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Safety and efficacy of the once-daily anticholinergic BEA2180 compared with tiotropium in patients with COPD

Roger Abrahams [a], Petra Moroni-Zentgraf [b,*], Joe Ramsdell [c], Hendrik Schmidt [b], Elizabeth Joseph [d], Jill Karpel [e]

[a] Morgantown Pulmonary Associates, Morgantown, 1265 Pineview Drive, Morgantown, WV 26505, USA
[b] Boehringer Ingelheim Pharma GmbH & Co KG, Binger Straβe 173, D-55216 Ingelheim am Rhein, Germany
[c] University of California San Diego Health Sciences Clinical and Translational Research Institute, 200 West Arbor Drive MC, 8415, San Diego, CA 92013-8415, USA
[d] Boehringer Ingelheim Pharmaceuticals Inc, 900 Ridgebury Road, Ridgefield, CT 06877, USA
[e] North Shore Medical Arts, LLP, 295 Community Drive, Great Neck, NY 11021, USA

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KEYWORDS
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Exacerbations;
Transition Dyspnoea Index

Summary
Background: To determine the safety and efficacy of BEA2180, an anticholinergic agent in patients with chronic obstructive pulmonary disease (COPD).
Methods: Smokers or ex-smokers ≥40 years with COPD and a postbronchodilator forced expiratory volume in 1 s (FEV_1) <80% predicted and FEV_1/forced vital capacity ≤70% participated in this multinational, randomised, double-blind, parallel study. Patients received BEA2180 (50, 100 or 200 μg), tiotropium (5 μg) or placebo once daily via Respimat® Soft Mist™. The primary endpoint was trough FEV_1 after 24 weeks. Secondary endpoints included Transition Dyspnoea Index (TDI) focal score, St George's Respiratory Questionnaire (SGRQ) total score, exacerbations and adverse events.
Results: Patients ($n = 2080$, 64.5% male) had a mean age of 64.2 years and a baseline FEV_1 of 1.2 L. Trough FEV_1 at 24 weeks with all BEA2180 doses (0.044–0.087 L) and tiotropium 5 μg (0.092 L) was significantly higher ($p < 0.0001$) than placebo (−0.034 L) and BEA2180 (200 μg) was noninferior to tiotropium. Mean TDI focal scores were higher with BEA2180 (1.43–1.48) or tiotropium (1.46) versus placebo (0.94; $p \leq 0.01$ for all). Mean SGRQ total scores also improved with BEA2180 (40.1–40.7) or tiotropium (39.5) compared with placebo (43.0, $p < 0.01$ for all). COPD exacerbation rates were reduced for all active treatments, reaching statistical significance for BEA2180 (50 and 200 μg) ($p < 0.05$, for both).

* Corresponding author. Tel.: +49 6132 77 7301; fax: +49 6132 72 7301.
E-mail address: petra.moroni-zentgraf@boehringer-ingelheim.com (P. Moroni-Zentgraf).

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Conclusion: All study doses of BEA2180 improved lung function, reduced symptoms and exacerbations, and improved health status in COPD; all treatments were well tolerated.

Clinical trial identifier: NCT00528996.

Introduction

The natural history of chronic obstructive pulmonary disease (COPD) is characterised by a progressive loss of lung function that is accompanied by worsening dyspnoea, exacerbations, potentially serious systemic consequences and comorbidity.[5,6] Not only does COPD lead to reduced physical activity and quality of life, but it also reduces life expectancy[22–24,30]; COPD is expected to become the third leading cause of death worldwide by 2030.[31] Current treatment guidelines recommend short-acting bronchodilators to manage intermittent symptoms in mild forms of the disease and advocate maintenance therapy with long-acting bronchodilators (anticholinergics, long-acting β_2-adrenergic agonists [LABAs]) in moderate-to-severe COPD or combinations of long-acting bronchodilators and inhaled corticosteroids (ICS) for those with exacerbations.[8]

Tiotropium is a once-daily, long-acting anticholinergic bronchodilator available for the management of COPD symptoms.[16] Long-term data have demonstrated that treatment with tiotropium leads to improved lung function, reduced exacerbations and increased quality of life in patients with COPD compared with placebo.[3,27,29] A 5-μg dose delivered once-daily via the Respimat® Soft Mist™ Inhaler (SMI) was recently shown to be noninferior to an 18-μg dose using the HandiHaler® system.[28] Clinical studies have supported the approval of 5 μg of once-daily inhaled tiotropium as the standard regimen for the management of COPD.[3] In a recent, 1-year study with exacerbations as the primary endpoint, a statistically nonsignificant trend of increased all-cause mortality was observed with tiotropium 5 μg SMI.[3] This led to the initiation of the currently on-going TIOSPIR® study, a large-scale, prospective, randomised trial, comparing tiotropium SMI 5 μg, 2.5 μg and HandiHaler® 18 μg in >17,000 patients. The result of a pooled analysis of all studies with tiotropium 5 μg SMI, including vital status follow up, showing a numerical trend of increased all-cause mortality is described in the local prescribing information. BEA2180 is a once-daily, inhaled, long-acting anticholinergic bronchodilator also delivered via Respimat® SMI. Although there are minor differences in the properties of BEA2180 based on animal/preclinical data, there were no significant differences in efficacy and safety, including onset of action, in late-stage development. A previous dose-ranging study provided a proof-of-concept 24-h duration of action for BEA2180 delivered via the Respimat® SMI in patients with moderate-to-severe COPD.[14] BEA2180 Respimat® SMI (10, 20, 50, 100 and 200 μg), tiotropium Respimat® SMI (5 μg) and placebo were administered once daily over 4 weeks of treatment. The primary endpoint (trough forced expiratory volume in 1 s [FEV_1]) was reached with BEA2180 (50, 100 and 200 μg), with trough FEV_1, $\Delta = -0.087$, -0.101 and -0.147 L, respectively, compared with placebo ($p < 0.05$ for all) and numerically higher than tiotropium (-0.100) with 100 and 200-μg doses. The safety profile for BEA2180 was similar to tiotropium. The most common adverse events (AEs) reported were nasopharyngitis and COPD exacerbations, as expected for this patient population and study period.

