The role of the novel D_2/β_2-agonist, Viozan™ (sibenadet HCl), in the treatment of symptoms of chronic obstructive pulmonary disease: results of a large-scale clinical investigation

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Abstract Viozan™ (sibenadet HCl, AR-C68397AA) is a novel dual D_2 dopamine receptor, β_2-adrenoceptor agonist, developed specifically to treat the key symptoms of chronic obstructive pulmonary disease (COPD), breathlessness, cough and sputum. The dual sensory nerve modulation and bronchodilator effects of sibenadet have been demonstrated in initial dose-ranging studies of patients with COPD and large-scale clinical evaluation has now been completed. Sibenadet efficacy was determined by assessing symptomatic changes, as defined by the novel assessment tool, the Breathlessness, Cough and Sputum Scale (BCSS®). The findings of two placebo-controlled studies are reported.

These multicentre, double-blind, placebo-controlled studies recruited over 2000 patients with stable COPD, randomized to receive sibenadet (500 μg) or placebo, pressurized metered-dose inhaler (pMDI) (three times daily) for a period of 12 or 26 weeks. Diary cards were completed daily by patients throughout the study to record BCSS scores, peak expiratory flow (PEF), study drug and rescue bronchodilator usage, changes in concomitant medication and adverse events. The primary endpoints were defined as change from baseline to the final 4 weeks of the treatment period in mean BCSS total score, and forced expiratory volume in one second (FEV_1) measured 1 hour after administration of the final dose of study drug and expressed as a percentage of the predicted FEV_1. In addition, clinic assessments were made to determine changes in pulmonary function, health-related quality of life, perception of treatment efficacy and adverse events.

Despite initial improvements in mean daily BCSS total scores in patients receiving sibenadet, the difference in the change from baseline to the final 4 weeks of the treatment period between the two treatment groups was neither statistically significant, nor considered to be of clinical importance. Although marked bronchodilator activity was seen early on with sibenadet treatment, the duration of effect diminished as the studies progressed. Sibenadet use was not associated with any safety concerns.

These studies, utilizing the novel BCSS, have clearly illustrated that, despite initial symptomatic improvement with sibenadet therapy, this clinical benefit was not sustained over the course of the study.

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INTRODUCTION

Despite the differing aetiologies of asthma and chronic obstructive pulmonary disease (COPD), therapeutic strategies for COPD rely largely on drugs developed for patients with asthma. Bronchodilators therefore represent the cornerstone of therapy for COPD, despite the fact that this patient population, by definition, has limited airway reversibility (1–3). Recognition of the increasing prevalence of COPD and its associated healthcare burden has led to the investigation of a number of potential new therapies in recent years. As sensory nerve pathways in the lung have been associated with COPD symptoms, modulation of reflex responses to stimuli has

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been one of the approaches investigated (4,5). Since agonism at dopamine receptors is generally associated with an inhibitory effect in the peripheral nervous system (6), the dopamine pathway in the lung has been identified as a potential target for drug intervention in controlling COPD symptoms (7). Expression of D_2 dopamine receptors on the sensory neurons of thoracic dorsal root ganglia has recently been demonstrated at the level of both mRNA and protein (8). Since these neurons activate pro-inflammatory reflex responses and neurogenic inflammation, D_2 dopamine receptor agonists may exert anti-inflammatory effects in a number of organs, including the airways.

Viozan™ (sibenadet HCl, AR-C68397AA) is the first in a novel class of dual D_2 dopamine receptor, β_2-adreno-ceptor agonists. This drug combines the activity of a conventional β_2-adrenoceptor agonist with the novel sensory modulatory effects of a dopaminergic mechanism. While the role of β_2-adrenoceptor agonists in the treatment of COPD is well established, dopamine agonism is an entirely unique approach. This activity has been investigated in animal models and the D_2-receptor agonist activity of sibenadet has shown the ability to inhibit sensory nerve activity, inhibiting reflex cough, mucus production and tachypnoea (9).

Symptom assessment has become a common outcome measure in intervention studies in COPD, despite the absence of a widely used symptom measurement tool. During the initial clinical investigation of sibenadet, a simple outcome measure for the assessment of the key symptoms of COPD was developed, the Breathlessness, Cough and Sputum Scale (BCSS®) (10,11). This novel, patient-reported outcome measure evaluates the severity of the three key symptoms of COPD and is described in detail by Leidy et al. (10,11). Independent assessment of the BCSS has shown it to be internally consistent and reproducible, and provides supportive evidence of its construct, concurrent, and divergent validity (10,11). These analyses support use of the BCSS to measure the benefit of therapeutic interventions in COPD. Utilization of this novel tool in early clinical studies enabled demonstration of symptomatic improvement in patients receiving sibenadet and indicated superiority over bronchodilator therapy (12).

The sibenadet efficacy observed in the initial clinical evaluations (12) provided the impetus to evaluate further the efficacy and safety of sibenadet in longer-term studies. Therefore, a large-scale clinical programme was initiated and has now been completed. The findings of two placebo-controlled studies of sibenadet, of 3- and 6-month duration, are reported. The primary objective of these investigations was to assess the clinical activity of sibenadet by recording change in key symptoms as determined by the BCSS total score, together with conventional forced expiratory volume in one second (FEV_1) measures.

