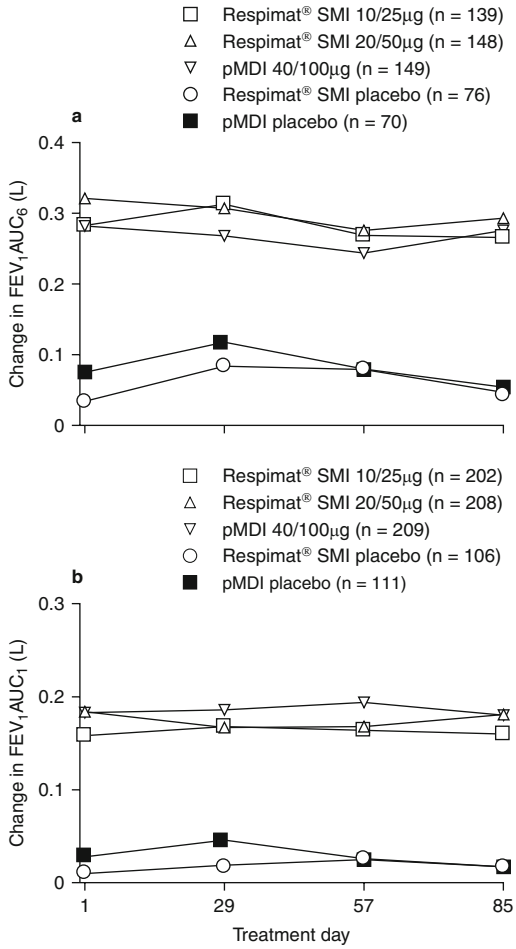

Fig. 3. Mean change in forced expiratory volume in 1 second (FEV_1) over a specified time period after dose administration on days 1, 29, 57 and 85, in 582 asthma patients (**a**)[12] and 836 patients with chronic obstructive pulmonary disease (COPD) (**b**)[14] treated for 12 weeks with ipratropium bromide/fenoterol hydrobromide (IB/FEN) or placebo, delivered via Respimat® Soft Mist™ Inhaler (SMI) or pressurised metered dose inhaler (pMDI). Changes shown are over 6 hours (asthma; FEV_1AUC_{6h}) and 1 hour (COPD; FEV_1AUC_{1h}). All doses taken four times daily. The results shown are from tests on the day concerned. **AUC_{Xh}** = area under the concentration-time curve from 0 to **X** hours

dosage of IB/FEN to be reduced by a factor of two or more, while providing similar therapeutic efficacy.[13]

1.1.2 Chronic Obstructive Pulmonary Disease

The third pivotal phase III trial was performed in 892 adult patients with moderate-to-severe COPD,[14] using similar methodology to the phase III asthma study described in the previous section.[12] Patients aged ≥40 years were eligible for inclusion if they had a diagnosis of COPD, as indicated by FEV_1 ≤65% of predicted normal and FEV_1/forced vital capacity (FVC) ≤70% at screening, and a smoking history of >10 pack-years. Patients were randomised to one of five treatment regimens for 12 weeks. The primary efficacy endpoint was the average change from pre-dose in FEV_1 over the first hour after dose administration on day 85 of treatment (calculated as the FEV_1AUC_{1h}).

The bronchodilator response to IB/FEN on day 85 in the per-protocol population showed that 20/50μg four times daily via Respimat® SMI was not inferior to 40/100μg four times daily via CFC-MDI (table III). The day 85 result was chosen as the primary endpoint because it tested for significant differences at the end of the pre-specified 12 weeks' treatment and is consistent with regulatory needs. For Respimat® SMI to be proved non-inferior, the lower 95% CI for the difference between the mean FEV_1AUC_{1h} measurements in each treatment arm had to be above −0.05L (the day 85 result was −0.0323L). The study failed by a narrow margin to demonstrate that IB/FEN 10/25μg four times daily via Respimat® SMI was also non-inferior to IB/FEN 40/100μg four times daily via CFC-MDI on day 85 (lower 95% CI −0.0532L). The average change in FEV_1 from pre-dose on all test days is shown in figure 3b and, as in the adult and paediatric asthma studies, time-response curves for FEV_1 on the final test day showed similar profiles for all active treatment groups (figure 4). The results for FEV_1AUC_{1h} on day 1 mirrored those of the analysis of the primary endpoint on day 85; non-inferiority to 40/100μg four times daily via CFC-MDI was demonstrated for 20/50μg four times daily via Respimat® SMI, but not for 10/25μg four times daily via Respimat® SMI. For test days 29 and 57, non-inferiority to CFC-MDI could not be shown for either Respimat® SMI dosage, although the margins of failure were very narrow; the lower 95% CIs for 20/50μg