The primary objective of the current study (Clinical Trial number: NCT00528996) was to compare the long-term bronchodilator efficacy and safety of three once-daily doses (50, 100 and 200 μg) of BEA2180 delivered by the Respimat® SMI with placebo and the marketed and approved tiotropium Respimat® SMI 5 μg[3] for 24 weeks in patients with COPD.

Methods

Study design

We conducted a 24-week, multiple-dose, multicentre, multinational, randomised, double-blind, parallel-group study. Following an initial screening phase and 2-week baseline period to ensure clinical stability, patients were randomly assigned to BEA2180 Respimat® SMI (50, 100 or 200 μg), tiotropium Respimat® SMI (5 μg) or placebo with clinic visits occurring at weeks 1, 2, 4, 8, 12, 18 and 24.

Rescue medication could be administered at any time during the study; open-label salbutamol was provided at visits 1 and 9 as required and patients were encouraged to document its use. If salbutamol was used during a test day visit, the patient did not complete the remainder of the pulmonary function testing (PFT) on that day. Temporary increases in the dose or addition of oral steroids was allowed during the study period, however PFTs did not occur within 5 days of either. The use of antibiotics was not restricted. The following medications were allowed as long as they had been administered in stable doses over 6 weeks prior to the study: oral corticosteroids (≤10 mg daily); inhaled LABAs, oral ICS, theophylline preparations and mucolytic agents not containing bronchodilators. Short-acting anticholinergic drugs were allowed during the 2-week baseline period and the 3-week follow-up period. The use of short-acting beta adrenergic therapies other than salbutamol, anticholinergic drugs other than the study drug and their combinations was prohibited.

The study was conducted in accordance with the provisions of the Declaration of Helsinki (1996) and Good Clinical Practice guidelines.[18] The protocol was approved by the ethics committee at each study centre, and all patients provided written informed consent before any study procedure was performed.

Patients

Patients were recruited at 178 investigational centres, based in 10 countries. Male and female smokers or ex-smokers with a smoking history of more than 10 pack-years

who were ≥40 years old and able to perform PFTs were included in the study. All patients were diagnosed with COPD and demonstrated postbronchodilator FEV_1 <80% predicted[20] with FEV_1/forced vital capacity (FVC) ≤70%. Patients were excluded if they had: never smoked or smoked <10 pack-years; a history of asthma; been treated for a myocardial infarction within the past year; unstable or life-threatening cardiac arrhythmia (or associated hospitalisations); been hospitalised for heart failure within the past 3 years; regular use of daytime oxygen therapy and the inability to abstain from the use of oxygen therapy during test days; thoracotomy with pulmonary resection and/or the presence of a significant disease other than COPD that could preclude participation in the study or interfere with the study results. The randomisation of patients with any respiratory infection or COPD exacerbation in the 6 weeks prior to screening or during the baseline period was postponed. Further details of patients' inclusion and exclusion criteria can be found in the online supplement.

Assessments

Spirometry was performed according to American Thoracic Society guidelines.[17] Qualifying PFTs (FEV_1 and FVC) were conducted at the screening visit. At weeks 3, 4, 6 and 8, PFTs (FEV_1 and FVC) were only performed for the trough (pre-dosing) measurement. At weeks 2, 5, 7 and 9, PFTs (FEV_1 and FVC) were performed prior to dosing (trough) and at 15, 30 and 60 min, 2 and 3 h after inhalation of study medication. Prebronchodilator and postbronchodilator responses were recorded prior to and 30 min after the administration of salbutamol (400 μg). Additional details of spirometry can be found in the online supplement. Trough FEV_1 was defined as the mean of two measurements, at −40 and −15 min time points at the end of the 24-h dosing interval, prior to drug administration in the morning. Trough FEV_1 response was defined as the change from baseline in trough FEV_1 defined as the mean of the pre-treatment FEV_1 values measured at randomisation prior to administration of the first dose of study medication. No significant treatment-by-subgroup interaction was observed between subgroups in terms of disease severity at baseline, LABA or ICS usage. The Mahler BDI[15] was performed at the randomisation visit, whereas the Mahler TDI was completed at treatment visits starting with week 5. The TDI was also administered at weeks 7, 9 and 10. The BDI/TDI questionnaires were administered by physicians, nurses, respiratory therapists or cardiopulmonary technicians. The SGRQ[13] was administered at weeks 2, 5, 7, 9 and 10, prior to PFTs at all visits and after the Mahler BDI/TDI questionnaires. Reports of any AEs were collected at each visit.