METHODS

Patient population

Male and female patients, aged 40–80 years, with stable COPD, symptoms for ≥ 2 years, a smoking history of at least 15 pack-years, pre- and post-bronchodilator FEV_1/FVC (forced vital capacity) $\leq 65\%$, and pre- and post-bronchodilator FEV_1 20–70% of the predicted normal, were included in the study. Concomitant corticosteroids, mucolytics, methylxanthines, anti-tussives and decongestants were allowed, provided that they were not initiated during the study, and that the doses remained constant during the 6 weeks before the study, and over the baseline period.

Patients not eligible for the study included those with other significant diseases, evidence of an exacerbation in the previous 6 weeks, requirement for domiciliary oxygen, previous participation in a clinical study of sibenadet, participation in any clinical study in the previous 3 months, laboratory abnormalities or use of disallowed medication (long-acting bronchodilators, oral β-agonists, anticholinergics, leukotriene antagonists, dopamine agonists or antagonists, β-adrenoceptor blockers, bupropion hydrochloride).

Study design

These multi-centre, double-blind, randomized, placebo-controlled studies were of 12- and 26-week duration (Studies 1 and 2 respectively). Eligible patients were enrolled into a 2-week baseline assessment period. Disallowed medications were withdrawn and patients were supplied with salbutamol (100 µg) (Ventolin™, Glaxo SmithKline) as pressurized metered-dose inhalers (pMDIs) for use as rescue medication. Patients were required throughout the study to complete daily diary cards recording symptoms, morning and evening peak expiratory flow (PEF) measurements, rescue medication usage, changes in concomitant medication and any adverse events.

At the end of the baseline period, patients were able to continue in the study if they exhibited a BCSS total score of ≥ 2 for any 7 consecutive days, had not experienced any exacerbations of COPD, had completed diary cards satisfactorily, and had not taken any disallowed medication.

At the randomization visit (day 1), eligible patients were randomized to receive placebo or sibenadet (500 µg) delivered via pMDI (two actuations, three times daily). Randomization was performed using random permuted blocks to ensure approximately equal numbers of patients in each centre received each treatment. The sibenadet dose was selected on the basis of results from earlier clinical trials (12). Sibenadet and placebo inhalers were withdrawn at the end of the treatment period and patients were required to

continue using only rescue medication (and other allowed medications) for a further 4-week follow-up period, after which one final clinic visit was made.

These studies were performed in accordance with the principles stated in the Declaration of Helsinki and approved by ethics committees at each participating centre. All patients gave written informed consent.

Assessment of symptoms and general pulmonary function

Symptom ratings and pulmonary function were primary outcome measures in these studies. Dual primary endpoints were selected in order to assess the efficacy of both the D_2 and β_2 components of sibenadet through determining changes in BCSS total score and FEV_1.

Changes in COPD symptoms were assessed using the BCSS. Each symptom (breathlessness, cough and sputum) was evaluated daily by the patient and recorded in a diary using a 5-point Likert scale (ranging from 0 to 4, with higher values indicating more severe symptoms). The three item scores were summed to calculate the BCSS total score, resulting in a value between 0 and 12.

The primary endpoint for assessing symptoms in these studies was defined as the difference between the two treatment groups in terms of change in mean BCSS total score over the baseline period to the mean BCSS total score over the final 4 weeks of the treatment period (Study 1: weeks 9–12; Study 2: weeks 23–26). Changes in mean BCSS total score and each of the item scores (breathlessness, cough and sputum) from baseline to each 2-week period within the treatment period and to the follow-up period were also examined.

The primary endpoint for assessing improvement in pulmonary function between the two groups was FEV_1 measured 1 hour after the final dose of study drug at the end of the treatment period (Study 1: week 12, Study 2: week 26) and expressed as a percentage of predicted FEV_1. This measure was also assessed at day 1 (Studies 1 and 2), week 4 (Study 1) and weeks 6 and 14 (Study 2). Predicted FEV_1 was calculated at enrolment using the Crapo algorithm (13).

Serial FEV_1 and PEF assessment

In a subset of patients (all of whom exhibited ≥ 5% reversibility of FEV_1 in response to inhaled salbutamol 400 μg), serial FEV_1 measurements were taken over an 8-hour period (at 5, 15, 30, 45, 60, 90 and 120 minutes and hourly thereafter until 8 hours post-dosing). Serial measurements were taken on day 1 (Studies 1 and 2), weeks 8 and 12 (Study 1), and weeks 14 and 26 (Study 2). The AUC_{0-8}, mean FEV_1 at 8 hours and mean maximum change from pre-dose were also calculated. These measurements were used to investigate the bronchodilator properties of sibenadet.

Spirometry was used to determine pulmonary function at all clinic visits. Patients were instructed not to use study or rescue medication 4 hours prior to spirometry measurements being taken. After resting for 15 minutes, slow vital capacity (SVC), FVC, and FEV_1 were measured for at least three separate manoeuvres. The greatest values for each parameter were recorded. Patients measured PEF each morning and evening, prior to taking study medication, and recorded the highest value of three manoeuvres in their diary cards. Patients were instructed to avoid using rescue medication in the 4 hours preceding each PEF measurement. The number of actuations of rescue medication used each day was recorded by patients in their diary cards.