Table II. Mean change in forced expiratory volume in 1 second (FEV_1) over the first hour after dose administration (FEV_1AUC_{1h}) on day 29 in 461 children with asthma, treated for 4 weeks with ipratropium bromide/fenoterol hydrobromide (IB/FEN) delivered via Respimat® Soft Mist™ Inhaler (SMI) or pressurised metered dose inhaler (pMDI) plus spacer. All doses were given three times per day. Respimat® SMI treatments are non-inferior to pMDI if the lower 95% CI for the difference is greater than −0.075L[13]

	Respimat® SMI		pMDI plus spacer
	IB/FEN 10/25μg	IB/FEN 20/50μg	IB/FEN 40/100μg
Number of patients	153	154	154
Mean FEV_1AUC_{1h} (L) [±SE]	0.189 ± 0.016	0.238 ± 0.016	0.215 ± 0.016
Difference[a] (Respimat® SMI − pMDI) [L]			
mean	−0.016	0.017	
lower 95% CI	−0.054	−0.022	
p-value	0.001	<0.001	

a Adjusted for country and treatment baseline.

four times daily were −0.0536L (day 29) and −0.0599L (day 57), and for 10/25μg four times daily, −0.0526L and −0.0643L, respectively.[14]

Results for the other secondary endpoints, such as FVC on all test days, confirmed the analysis of the primary endpoint. All FEV_1 analyses also showed a trend towards a higher bronchodilator response to IB/FEN 20/50μg four times daily via Respimat® SMI than for the 10/25μg four times daily dosage via Respimat® SMI.[14]

Thus, in COPD patients, IB/FEN via Respimat® SMI can be administered at half the dosage administered via CFC-MDI without any loss of efficacy, resembling the trend seen in both the phase III asthma studies.

1.2 Tolerability and Safety

In both the phase II and III studies all treatments were well tolerated and had comparable safety profiles.

In the phase II studies, no clinically relevant changes on physical examination or in vital signs, laboratory parameters or ECG were observed.[8,11] The adverse event profile for IB/FEN via Respimat® SMI was similar to that of IB/FEN via CFC-MDI. Most adverse events were mild or moderate in intensity. In one of the studies,[8] the 320/800μg dose of IB/FEN via Respimat® SMI was associated with a slightly higher incidence of adverse effects resulting from β_2-adrenergic stimulation and cholinergic blockade (headache, nervousness and tremor) than the same dose via CFC-MDI. This was prob-

Table III. Mean change in forced expiratory volume in 1 second (FEV_1) over the first hour after dose administration (FEV_1AUC_{1h}) on day 85 in 836 chronic obstructive pulmonary disease patients treated for 12 weeks with ipratropium bromide/fenoterol hydrobromide (IB/FEN) or placebo, delivered via Respimat® Soft Mist™ Inhaler (SMI) or pressurised metered dose inhaler (pMDI). All doses were given four times per day. Respimat® SMI treatments are non-inferior to pMDI if the lower 95% CI for the difference is greater than −0.05L[14]

	Respimat® SMI			pMDI	
	IB/FEN 10/25μg	IB/FEN 20/50μg	placebo	IB/FEN 40/100μg	placebo
Number of patients	202	208	106	209	111
Mean FEV_1AUC_{1h} (L) [±SE]	0.160 ± 0.013	0.181 ± 0.013	0.006 ± 0.017	0.180 ± 0.013	0.027 ± 0.017
Difference[a] (Respimat® SMI − CFC-MDI) [L]					
mean	−0.020	0.001			
lower 95% CI	−0.053	−0.032			
p-value	0.038	0.001			

a Adjusted for country and treatment baseline.