An exacerbation was defined as a complex of lower respiratory events/symptoms (increased or new onset) related to the underlying COPD, with a duration of 3 days or more, requiring a change in treatment where a complex of lower respiratory events/symptoms meant at least two of the following: Shortness of breath; sputum production (volume); occurrence of purulent sputum; cough; wheezing; chest tightness.

Exacerbations were recorded as mild when there was a significant change of prescribed respiratory medication (i.e. bronchodilators, including theophylline). Exacerbations were classified as moderate or severe when the required change in treatment also included the prescription of antibiotics and/or systemic steroids. COPD exacerbations were captured as AEs and recorded on the AE electronic case report form.

Inhalers

The Respimat inhaler was used for all medications. There were no differences in the resulting *in vitro* aerodynamic particle size distribution for all medications, irrespective of strength and compound.

Statistical analyses

Using previous calculations (unpublished data); the standard deviation (SD) for trough FEV_1 was estimated at 0.215 L. On this basis, a sample size of approximately 1950 randomised patients (390 per treatment group) was deemed sufficiently sensitive to detect a difference of 0.05 L between all BEA2180 doses and tiotropium at the 0.025 level of significance (one-sided) with 90% power. The noninferiority margin for FEV_1 was chosen to be 0.05 L. Further details on the statistical hypotheses and testing procedures can be found in the online supplement.

All analyses, except where stated otherwise, were performed using data from all patients in the full analysis set. This consisted, individually for each endpoint, of all randomised patients with baseline data (pretreatment at the end of the 2-week baseline) and at least one adequate trough PFT following at least 5 days of randomised treatment. All spirometry endpoints (trough, area under the curve from 0 to 3 h [AUC_{0-3h}], peak and measurements at individual time points) physician's global evaluation, peak expiratory flow rate measurements and rescue medication use were summarised using analysis of covariance (ANCOVA) with terms for baseline (trough, $AUC0_{-3h}$ or peak), centre and treatment. The baseline was used as a linear covariate. A separate ANCOVA was performed for each time point (test day, week of diary data or time point within test day).

Exacerbation analysis was performed on the treated set presented as Kaplan–Meier estimates for COPD exacerbations by treatment arm. Patients with a TDI focal score of one or more were considered to be responders. A change of four units in the SGRQ total score was considered to be clinically meaningful and patients with a reduction of four units were considered responders. Both SGRQ and TDI focal score data were analysed using ANCOVA. All safety data were displayed and analysed using descriptive statistical methods. Full details of statistical analyses can be found in the online supplement.

Results

Study population

All randomised patients (n = 2080) received at least one dose of study medication; 429 received placebo, 419 were treated with BEA2180 50 μg, 415 with BEA2180 100 μg, 390

with BEA2180 200 μg and 427 with tiotropium 5 μg. The retention rate was high and the total of 1862 (89.5%) patients completed taking study medication according to the study protocol (Fig. 1). The overall demographic profile, and concomitant disease profile was similar between the treatment groups. The mean (SD) age of patients was 64.2 (8.8) years, 64.5% were male with a mean COPD duration of 8.4 years (Table 1a). All patients were either current (45.2%) or ex-smokers (54.8%) with a mean smoking history of 47.5 pack-years. The COPD disease characteristics profile was balanced across the treatment groups and consistent with values expected for COPD patients.[20] The mean baseline prebronchodilator FEV_1 was 1.2 L (43% of predicted value) and postbronchodilator FEV_1 was 1.3 L (49% of predicted value) (Table 1b). There was no difference between screening (1.2 L) and randomisation (1.2 L) FEV_1 values. The common mean baseline focal score was 6.5 and SGRQ total score was 42.9. A total of 77.1% of patients were taking respiratory medication (s) at baseline, including: 11.7% long-acting anticholinergics, 53.1% ICS and 56.3% LABAs; pulmonary medication use was similar between treatment groups.

Lung function

The mean trough FEV_1 at 24 weeks (primary efficacy endpoint) was significantly greater ($p < 0.0001$) after treatment with all three BEA2180 doses as well as after treatment with tiotropium in comparison with placebo (Fig. 2). The 50- and 100-μg doses reached statistical significance compared with placebo but did not achieve non-inferiority compared with tiotropium. The highest dose of BEA2180, 200 μg, was shown to be noninferior to tiotropium for the chosen margin (0.05 L).