COPD exacerbations

COPD exacerbations were defined as worsening symptoms of COPD requiring drug therapy in addition to study drug, rescue medication and doses of concomitant COPD medications. COPD exacerbations since the previous clinic visit were recorded at each visit after randomization. Investigators were asked to indicate whether each adverse event a patient experienced was consistent with the definition of a COPD exacerbation. Both adverse events that had been flagged by the investigator as an exacerbation and adverse events that were described as an 'exacerbation' were included in the secondary analysis.

Health-related quality of life (HRQL)

HRQL was assessed using the disease-specific St George's Respiratory Questionnaire (SGRQ) (14,15) and the generic EuroQol-5D (EQ-5D) (16). Questionnaires were completed unaided by patients before other study-related procedures were performed. This was performed at the beginning and end of the treatment period and at the end of the follow-up period. In Study 2, an additional assessment was made at week 14.

Patients' and investigators' opinions of efficacy

Patients' opinions of treatment efficacy were recorded at all clinic visits after randomization. Opinion was scored from 0 to 4, where 0 = highly effective, 1 = moderately effective, 2 = mildly effective, 3 = not effective and 4 = made condition worse. The investigators recorded their opinions at the end of the treatment period only, using the same scale.

Safety

The safety of study treatment was assessed at each clinic visit by examining the incidence of adverse events. In

addition, clinically significant changes in laboratory and other safety variables (ECG, pulse and blood pressure, physical signs) were assessed at the start and end of the study.

Statistical analyses

An intention to treat population (ITT) was defined as all randomized patients receiving at least one dose of study medication with useable post-randomization efficacy data, and was used to summarize all efficacy data according to the treatment the patient was randomized to receive. In addition, exploratory sensitivity analyses were performed using this population to assess the impact of data missing due to patient withdrawal from the study. A safety population was defined as all randomized patients receiving at least one dose of study medication and was used to summarize all safety data according to the treatment the patient received.

The primary hypotheses were tested using analysis of covariance with treatment and country as fixed factors. The BCSS primary endpoint included the mean BCSS total score over the baseline period as a covariate, and the FEV_1 primary endpoint included the value for FEV_1 recorded immediately prior to the final dose of study medication and expressed as a percentage of the predicted FEV_1, as a covariate. These tests were two-sided and both performed at the 5% significance level. All assumptions implicit in the ANCOVA methodology were checked and potential interactions were investigated.

Supportive and exploratory analyses were conducted on the secondary efficacy variables using analysis of covariance including treatment and country as fixed factors and a baseline value as a covariate for continuous variables, and using the chi-square test for categorical variables. No correction was made to the significance level given both the non-confirmatory purpose of the analyses, and that the study was not prospectively powered to detect differences in these secondary variables.

The sample size calculation was based on the mean differences from baseline and associated variability shown in the Phase IIb study (12). A total of 371 patients in each treatment group were required to show a difference of at least 0·34 between treatment groups in the change from baseline in mean BCSS total score, assuming a pooled standard deviation of 1·425; 217 patients in each treatment group were required to show a difference of at least 5% in FEV_1 expressed as a percentage of predicted FEV_1 1 hour after the final dose of study drug, assuming a pooled standard deviation of 16. Therefore, it was aimed that a minimum of 950 and 1060 patients be randomized into Studies 1 and 2 respectively to ensure that at least 742 patients would complete each study.
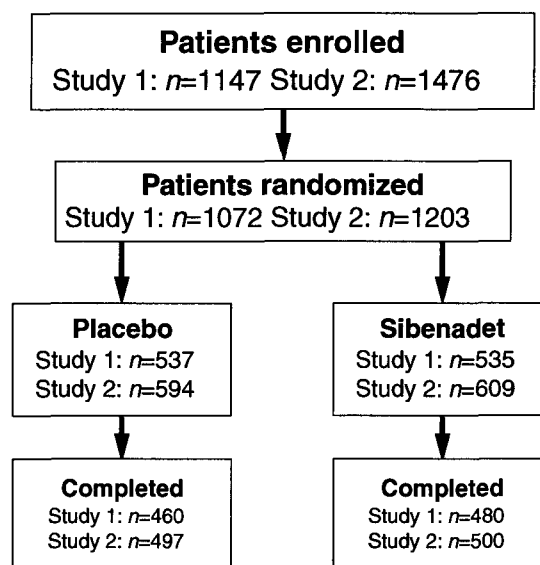

FIGURE 1. Flow chart of patient disposition.

RESULTS

Patient demographics

Patient disposition for Studies 1 and 2 is summarized in Figure 1. The safety population comprised 1072 and 1203 patients in Studies 1 and 2 respectively. The ITT population comprised fewer patients (1050 and 1169 respectively) as patients from two centres in each study were excluded as their efficacy data was deemed unreliable. The decision to exclude these patients from the ITT population was taken prior to unblinding the study. 12% and 17% of patients in the safety population withdrew from Studies 1 and 2 respectively, the primary reasons being adverse events, deterioration of patient condition, withdrawal of consent or a protocol deviation. In each of the studies, the proportion of patients withdrawing in each treatment group was similar with no obvious differences in the reasons for withdrawal.

The baseline characteristics of patients in the ITT populations are summarized in Table 1. Any differences noted between treatment groups at baseline were not considered clinically relevant.

Compliance with study medication as recorded by the patients on their diary cards was high. The mean percentage compliance with study medication was 97% across all treatment groups in both studies.