CFC = chlorofluorocarbon.

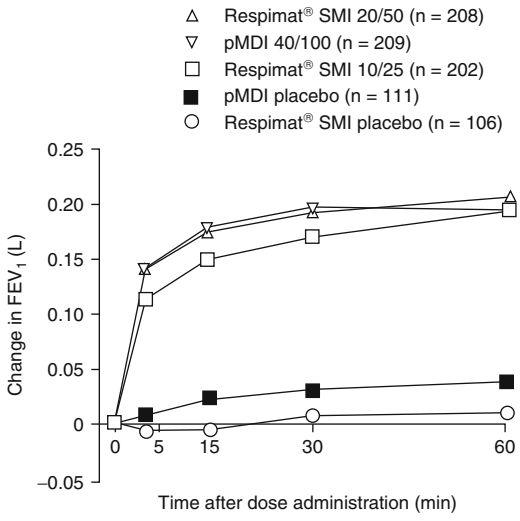

Fig. 4. Mean change in forced expiratory volume in 1 second (FEV_1) over the first hour after dose administration on day 85 in 836 patients with chronic obstructive pulmonary disease treated for 12 weeks with ipratropium bromide/fenoterol hydrobromide (IB/FEN) or placebo, delivered via Respimat® Soft Mist™ Inhaler (SMI) or pressurised metered dose inhaler (pMDI) [reproduced from Kilfeather et al.,[14] with permission from Elsevier].

ably due to the greater drug delivery to the lungs achieved with Respimat® SMI compared with the CFC-MDI.

In the phase III studies, the safety profiles of IB/FEN 10/25 and 20/50μg via Respimat® SMI were comparable with that of IB/FEN 40/100μg via CFC-MDI taken at the same frequency.[12-14] The overall adverse event profile from the three phase III studies is shown in table IV and table V. The frequency of adverse events considered to be treatment related was generally low across all groups; most of these were associated with the respiratory system and were of mild or moderate intensity. There were no reports of paradoxical bronchoconstriction in any of the 966 asthma and COPD patients treated with IB/FEN delivered via Respimat® SMI.[15]

In the three phase III studies, the effect of switching from CFC-MDI to Respimat® SMI was assessed by comparing morning and evening peak expiratory flow rate, respiratory symptoms and adverse events, and rescue medication use in the first 2 weeks of the treatment period and the last week of the run-in. No changes were seen that would indicate that patients reacted adversely to the change from one formulation to the other.

2. Discussion

Inhaled bronchodilators are widely recommended for the treatment of asthma and COPD. IB induces bronchodilatation through blockade of muscarinic cholinergic receptors (it is selective for muscarinic rather than nicotinic receptors). FEN is a relatively selective β_2-adrenergic agonist, indicated for the symptomatic treatment of acute asthma episodes and prophylaxis of exercise-induced asthma. Both IB and FEN are indicated for the symptomatic treatment of airway narrowing in patients with COPD or bronchial asthma.[16,17]

International guidelines for the management of COPD[4,18] state that greater bronchodilator efficacy can be obtained by using a combination of a short-acting β_2-adrenergic agonist and an anticholinergic. Hence, a single combination product containing an anticholinergic and a β_2-adrenergic agonist, such as IB/FEN, should be considered for those patients requiring more than one bronchodilator to control their symptoms. The fixed combination of IB/FEN has been available in a CFC-MDI formulation (IB/FEN 20/50μg per actuation) for the treatment of asthma in both adults[19,20] and children[21,22] for many years. Several studies have shown that the fixed combination of IB/FEN provides superior efficacy to the single substances.[23,24]