Exacerbations

Compared with placebo, the risk of having a COPD exacerbation was significantly reduced for patients receiving the 50-μg or 200-μg dose of BEA2180 (hazard ratio [95% confidence interval]: 0.65 [0.47, 0.91] and 0.72 [0.51, 1.00], respectively (Fig. 3). No significant difference from placebo was observed for patients receiving the 100-μg dose of BEA2180 or tiotropium 5 μg. In comparison with tiotropium, no significant differences were observed for all doses of BEA2180.

TDI

The TDI focal scores were significantly higher ($p \leq 0.01$) for patients receiving active medication (tiotropium or BEA2180) versus patients receiving placebo over weeks 4, 12 and 24 (Fig. 4). No significant differences between tiotropium and BEA2180 doses were observed at either time point.

SGRQ

The means for SGRQ total score were significantly lower ($p < 0.01$) for patients receiving active medication (tiotropium or BEA2180) versus patients receiving placebo over weeks 12—24 (Fig. 5). No significant differences in SGRQ total score were found for the comparisons between tiotropium and any of BEA2180 doses.

Safety

The frequency of reported AEs was similar across all treatment groups, with a total of 1274 (61.3%) patients reporting any event. Adverse events were reported in 62.8% of patients treated with BEA2180 50 μg, in 59.0% receiving BEA2180 100 μg, and 64.4% treated with BEA2180 200 μg. Of those receiving tiotropium 5 μg or placebo, 59.5% and 60.8%, respectively, experienced AEs (Table 2). The most common AEs, reported in >3% of patients, included COPD exacerbation (332 [16%]), nasopharyngitis (153 [7.4%]), upper respiratory tract infection (99 [4.8%]), dyspnoea (78 [3.8%]) and cough (75 [3.6%]). COPD exacerbation was reported in 13.6—15.9% of BEA2180-treated patients, 15.9% of

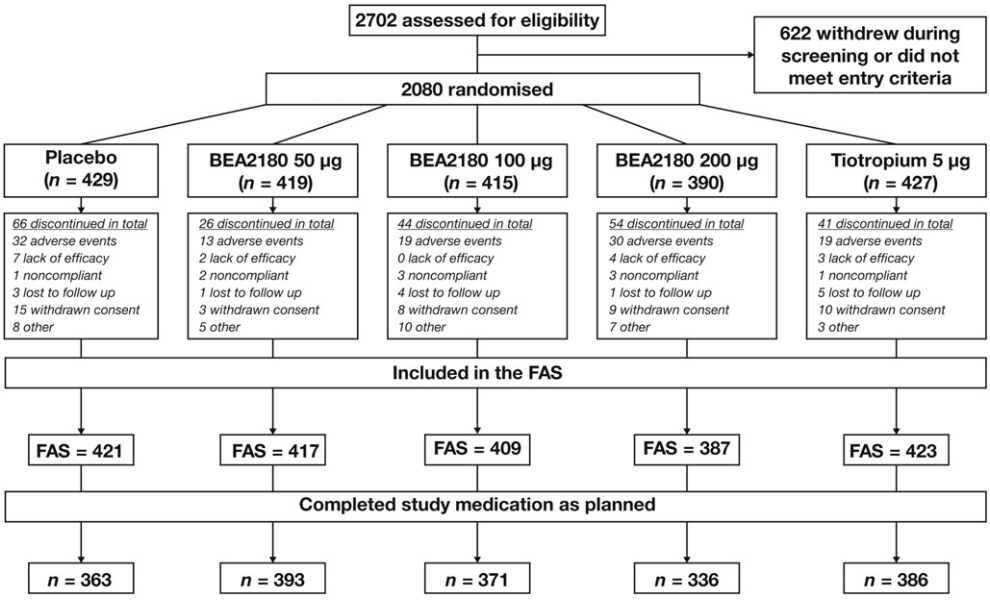

Figure 1 CONSORT diagram illustrating the flow of patients through the study. FAS, full analysis set.

Table 1a Baseline characteristics.

	Placebo	BEA2180 50 μg	BEA2180 100 μg	BEA2180 200 μg	Tiotropium 5 μg	Total
Patients, *N*	429	419	415	390	427	2080
Male gender, *N* (%)	274 (63.9)	267 (63.7)	269 (64.8)	250 (64.1)	281 (65.8)	1341 (64.5)
Age, mean (SD), y	64.4 (8.6)	64.0 (8.7)	64.6 (9.1)	63.9 (8.9)	63.9 (8.7)	64.2 (8.8)
White race, *N* (%)	384 (89.5)	371 (88.5)	363 (87.5)	340 (87.2)	382 (89.5)	1840 (88.5)
BMI, mean (SD), kg/m^2	27.2 (6.4)	26.9 (5.7)	27.1 (5.9)	27.5 (5.9)	26.8 (6.0)	27.1 (6.0)
Current smoker, *N* (%)	194 (45.2)	189 (45.1)	191 (46.0)	176 (45.1)	190 (44.5)	940 (45.2)
Ex-smoker, *N* (%)	235 (54.8)	230 (54.9)	224 (54.0)	214 (54.9)	237 (55.5)	1140 (54.8)
Smoking history, mean (SD), pack-years	46.4 (22.0)	48.9 (27.6)	46.8 (23.9)	48.3 (26.8)	47.3 (24.9)	47.5 (25.1)
COPD duration, mean (SD), y	8.6 (6.6)	8.3 (6.4)	8.5 (6.4)	8.3 (6.7)	8.4 (6.5)	8.4 (6.5)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

tiotropium-treated patients and in 19.8% of placebo-treated patients (Table 2).