Symptom ratings

The Least Squares (LS) mean differences from baseline to the final 4 weeks of treatment are outlined in Table 2,

Table 1. Summary of demographics and baseline characteristics

	Study 1 (12 weeks)		Study 2 (26 weeks)	
	Placebo	Sibenadet	Placebo	Sibenadet
No. randomized	526	524	578	591
Sex: male/female	381/145	387/137	445/133	417/174
Mean age in years ($\pm$ SD)	65 (8·6)	65 (7·9)	63 (8·9)	62 (9·0)
(range)	(40–80)	(41–80)	(40–79)	(40–79)
Previous smoker	55%	55%	47%	47%
Current smoker	45%	46%	53%	53%
Mean pack-years ($\pm$ SD)	49 (25·5)	53 (27·8)	40 (19·3)	39 (19·5)
Mean daily BCSS total score ($\pm$ SD)	4·89 (1·83)	5·11 (1·9)	5·35 (1·89)	5·21 (1·83)
Mean % predicted FEV_1 ($\pm$ SD)	39·7 (11·9)	39·0 (11·7)	39·5 (12·2)	41·1 (11·7)
Mean % reversibility in FEV_1 ($\pm$ SD)	13·4 (13·9)	14·3 (14·0)	12·8 (4·6)	12·5 (14·9)
Mean morning PEF (litres min^{-1} $\pm$ SD)	234 (81·4)	232 (82·4)	235 (83·5)	240 (86·2)
Mean rescue medication usage (actuations day^{-1} $\pm$ SD)	5·3 (4·1)	5·4 (3·9)	4·8 (4·0)	4·6 (3·6)

a decrease in LS mean signifying improvement in symptoms. Although the results indicate a greater decrease in BCSS total score in the sibenadet group than in the placebo group, these differences were neither statistically significant nor considered to be of clinical significance (12,13).

Sensitivity analyses were performed using the mean of the BCSS total scores recorded in 3 days prior to withdrawal from the study to represent the daily score to the end of the scheduled treatment period. Although these data yielded larger LS mean estimates for the difference between the two treatment groups, they did not represent differences judged to be of clinical importance.

At the start of the treatment period in both studies, there was an immediate reduction in BCSS total score in the sibenadet group, followed by a gradual increase in symptom scores, indicating an initial symptom improvement and subsequent deterioration (Figure 2a, b). In Study 1, the LS mean difference in BCSS total score between the two groups (for the whole of the treatment period) was –0·39 with a corresponding 95% confidence interval of (–0·55, –0·22); $P < 0·001$. In Study 2, the LS mean difference in BCSS total score (for the whole of the treatment period) between the two treatment groups was –0·22 (95% CI –0·37, –0·07); $P=0·005$. Neither the sibenadet group nor the placebo group returned to the mean BCSS total score recorded during the baseline period.

There were initial decreases from baseline for each of the mean BCSS item symptom scores (breathlessness, cough and sputum) at the start of treatment in the sibenadet groups. A gradual increase in the symptom scores was, however, subsequently seen.

Pulmonary function 1 hour post-dose

In Study 1, the LS mean FEV_1 expressed as a % of predicted FEV_1 1 hour after taking the final dose of study drug at the end of the scheduled treatment period (week 12) for placebo was 40·20 (SE $\pm$ 0·51, n=415), and for sibenadet was 44·59 ($\pm$ 0·51, n=430). The least squares (LS) mean difference between sibenadet and placebo groups (n=845) was 4·39% (SE $\pm$ 0·59) predicted FEV_1 (95% CI 3·2, 5·6). In Study 2, the LS mean FEV_1 at week 26 for placebo was 41·83 (SE $\pm$ 0·52, n=419), and for sibenadet was 47·31 (SE $\pm$ 0·51, n=423). The LS mean difference between the sibenadet and placebo groups (n=842) was 5·47% (SE $\pm$ 0·66) predicted FEV_1 (95% CI 4·2, 6·8). Both results were highly statistically significant ($P < 0·001$).

Including FEV_1 measurements made closest to the end of the treatment period for patients who withdrew (i.e., last observation carried forward) demonstrated similar results.

Serial FEV_1 measurements

Serial measurements of FEV_1 were obtained from a subset of patients (Study 1: n=130; Study 2: n=152). FEV_1 continued to increase for up to 2 hours post-dose in the sibenadet group. In both studies, an increase from pre-dose FEV_1 was noted 5 minutes after study drug in patients randomized to sibenadet. The maximum increase (LS mean maximum difference from placebo) was between 1 and 2 hours after study drug. At weeks 8 and 12 (Study 1) and weeks 14 and 26 (Study 2) there were smaller increases in FEV_1 and the duration of effect is seen to diminish (Figure 3).