The efficacy of IB/FEN given via inhalation is markedly influenced by the type of delivery device used. Pressurised CFC-MDIs are widely used, portable and relatively inexpensive.[6] Unfortunately, a high proportion of the drug is lost through oropharyngeal deposition as a result of the high velocity of expelled particles; this results in only a fraction of the nominal dose reaching the lungs.[9,10] To achieve optimal therapeutic efficacy an adequate drug dose must be deposited in the lower respiratory tract. Another disadvantage of the pMDI is that a high proportion of patients exhibit poor inhaler tech-

nique, which may result in inadequate therapeutic efficacy.[25-27] Coordination of inhalation with actuation of the pMDI is crucial for lung deposition. This problem can, to some extent, be overcome by the use of spacer devices, which slow the aerosol cloud by allowing propellants to evaporate, and by using pMDIs that are activated by inhalation, thus removing the requirement for breath-actuation coordination. However, the intrinsic problems of pMDIs have stimulated the development of alternative methods for the delivery of inhalation aerosols. DPIs are breath-actuated devices that overcome difficulties with hand-lung coordination and improve lung deposition of drug. However, their effectiveness is dependent on the inspiratory flow of the patient. Furthermore, the flow needed to generate a therapeutic dose may vary between devices.[6]

Respimat® SMI is a new generation inhaler that has been developed to improve drug delivery to the lung compared with pMDIs and DPIs. Respimat® SMI is a propellant-free multidose (120 per cartridge) inhaler with a unique delivery mechanism that uses the energy released from a tensioned spring. This delivery mechanism emits the dose slowly as a Soft Mist™ over a period of 1.2–1.6 seconds (five times more slowly than from a conventional CFC-MDI),[28] with a high proportion of the dose in the fine particle fraction (droplets of <5.8μm in diameter).[29] These particles are small enough to penetrate into, and be deposited in, the lungs after inhalation. The mass fraction of particles of <1μm in size is estimated to be <1%.[30]

The fine particle size and the low velocity of the cloud generated by Respimat® SMI enable more of the emitted dose to reach the airways and less to be lost by oropharyngeal deposition compared with pMDIs; this has been confirmed in a number of scintigraphic studies.[7,31,32] As a consequence of improved lung deposition it is possible that bronchodilators can be delivered in smaller dosages via Respimat® SMI than are now delivered via pMDI, without loss of efficacy. Two recent studies have provided evidence that this is achievable.[33,34]

Table IV. Proportion of asthma patients (as percentage of those treated) who reported adverse events in the two phase III trials (A = adults; B = children). Patients were randomised to receive ipratropium bromide/fenoterol hydrobromide (IB/FEN) or (in study A only) placebo, delivered via either Respimat® Soft Mist™ Inhaler (SMI) or pressurised metered dose inhaler (pMDI; with a spacer in study B). Treatments were taken four times daily in study A and three times daily in study B. Specific adverse events listed are those with an incidence in any treatment group of >3% (study A) and >2% (study B)[12,13]

	Respimat® SMI					pMDI		
	IB/FEN 10/25μg		IB/FEN 20/50μg		placebo	IB/FEN 40/100μg		placebo
	A (n = 152)	B (n = 178)	A (n = 161)	B (n = 180)	A (n = 79)	A (n = 159)	B (n = 177)	A (n = 80)
All adverse events	**66.4**	**24.7**	**64.0**	**23.9**	**58.2**	**58.5**	**33.9**	**57.5**
Exacerbation of asthma	20.4	6.7	16.1	5.6	3.8	11.9	9.0	12.5
URTI	11.2	2.2	9.9	4.4	13.9	8.2	4.0	13.8
Headache	7.2	2.2	6.8	1.7	17.7	10.7	2.8	16.3
Influenza-like symptoms	3.9	0.6	5.0	2.2	6.3	6.9	1.7	10.0
Rhinitis	6.6	2.8	8.7	3.3	6.3	5.0	2.8	1.3
Coughing	1.3	6.2	2.5	6.7	1.3	3.1	7.9	0.0
Bronchitis	7.9	2.2	5.0	0.6	6.3	5.7	0.6	3.8
Dyspnoea	5.9	1.7	5.6	0.0	2.5	7.5	3.4	3.8
Pharyngitis	2.6	2.2	2.5	2.2	7.6	3.1	2.3	1.3
Sinusitis	2.0	1.7	3.7	1.7	5.1	0.6	2.3	0.0
Deaths	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Serious adverse events								
All	6.6	0.6	3.1	0	1.3	1.3	1.7	0
Drug related	0	0	0	0	0	0	0	0

URTI = upper respiratory tract infection.