Drug-related AEs were reported in fewer than 10% of patients overall (126 [6.1%]), and in 6.0% of those treated with BEA2180 50 μg, in 5.3% receiving BEA2180 100 μg and in 8.7% of patients treated with BEA2180 200 μg. In the tiotropium 5 μg and placebo groups, 4.2% and 6.3% of patients, respectively, experienced drug-related AEs. In order of increasing frequency, the following drug-related AEs were reported in 0.4—0.9% of all patients combined: COPD, taste disturbance, dyspnoea, cough and dry mouth. The incidence of cough was highest with BEA2180 200 μg (1.5%) and the incidence of dry mouth was highest with tiotropium (1.6%).

More patients randomised to placebo (30 [7.0%]) reported AEs that led to discontinuation of study medication than those treated with BEA2180 50 μg (13 [3.1%]), 100 μg (17 [4.1%]), 200 μg (29 [7.4%]) or tiotropium 5 μg (18 [4.2%]). More serious AEs were reported with placebo (10.0%) than with any BEA2180 (8.0—9.2%) or tiotropium

Table 1b Baseline spirometry.

	Placebo	BEA2180 50 μg	BEA2180 100 μg	BEA2180 200 μg	Tiotropium 5 μg	Total
Patients, N	429	419	415	390	427	2080
Before bronchodilation						
FEV_1, mean (SD), L	1.18 (0.46)	1.18 (0.46)	1.18 (0.48)	1.19 (0.49)	1.20 (0.47)	1.18 (0.47)
FEV_1, mean (SD), % predicted	43.2 (14.5)	43.0 (14.8)	43.5 (15.1)	43.5 (14.8)	43.2 (14.3)	43.3 (14.7)
After bronchodilation						
FEV_1, mean (SD), L	1.34 (0.50)	1.34 (0.49)	1.33 (0.51)	1.36 (0.52)	1.35 (0.49)	1.34 (0.50)
FEV_1, mean (SD), % predicted	49.1 (14.8)	49.0 (15.5)	48.9 (15.3)	49.8 (15.1)	48.6 (14.3)	49.1 (15.0)
FEV_1 % change from pre-bronchodilator value	15.5	16.0	14.9	16.7	15.0	15.6
BDI (focal score)	6.6 (2.0)	6.4 (2.1)	6.5 (2.2)	6.4 (2.1)	6.5 (2.0)	NA
SGRQ total score, units	43.2 (18.1)	42.0 (17.5)	43.0 (17.7)	44.0 (18.8)	43.1 (18.0)	NA
Respiratory medication, %						
Any	74.6	77.3	76.1	78.7	78.7	77.1
Short-acting anticholinergics	27.7	28.9	28.4	33.1	30.4	29.7
Long-acting anticholinergics	11.9	11.7	11.8	10.5	12.4	11.7
SABAs	16.3	15.5	13.3	18.5	16.6	16.0
LABAs	54.6	58.0	54.9	56.9	56.9	56.3
ICS	52.0	53.0	51.8	53.1	55.5	53.1
LABA + ICS[a]	35.0	36.0	37.3	39.2	36.8	36.8
Leukotriene receptor antagonists	1.9	3.1	2.7	4.4	1.9	2.7
Oral steroids	3.0	2.2	3.9	2.8	1.6	2.7
Xanthines	14.0	14.1	13.5	17.2	16.4	15.0
Oxygen	4.2	2.4	3.9	3.9	3.0	3.5

BDI, Baseline Dyspnoea Index; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

[a] Patients may have received more than one LABA + ICS.

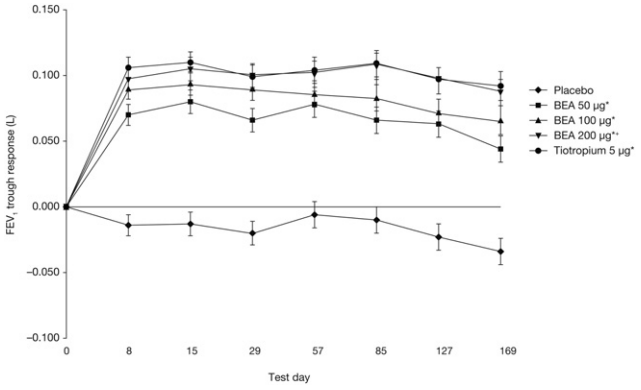

Figure 2 FEV_1 trough BEA2180 (50, 100, 200 μg) versus placebo and tiotropium (5 μg). Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed). *$p < 0.0001$ compared with placebo. Number of patients; +Noninferiority to tiotropium 5 μg, noninferiority delta = 0.05 L; placebo (421), BEA2180 50 μg (417), BEA2180 100 μg (409), BEA2180 200 μg (387), tiotropium 5 μg (423). Common baseline mean (SE) = 1.184 (0.010). ANCOVA, analysis of covariance; FEV_1, forced expiratory volume in 1 s; SE, standard error.