Table 2. LS mean change in BCSS total score (from baseline to final 4 weeks of treatment period)

	Placebo		Sibenadet		Sibenadet-placebo		
	n	LS Mean (SE)	n	LS Mean (SE)	LS Mean (SE)	95% CI	P value
Study 1 (12 weeks)	459	−0·39 (0·09)	484	−0·54 (0·09)	−0·15 (0·11)	(−0·36, 0·06)	0·163
Study 2 (26 weeks)	498	−0·23 (0·08)	500	−0·36 (0·08)	−0·14 (0·11)	(−0·34, 0·07)	0·191

(a)

| Placebo (n) | 522 | 504 | 484 | 472 | 459 | 454 | 475 |
| Sibenadet (n) | 521 | 506 | 499 | 493 | 484 | 477 | 476 |

-●- Placebo   -■- Sibenadet

(b)

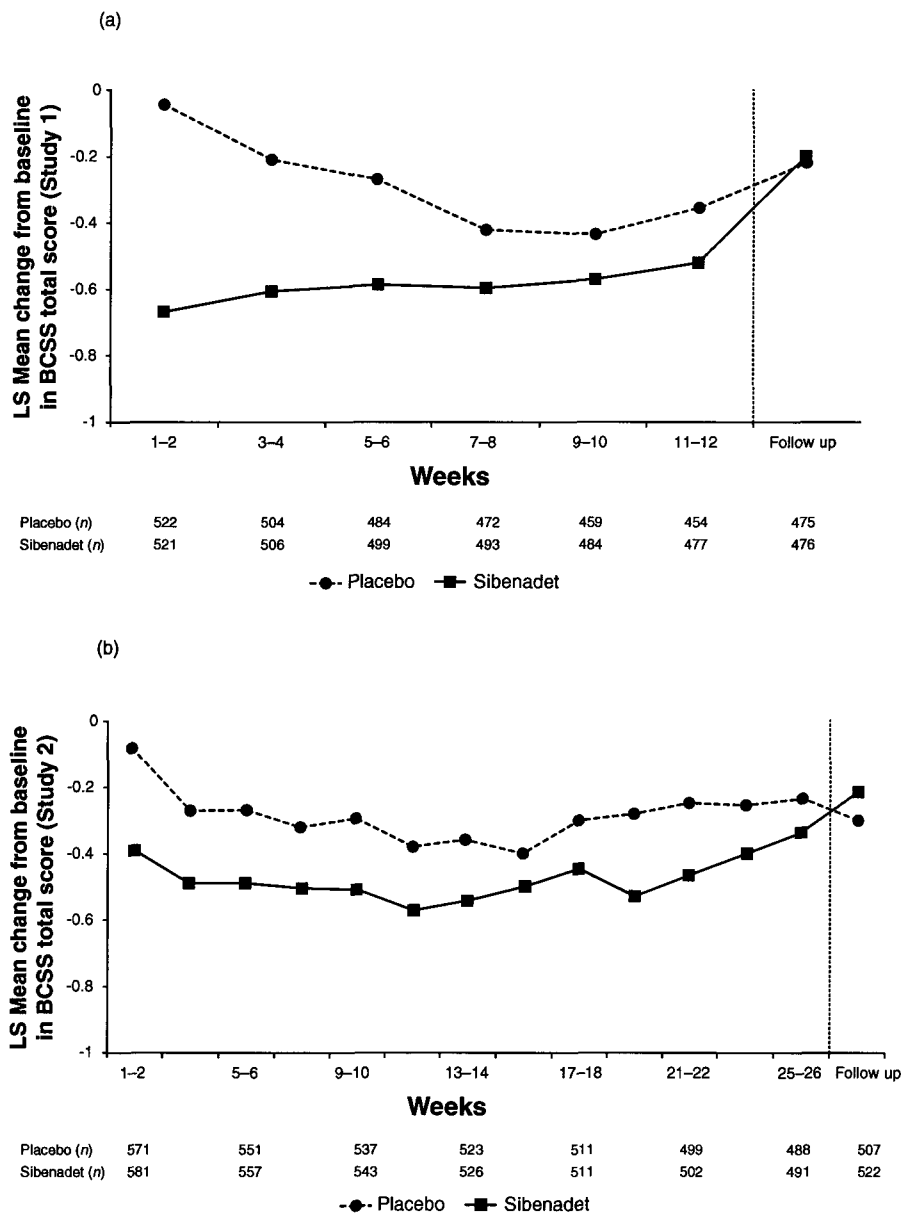| Placebo (n) | 571 | 551 | 537 | 523 | 511 | 499 | 488 | 507 |
| Sibenadet (n) | 581 | 557 | 543 | 526 | 511 | 502 | 491 | 522 |

-●- Placebo   -■- Sibenadet

FIGURE 2. Summary of change from baseline in mean BCSS over the treatment period. a) Intention to treat (ITT) population, all available dataset from Study 1; b) ITT population, data from Study 2.
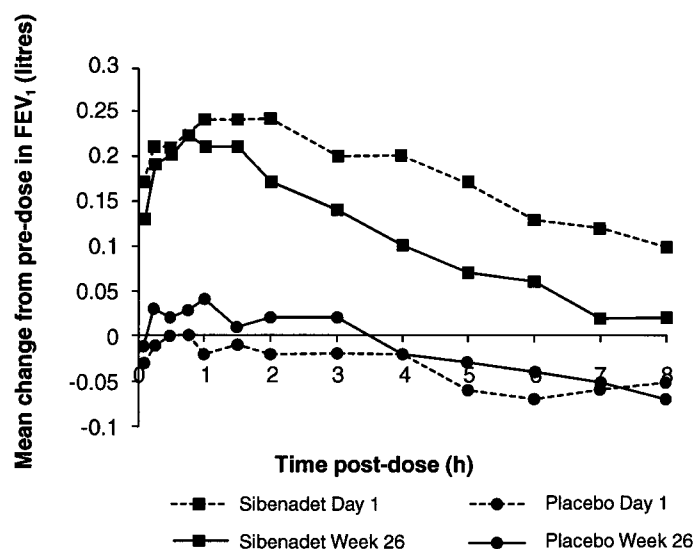
FIGURE 3. Serial FEV_1 over 8 hour (data from Study 2, excluding post-rescue medication measurements).