Table V. Proportion of chronic obstructive pulmonary disease (COPD) patients (as percentage of those treated) who reported adverse events in the phase III trial. Patients were randomised to receive ipratropium bromide/fenoterol hydrobromide (IB/FEN) or placebo, delivered via either Respimat® Soft Mist™ Inhaler (SMI) or pressurised metered dose inhaler (pMDI). Treatments were taken four times daily. Specific adverse events listed are those with an incidence of >3% in any treatment group[14]

	Respimat® SMI			pMDI	
	IB/FEN 10/25μg (n = 217)	IB/FEN 20/50μg (n = 224)	placebo (n = 114)	IB/FEN 40/100μg (n = 220)	placebo (n = 117)
All adverse events	**56.2**	**55.8**	**50**	**52.3**	**48.7**
Exacerbation of COPD	20.3	26.8	19.3	20.9	17.9
Dyspnoea	7.8	7.6	12.3	10.9	9.4
URTI	6.9	5.8	6.1	4.1	2.6
Cough	5.5	3.1	3.5	5.9	2.6
Urinary tract infection	3.2	2.2	2.6	0.9	2.6
Drug-related adverse events	4.2	7.3	9.3	4.1	5.6
Deaths (all causes)	**0**	**0.4**	**0**	**0.2**	**0.5**
Serious adverse events					
All	5.1	4.8	3.1	3.6	2.0
Drug related	0	0.5	0	0	0

URTI = upper respiratory tract infection.

The longer duration of the aerosol cloud generated by Respimat® SMI also facilitates the coordination of inspiration and actuation during drug administration, giving the patient time to inhale after pressing the dose-release button; this contrasts with the need for simultaneous actuation and inspiration with a pMDI.[29] For this reason, Respimat® SMI is likely to be of benefit to all patients who require inhaled bronchodilator therapy, especially those who have difficulty achieving good inhaler technique with pMDIs.

Since scintigraphy studies have shown improved lung deposition with Respimat® SMI compared with the CFC-MDI, a programme of clinical studies was conducted to explore the possibility that IB/FEN delivered via Respimat® SMI might be as efficacious as when delivered via a CFC-MDI when the dosage via Respimat® SMI is only half or a quarter of that via the CFC-MDI. Phase II studies in asthma patients showed the dose-response relationship for IB/FEN delivered via Respimat® SMI to be linear over the range 5/12.5 to 80/200μg, which agrees with the findings of an earlier study in which IB/FEN was delivered by a hydrofluoroalkane-based MDI.[35] Cumulative doses of IB/FEN 160/400 and 320/400μg via Respimat® SMI produced bronchodilation equivalent to that achieved with a cumulative 320/800μg dose via CFC-MDI.[8]

Pivotal phase III clinical trials were performed in adults and children with asthma and adults with COPD, using the dosages that produced similar degrees of bronchodilation to that seen with the registered pMDI dosage of 40/100μg four times daily.[12-14] In the two asthma studies, both Respimat® SMI dosages (IB/FEN 10/25 and 20/50μg) were at least as good as the higher dosage delivered via CFC-MDI (40/100μg). In the COPD study only the 20/50μg dosage demonstrated comparable efficacy to the CFC-MDI 40/100μg dosage. In all three studies, FEV_1 analyses and other secondary endpoints for the two Respimat® SMI treatment arms showed a trend towards a higher bronchodilator response with the 20/50μg dosage. All treatments were well tolerated; Respimat® SMI treatment groups exhibited similar safety profiles to CFC-MDI groups in all three studies. The tolerability of higher dosages of IB/FEN given long-term via Respimat® SMI has not been studied; although it is possible that adverse effects would be more common at higher dosages, the safety and tolerability of this drug combination after long-term use are well

known from its use in practice in other formulations.[36]

3. Conclusion

The results of these studies show that Respimat® SMI enables a 2- to 4-fold reduction in the nominal dosage of IB/FEN in patients with asthma and a 2-fold reduction in patients with COPD, while offering similar therapeutic efficacy and safety to that achieved when administered via a CFC-MDI. Moreover, this performance is achieved without the use of a spacer. Thus, Respimat® SMI appears to be an important new inhaler for administering IB/FEN to both asthma and COPD patients.

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