(8.2%) treatment. Among the BEA2180-treated patients, serious AE frequencies were consistent across all dosing groups. The proportion of serious AEs was comparable among all treatments: among the 2080 patients, there were 20 fatal events; three randomised to BEA2180 50 μg, three to BEA2180 100 μg, seven to BEA2180 200 μg, two to tiotropium 5 μg and five receiving placebo. In addition, two patients died post-study; both were randomised to tiotropium. All cases were considered by the investigator to be unrelated to study medication. Further details of AEs can be found in the Online Supplement.

Discussion

This study was the first, long-term head-to-head comparison of the once-daily anticholinergic BEA2180 with the once-daily tiotropium in patients with COPD. Both long-acting bronchodilators were inhaled via the Respimat® SMI delivery system.

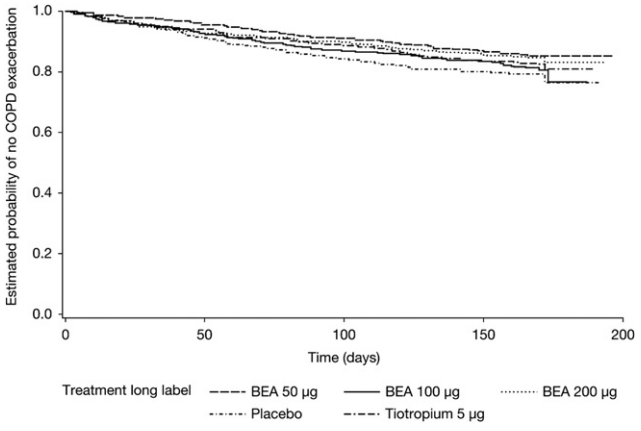

Figure 3 Kaplan–Meier estimates of no COPD exacerbations, BEA2180 (50, 100, 200 μg) versus tiotropium (5 μg) and placebo. COPD, chronic obstructive pulmonary disease.

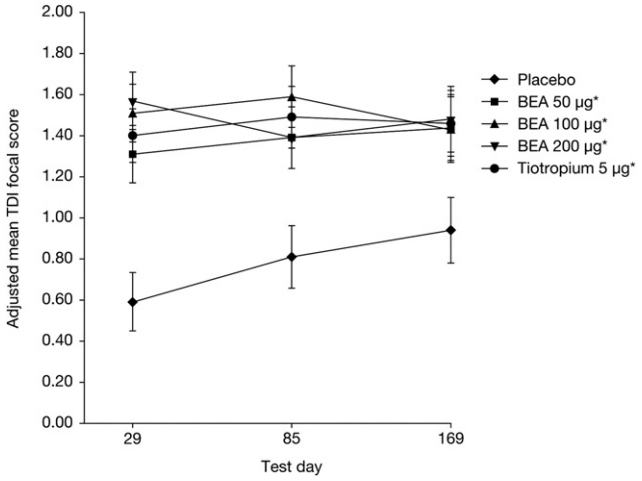

Figure 4 Adjusted mean TDI focal scores at 4, 12 and 24 weeks comparison to placebo and tiotropium. Based on ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed). Number of patients: Placebo (406), BEA2180 50 μg (410), BEA2180 100 μg (398), BEA2180 200 μg (379), tiotropium 5 μg (416). Common baseline mean (SE) = 6.48 (0.05). *$p \leq 0.01$ compared with placebo; ANCOVA, analysis of covariance; SE, standard error; TDI, Transition Dyspnoea index.

Overall, in this trial of 2080 patients, both tiotropium and BEA2180 were effective at improving lung function, reducing the symptoms of COPD and were generally well tolerated. The primary endpoint for this trial was achieved and BEA2180 at all three doses was significantly better than placebo with respect to FEV_1 trough after 24 weeks of treatment, although only the 200-μg dose of BEA2180 was noninferior to tiotropium. There was no plateau in the BEA2180 dose response curves at the studied doses and results revealed that symptom assessments including SGRQ and TDI were improved for all four active treatments versus placebo, with little separation among treatment groups.