Table 3. Serial FEV_1 measurements

	Study 1 (12 weeks)		Study 2 (26 weeks)	
	Placebo (n=66)*	Sibenadet (n=64)*	Placebo (n=74)*	Sibenadet (n=78)*
Mean AUC_{0-8}, l min^{-1} (SD)				
Day 1	3·2 (52·7)	86·3 (66·6)	−14·5 (81·4)	85·4 (81·2)
Week 8/14	7·9 (40·5)	48·8 (58·1)	7·2 (55·3)	54·0 (66·0)
Week 12/26	16·2 (43·4)	57·7 (63·6)	−6·3 (59·7)	52·4 (89·7)
Mean FEV_1 at 8 h, l (SD)				
Day 1	1·1 (0·46)	1·2 (0·36)	1·2 (0·46)	1·4 (0·49)
Week 8/14	1·1 (0·40)	1·1 (0·40)	1·2 (0·44)	1·4 (0·45)
Week 12/26	1·1 (0·48)	1·1 (0·40)	1·2 (0·42)	1·3 (0·50)
Max change in FEV_1, l (SD)				
Day 1	0·1 (0·13)	0·3 (0·15)	0·1 (0·17)	0·3 (0·18)
Week 8/14	0·1 (0·12)	0·3 (0·14)	0·2 (0·19)	0·3 (0·21)
Week 12/26	0·2 (0·12)	0·3 (0·16)	0·1 (0·14)	0·3 (0·23)

* Number of patients assessed on day 1.

The AUC_{0-8} for the change from pre-dose in FEV_1 was greater for the sibenadet group compared with the placebo group in both studies. The actual value of AUC_{0-8} in the sibenadet group was greater for the serial FEV_1 measurements taken on day 1 than for the measurements taken at weeks 8 and 12 (Study 1) or weeks 14 and 26 (Study 2) (Table 3). All differences in AUC_{0-8} between the sibenadet and placebo groups were statistically significant.

Other measures of efficacy

There was an immediate increase in the morning and evening PEF at the start of the treatment period in the sibenadet group. This increase appeared to be maintained for the duration of the treatment period. In the placebo group, there was a gradual increase in both morning and evening PEF. These increases were smaller than the increases observed for the sibenadet group. The LS mean difference between the treatment groups in both morning and evening PEF (from baseline to last 4 weeks of study period) were; Study 1 a.m. 12·1 (95% CI 7·4, 16·8), p.m. 13·0 (95% CI 8·1, 17·8); Study 2 a.m. 12·4 (95% CI 7·0, 17·7), p.m. 13·5 (95% CI 8·3, 18·8) ($P < 0·001$ in both studies). The clinical relevance of these differences is unclear.

In the sibenadet group there appeared to be an increase in SVC, FEV_1 and FVC from the baseline period

(Visit 2) to subsequent visits over the treatment period. The magnitude of these increases diminished as the treatment period progressed. In the placebo group, there was little change from baseline to each of the subsequent visits during the treatment period. However, there was an increase in these pulmonary function variables from the baseline to the follow-up period.

There was a gradual increase in the mean number of actuations of rescue medication recorded by patients in both treatment groups over the baseline period. There was an immediate decrease in the number of actuations of rescue medication taken at the start of the treatment period, in both treatment groups. The decreases observed appeared to be maintained for the duration of the treatment period. The LS mean difference in the change from baseline to the final 4 weeks of the treatment period was: Study 1: −1·51 actuations per day (95% CI −1·89, −1·15), Study 2: −1·1 actuations per day (95% CI −1·47, −0·75). The differences between the placebo and sibenadet groups were statistically significant at all time intervals examined ($P < 0.001$). At the start of the follow-up period there was an immediate increase in the daily number of actuations of rescue medication taken in each treatment group, which in Study 2 was more marked in the sibenadet group.

Health-related quality of life

In both studies, SGRQ total and domain scores of patients receiving sibenadet showed reduction from baseline to the end of the treatment period, although reduced scores were also seen in the placebo groups. In Study 1, large changes were observed in both the sibenadet and placebo groups for the symptom domain (LS mean difference of −8·2 [SE ± 1·0] in the sibenadet group and −5·9 [SE ± 1·1] in the placebo group). For the SGRQ total score and the remaining domain scores (activity and impacts), the differences between the two treatment groups in their respective changes from baseline scores showed a trend towards superiority of sibenadet, but no statistically significant differences were seen. For both treatment groups in Study 2 the improvement in symptom domain from baseline to week 14 was statistically significant (LS mean changes of −4·1 [SE ± 0·4] and −6·6 [SE ± 0·9] for the placebo and sibenadet groups, respectively). However, this difference was not maintained by week 26 (−5·0 and −5·2 respectively) (Figure 4).

The EQ-5D data obtained from both studies failed to demonstrate any differences in weighted health index between the treatment groups. An improvement in patients' evaluation of their own health was seen in patients receiving sibenadet in Study 1.

Patient and investigator opinion of efficacy

In both studies, sibenadet treatment was more frequently considered to be highly or moderately effective than placebo. At the end of Study 1, 23% of investigators and 34% of patients rated placebo as highly or moderately effective. In contrast 52% of investigators and 62% of patients rated sibenadet as highly or moderately effective. At the end of Study 2, 26% of investigators and 39% of patients rated placebo as highly or moderately effective. Again, a higher proportion of investigators and patients rated sibenadet as highly or moderately effective (52% and 59% respectively).

Exacerbations

The proportion of patients experiencing at least one exacerbation was similar in both study groups (Study 1: 17·9%/14·7% placebo and sibenadet groups respectively; Study 2: 25·8%/23·5% placebo and sibenadet groups respectively). There was also no difference in the time to the first exacerbation between the two treatment groups.

Adverse events

The most frequently reported adverse events starting in the treatment period are summarized in Table 4. No differences were seen in the incidence of serious adverse events between the placebo and sibenadet groups of either study during the treatment and follow-up period. A similar proportion of patients in placebo and sibenadet groups discontinued study drug due to adverse events (Study 1: 7% and 5% respectively; Study 2: 8% and 10% respectively). Respiratory events were the most frequent type of event resulting in discontinuation, namely deterioration of chronic obstructive airways disease and aggravated dyspnoea.

In both studies, the majority of laboratory abnormalities were not considered clinically significant and no differences between the sibenadet and placebo groups were evident. Vital signs and ECG abnormalities occurred as isolated incidents. In Study 2 there was an excess of ECG abnormalities recorded as adverse events in the sibenadet group but the nature of these abnormalities was diverse and fell into no distinguishable pattern. There were no clinically relevant trends evident from vital signs data or from the changes in numbers of aggravated abnormalities found on physical examination.

In Study 1, three deaths were reported during the treatment period (two in the sibenadet, one in the placebo group) and four deaths during follow-up (two in both treatment groups). Two deaths were considered probably or possibly due to study drug: one placebo patient with exacerbation of chronic obstructive airways disease and
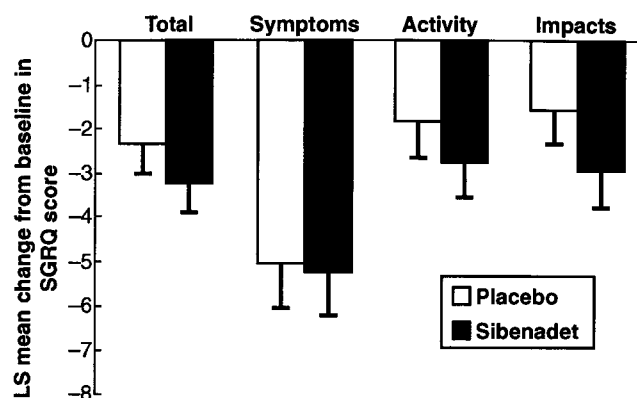
FIGURE 4. Least squares mean changes from baseline to the end of the treatment period in SGRQ scores (bars indicate standard error; Intention to treat (ITT) population, data from Study 2).

Table 4. Summary of most frequently reported adverse events commencing during study drug period (≥ 3% in any group)

	Study 1 (12 weeks)		Study 2 (26 weeks)	
	Placebo	Sibenadet	Placebo	Sibenadet
Adverse event	n=537	n=535	n=594	n=609
At least one event	313 (58%)	365 (68%)	398 (67%)	449 (74%)
At least one serious adverse event	26 (5%)	26 (5%)	54 (9%)	67 (11%)
At least one event probably or possibly related to study treatment	106 (20%)	206 (39%)	117 (20%)	185 (30%)
At least one event with severe intensity	48 (9%)	55 (10%)	90 (15%)	90 (15%)
General disorders				
Back pain	16 (3%)	12 (2%)	27 (5%)	26 (4%)
Chest pain	17 (3%)	13 (2%)	13 (2%)	12 (2%)
Pain	17 (3%)	10 (2%)	20 (3%)	28 (5%)
Central and peripheral nervous disorders				
Dizziness	14 (3%)	23 (4%)	8 (1%)	23 (4%)
Headache	48 (9%)	47 (9%)	65 (11%)	60 (10%)
Tremor	3 (1%)	39 (7%)	5 (1%)	46 (8%)
Respiratory system disorders				
Chronic obstructive airways disease	64 (12%)	56 (10%)	115 (19%)	128 (21%)
Bronchitis	17 (3%)	4 (1%)	13 (2%)	9 (1%)
Coughing	20 (4%)	23 (4%)	22 (4%)	28 (5%)
Dyspnoea	9 (2%)	21 (4%)	29 (5%)	25 (4%)
Dyspnoea (aggravated)	34 (6%)	22 (4%)	20 (3%)	15 (2%)
Respiratory infection	45 (8%)	73 (14%)	102 (17%)	118 (19%)
Pharyngitis	11 (2%)	17 (3%)	20 (3%)	20 (3%)
Rhinitis	18 (3%)	21 (4%)	18 (3%)	13 (2%)
Other				
Discernible taste	15 (3%)	113 (21%)	8 (1%)	48 (8%)

one sibenadet patient with acute hepatitis. In Study 2 there were six deaths during the treatment period (two in the sibenadet group, four in the placebo group) and 15 deaths during follow-up (10 in the sibenadet group, five in the placebo group). Two deaths were considered probably or possibly due to study drug: one placebo patient (fatal ventricular tachycardia and fibrillation) and one sibenadet patient (myocardial infarction).