The prevention of exacerbations is a key component of COPD management strategies,[8] so it was a welcome finding that COPD exacerbation yearly rates and time to first exacerbation were numerically reduced in all active treatments compared with placebo, reaching statistical significance for the BEA2180 50- and 200-μg doses. The observed effects of BEA2180 on exacerbations are surprising given the comparatively short duration of the trial, which may explain the lack of an observed significant effect of tiotropium on exacerbations. In this respect, the data contrast with other studies of tiotropium, for example, the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT®) study, carried out over a 4-year period, demonstrated that tiotropium led to a reduction in exacerbations amongst COPD patients compared with placebo.[27] Similarly, data from a recent 48-week study revealed that tiotropium reduced the time to first exacerbation and the time to first hospital-treated exacerbation relative to placebo.[3] Results from a patient-level pooled analysis also confirmed that tiotropium reduced the risk of exacerbations and associated hospitalisations compared with placebo in randomised, placebo-controlled trials.[10]

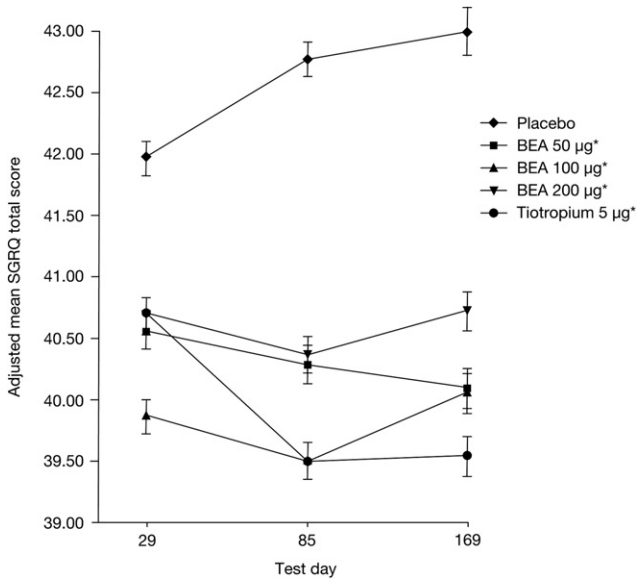

Figure 5 Adjusted mean SGRQ total score comparison to placebo and tiotropium over 24 weeks. Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed). Number of patients: Placebo (411), BEA2180 50 µg (415), BEA2180 100 µg (404), BEA2180 200 µg (379), tiotropium 5 µg (419). Common baseline mean (SE) = 42.87 (0.40). *$p < 0.01$ compared with placebo; ANCOVA, analysis of covariance; SE, standard error; SGRQ, St George's respiratory questionnaire.

Our study was not powered to detect differences in exacerbation rates; however, the efficacy data were comparable for both compounds, suggesting BEA2180 might also lead to reduced exacerbation rates in patients.

All active treatments were safe at the doses studied and the overall safety profile of BEA2180 was consistent with the patient population and with the known side-effect profile of anticholinergics.[9] None of the events leading to death were considered to be related to study medication and the causes of death were consistent with those expected in a patient population of >10 pack-year smokers.

Therapeutic delivery is a key concern of COPD maintenance treatment, given issues of device use and compliance.[2,19] In many countries, tiotropium is administered via the Respimat® SMI, a novel propellant-free inhaler with a soft-mist aerosol delivering fine-particle fraction. It generates a soft mist released over approximately 1.5 s, as opposed to standard propellants.[11] The low-cloud velocity combined with <5 µm particle size, reduces oropharyngeal deposition and allows for pervasive lung delivery,[1] even with poor inhalation technique.[11] Previous studies have also demonstrated significantly higher ($p < 0.05$) total satisfaction scores for Respimat® SMI compared with a dry-powder and a metered-dose inhaler; in addition, more patients preferred and were willing to continue using the Respimat® SMI.[12,21] The recommended dosage of two puffs of tiotropium (2.5 µg per puff) once daily[3] was the basis for the dosage frequency used in the current trial. The main strength of the trial is that it tested two compounds head to

Table 2 Summary of adverse events.

	Placebo *N* (%)	BEA2180 50 µg *N* (%)	BEA2180 100 µg *N* (%)	BEA2180 200 µg *N* (%)	Tiotropium 5 µg *N* (%)	Total *N* (%)
Number of patients	429 (100.0)	419 (100.0)	415 (100.0)	390 (100.0)	427 (100.0)	2080 (100.0)
Patients with any AE	261 (60.8)	263 (62.8)	245 (59.0)	251 (64.4)	254 (59.5)	1274 (61.3)
COPD	85 (19.8)	60 (14.3)	66 (15.9)	53 (13.6)	68 (15.9)	332 (16.0)
Nasopharyngitis[a]	38 (8.9)	28 (6.7)	33 (8.0)	27 (6.9)	27 (6.3)	153 (7.4)
Upper RTI[a]	20 (4.7)	26 (6.2)	21 (5.1)	13 (3.3)	19 (4.4)	99 (4.8)
Dyspnoea[a]	25 (5.8)	15 (3.6)	14 (3.4)	11 (2.8)	13 (3.0)	78 (3.8)
Cough[a]	13 (3.0)	17 (4.1)	17 (4.1)	18 (4.6)	10 (2.3)	75 (3.6)
Bronchitis[a]	10 (2.3)	16 (3.8)	11 (2.7)	10 (2.6)	12 (2.8)	59 (2.8)
Headache[a]	7 (1.6)	9 (2.1)	9 (2.2)	11 (2.8)	16 (3.7)	52 (2.5)
Sinusitis[a]	7 (1.6)	6 (1.4)	7 (1.7)	13 (3.3)	10 (2.3)	43 (2.1)
Patients with severe AEs	39 (9.1)	33 (7.9)	30 (7.2)	34 (8.7)	25 (5.9)	161 (7.7)
Patients with other significant AEs (according to ICH E3)	18 (4.2)	5 (1.2)	13 (3.1)	16 (4.1)	14 (3.3)	66 (3.2)
Patients with AEs leading to discontinuation of trial drug	30 (7.0)	13 (3.1)	17 (4.1)	29 (7.4)	18 (4.2)	107 (5.1)
Patients with serious AEs	43 (10.0)	37 (8.8)	33 (8.0)	36 (9.2)	35 (8.2)	184 (8.8)
Fatal	5 (1.2)	3 (0.7)	3 (0.7)	7 (1.8)	2 (0.5)	20 (1.0)
Immediately life threatening	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.8)	0 (0.0)	4 (0.2)
Disability/incapacitation	1 (0.2)	2 (0.5)	1 (0.2)	2 (0.5)	0 (0.0)	6 (0.3)
Required hospitalisation	37 (8.6)	32 (7.6)	30 (7.2)	30 (7.7)	32 (7.5)	161 (7.7)
Prolonged hospitalisation	3 (0.7)	3 (0.7)	1 (0.2)	3 (0.8)	0 (0.0)	10 (0.5)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	5 (1.2)	3 (0.7)	3 (0.7)	3 (0.8)	3 (0.7)	17 (0.8)