DISCUSSION

In both studies reported, sibenadet therapy (pMDI 500 μg three times daily) was initially more effective than placebo in reducing COPD symptoms, as determined by a reduction in mean daily BCSS total score. This initial improvement was consistent with the promising efficacy seen in the initial clinical studies over

a similar timeframe (12). However, this initial effect diminished over the course of the treatment period and by the end of the study differences were of neither statistical nor clinical significance. Although symptomatic improvement in the sibenadet group was more marked at the beginning of the study, the placebo group also demonstrated improved symptomatology over the course of the study, with both treatment groups exhibiting lower mean BCSS total scores at the end of the study period than baseline values.

While it may be noted that baseline demographics indicate that the study represented a relatively severe COPD population, mean BCSS total scores at baseline were relatively low. As patient severity is determined according to pulmonary function measurements (largely FEV_1), it would appear that airflow limitation is not directly reflective of symptom severity. This observation highlights the need to assess patient symptoms and supports the use of a dual endpoint to determine changes in COPD symptoms as well as pulmonary function. A patient-reported outcome measure, such as the BCSS, is a highly appropriate approach to detecting changes in patient symptoms. Use of this tool in well-designed and adequately powered studies has enabled clear conclusions regarding sibenadet efficacy to be drawn.

FEV_1 measurements clearly demonstrated the significant bronchodilatory effects of sibenadet, with serial FEV_1 assessments demonstrating an immediate improvement. The duration and magnitude of these effects was not, however, maintained throughout the study course, as reflected by decreased pulmonary function over time. The reduced bronchodilator effect of sibenadet seen over the course of the study can most likely be attributed to tachyphylaxis, a recognized potential response to regular β_2-agonist use. The mechanisms for this effect are unclear, but could be brought about by down-regulation of β-receptors, changes in regulatory mechanisms, or the high potency of sibenadet at the β_2-receptors (9). It remains to be determined whether this phenomenon was active in all patients or in just a subset of patients with a particular genetic background.

The fact that initial improvements in symptomatology tailed off over time could be indicative of tolerance to sibenadet. One explanation may be that the early symptomatic benefit was β_2- rather than D_2-driven and symptomatic benefits therefore diminished in response to tachyphylaxis to the β_2-agonist activity. It is also possible that the β_2-effect, through reducing the perception of breathlessness, resulted in the perception of general symptom improvement. Support for a direct effect of D_2 agonism on the cough component has, however, been demonstrated in an early study of sibenadet, which established that D_2 dopamine receptor agonism

effectively inhibits aerosol-induced cough (9,17). Alternatively, it is possible that the tachyphylaxis of β_2-agonist effects diminishes the total efficacy of the dual D_2/β_2 mechanism of action, thereby effectively masking the D_2 component. It is likely that the improvement noted for the Breathlessness score in the sibenadet group at the end of the treatment period was due to the bronchodilator activity of sibenadet. This is supported by the observation that this is most marked in the shorter-term study, whereas in the 6-month study it is possible that tachyphylaxis has diminished this result by the end of the treatment period.

It is important to note that tolerance to the positive effects of sibenadet on pulmonary function and COPD symptoms was not associated with increased exacerbations, or increased use of rescue therapy. This indicates that this phenomenon was not associated with an adverse clinical outcome.

Despite the apparent lack of symptomatic benefits in these studies, these data demonstrate the need for a tool such as the BCSS in order to assess therapeutic effects in terms of symptom improvement. It is apparent that, although peak flow and rescue medication use remained stable throughout the study, symptomatic benefit deteriorated illustrating that sole reliance on pulmonary function provides an incomplete picture of patient response to a therapeutic intervention. This emphasizes the need for routine measurements of other endpoints in COPD clinical trials in addition to pulmonary function.

Large changes in SGRQ were demonstrated, particularly for the symptoms domain, but a considerable placebo effect was also seen. Whilst it is difficult to interpret the clinical meaning of these data, it may be that the improvement in SGRQ in placebo patients is simply a result of the patients' involvement in the clinical study. COPD patients classically represent an isolated and often depressed population who may benefit greatly from the attention and regular contact inherent in the clinical trial environment. This theory is perhaps supported by the fact that, while over half the patients considered sibenadet to be either highly or moderately effective, approximately one third also perceived this level of efficacy with the placebo.

Sibenadet had an acceptable safety and tolerability profile with few differences in incidence between the treatment groups, with the exception of respiratory infection, taste of treatment and tremor (a known β_2-adrenoceptor agonist effect), which occurred more frequently in the sibenadet group. While D_2 agonists are known to induce nausea, vomiting, dizziness and somnolence, the frequencies of these events were low and were similar in both treatment groups, confirming the lack of centrally mediated D_2 effects with sibenadet use.

In conclusion, despite a well-founded theoretical rationale for sibenadet efficacy, supported by promising preclinical and early clinical data, the clinical development programme has enabled clear conclusions to be drawn regarding the long-term clinical benefit of sibenadet therapy. Initial symptomatic benefits were not sustained throughout the duration of the studies and these studies therefore demonstrated no evidence of long-term, clinically significant D_2 agonist effect. Sibenadet therefore does not appear to offer any additional benefit over existing bronchodilator therapy for COPD, and clinical development of this agent has now been discontinued.

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