A patient may be counted in more than one seriousness criterion. Percentages are calculated using total number of patients per treatment as the denominator. Medical Dictionary for Regulatory Affairs version12.0 used for reporting.
AE, adverse event; COPD, chronic obstructive pulmonary disease; ICH, International Conference on Harmonisation; RTI, respiratory tract infection.
[a] Preferred term.

head, versus each other and placebo, using the same delivery system without differences in the *in vitro* aerodynamic particle size distributions. This design resulted in a true comparison without the need for using a double dummy, which could have negatively impacted the data for a variety of reasons.[11,21]

A limitation of this study was that it was a single trial, and there are currently no confirmatory data to support the findings. The timeframe and sample size may have been insufficient to enable the true clinical impact of tiotropium and BEA2180 on exacerbations; it is possible that a longer study might have given a more representative result for both. A short trial duration may also explain why we found significance for exacerbation reduction in 50- and 200-μg, but not in the 100-μg treatment arm; this discrepancy between the low, high and intermediate dose is difficult to interpret, and may reflect borderline data, or alternatively a statistical artefact. However, all active treatments showed a positive numerical trend, suggesting the effect of BEA2180 might be similar to tiotropium. Longer trials, powered to further evaluate the effect of BEA2180 on exacerbation rates, are required before more solid conclusions can be drawn.

There are several other avenues that future studies might explore; one particular aspect of importance is patient acceptance of therapy, as adherence to a prescribed regimen is clearly vital in the management of COPD as a long-term, chronic condition.[4] Rapid onset and long duration of action are similarly important issues to patients[7,26] as earlier relief of symptoms helps improve compliance and has a direct impact on quality of life in patients with COPD.[25] TIOSPIR®, a large scale, prospective, randomised trial comparing tiotropium SMI 5 μg, 2.5 μg and HandiHaler® 18 μg in >17,000 patients was initiated by Boehringer Ingelheim in 2009. The study is due to end in 2013 and was designed to elucidate the all-cause mortality risks associated with tiotropium SMI 5 μg. In the present study, there were numerically fewer fatal adverse events in the tiotropium group (2 vs 5 for placebo).

Conclusions

The long-acting anticholinergic bronchodilators, BEA2180 and tiotropium, both delivered via Respimat® SMI, were effective at improving lung function and reducing the symptoms of COPD. Only the 200-μg dose of BEA2180 was comparable to tiotropium with respect to FEV_1 trough. The risk of COPD exacerbations was reduced with all active treatments, reaching statistical significance for BEA2180 50 and 200 μg. Overall, the safety profile of both trial drugs was consistent with the patient population and with the known anticholinergic side-effect profile. All active treatments were well tolerated at the doses studied in this trial.

Author contributions

RA was the study coordinating investigator and reviewed, edited, and approved the final draft of the manuscript; PMZ was the clinical program leader and was involved in protocol development, data analyses and manuscript review; JR recruited patients, analysed data and reviewed the manuscript; HS was involved in data analyses, interpretation and manuscript review; JK participated in the trial and critically reviewed the manuscript. EJ contributed to protocol development, running the trial, reporting of data and manuscript review.

Conflicts of interests

RA is a speaker for GlaxoSmithKline (GSK). Over the past 3 years he has conducted clinical research for GSK, Forest, Pearl Therapeutics, Pfizer, and is coordinating investigator for BI. JR received research support from BI. JK is a member of the BI Speaker's Bureau and received research support from BI. She is also a member of the Speaker's Bureau for Forest Labs, Genentech, Novartis and Merck. She received research support from Forest Labs, Genentech, Novartis and Astra-Zeneca. PMZ, EJ and HS are employees of BI.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.02.005.

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