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Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations

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Summary
The FORWARD study is a randomised, double-blind trial that compares the efficacy and safety of 48 weeks treatment with extrafine beclomethasone dipropionate/formoterol fumarate (BDP/FOR), 100/6 μg pMDI, 2 inhalations BID, vs. FOR 12 μg pMDI, 1 inhalation BID, in severe COPD patients with a history of exacerbations. Co-primary endpoints were exacerbation rate over 48 weeks and pre-dose morning FEV_1 at 12 weeks.

The ITT population included 1186 patients (69% males, mean age 64 years) with severe airflow limitation (mean post-bronchodilator FEV_1 42% predicted). Salbutamol as rescue therapy, theophylline and tiotropium (if stable regimen prior to screening) were allowed.

Compared to FOR, BDP/FOR: *(1)* reduced the exacerbation rate (rate ratio: 0.72 [95% confidence interval 0.62–0.84], $p < 0.001$); *(2)* improved pre-dose morning FEV_1 (mean difference:

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[1] Investigators in the Foster 48-week Trial to Reduce Exacerbations in COPD (FORWARD) trial are listed in the on-line supplement.

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0.069 L [0.043−0.095] $p < 0.001$); *(3)* prolonged the time to first exacerbation; *(4)* improved the SGRQ total score. The percentage of patients with adverse events was similar (52.1% with BDP/FOR and 49.2% with FOR). Pneumonia incidence was low, slightly higher with BDP/FOR (3.8%) than with FOR (1.8%). No difference for laboratory values, ECG or vital signs.

Extrafine BDP/FOR significantly reduces the exacerbation rate and improves lung function of patients with severe COPD and history of exacerbations as compared to FOR alone.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem that imposes considerable economic and healthcare burdens on society, with the disease being projected to be the third leading cause of morbidity and mortality worldwide by 2030 [1].

Current pharmacological treatment reduces symptoms of the disease, improves lung function and prevents exacerbations, the latter being an important outcome in COPD that affects disease progression [2].

A combination of beclomethasone dipropionate/formoterol fumarate (BDP/FOR) has been developed in a pressurized metered dose inhaler (pMDI) device delivering extrafine particles which enable the drug to reach also the small airways, a relevant site of inflammation in COPD, and have, therefore, the potential to improve therapeutic efficacy [3]. Recent evidence showed that, in patients with severe COPD, the use of BDP/FOR for 48 weeks improved FEV_1 to the same degree as budesonide/FOR with a nominal dose of BDP two-fold lower than the equipotent daily dose of budesonide; however, in this study, no combination showed reduction of COPD exacerbations compared to FOR alone [4]. The most likely explanation for this finding is that the population enrolled had a low rate of exacerbations, due in part to the study design which required patients to be stable at enrolment and therefore less likely to exacerbate during the study. Further investigations were therefore needed to assess the potential benefit of BDP/FOR on exacerbation rates in patients with frequent exacerbations.

To better understand the effects of BDP/FOR on the prevention of COPD exacerbations, a double-blind, randomised, controlled study was designed in severe COPD patients with a documented history of exacerbations [5]. Previous history of exacerbations is the best predictor for future exacerbation [6], but since exacerbations are often not reported by patients [7—9], two innovative aspects were implemented in the study. Firstly, we used an electronic real-time transmission of EXACT diary data to enhance contact between patients and physicians and to improve the reporting of exacerbations. Secondly, by coordinating recruitment waves in the northern and southern hemispheres, different winter exacerbation peaks were captured across the globe, thus increasing the chance of catching winter respiratory viral infections. The primary aim of the study was to test the superiority of extrafine BDP/FOR 100/6 μg, 2 inhalations BID over extrafine FOR alone 12 μg, 1 inhalation BID in both the reduction of exacerbations and the improvement of pre-dose morning FEV_1 in COPD patients.

Methods

The on-line supplement presents an extended and detailed version of the methodology used in the FORWARD study. A summary is shown below.

Study participants and ethics

Eligible patients were outpatients, aged >40 years, current or former smokers (≥10 pack-years) with a diagnosis of severe COPD (post-pMDI salbutamol $FEV_1/FVC < 0.7$ and $30\% \leq FEV_1 < 50\%$ of predicted normal value) and a documented history of at least one exacerbation in the previous year. Patients were not eligible in case of asthma diagnosis and other unstable concurrent diseases, which might have affected the feasibility of the results according to investigator's judgement.

The study, approved by an institutional review board for each of the clinical sites, was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable local regulations. All participants signed the informed consent.

Study design

The FORWARD study was a phase III, double-blind, randomised, 2-arm parallel-group study that compares the efficacy and tolerability of BDP/FOR 100/6 μg, 2 inhalations BID, vs. FOR 12 μg, 1 inhalation BID, both administered using a pMDI over 48 weeks [5]. Inhalers were identical for BDP/FOR and FOR alone and blinding on the 2 vs. 1 inhalation b.i.d for FOR was guaranteed by providing 2 inhalers to each patient (one for each inhalation), the second inhaler containing placebo for those patients randomised to receive FOR alone. After a 2-week run-in period under FOR 12 μg BID, patients were centrally randomised stratifying by country and smoking status. Visits were planned at 4, 12, 24, 36 and 48 weeks after randomisation. Theophylline and Tiotropium were allowed during the study if the dose was stable before screening and maintained constant throughout the study, salbutamol was allowed per rescue use. Electronic diaries were used daily to record treatment intake, use of rescue

medication and symptoms completing the EXACT questionnaire [10].

Seasonal recruitment

Because COPD exacerbations peak during winter, patient recruitment was initiated before the end of winter in three waves across the globe to capture more winter-related exacerbations: two in the Northern (waves 1 and 3) and one in the Southern Hemisphere (wave 2). The recruitment was from 02/10/2009 to 22/12/2009 and from 05/10/2010 to 17/02/2011 (waves 1 and 3 respectively); from 30/04/2010 to 12/02/2011 (wave 2).

Efficacy endpoints

The two *co-primary efficacy endpoints* of the study were: COPD exacerbation rate over the entire treatment period and change in pre-dose morning FEV_1 (L) from baseline (randomisation visit) to Week 12.

Secondary efficacy endpoints included; time to first COPD exacerbation, change from baseline in pre-dose morning FEV_1 at other visits and health status as assessed by St. George's Respiratory Questionnaire (SGRQ) total score at the end of the treatment.

Safety endpoints

Safety evaluation included adverse events (AEs), serious AEs (SAEs), vital signs, laboratory data (haematology and chemistry), and 12-lead electrocardiograms (ECGs). Laboratory tests and ECGs were performed at screening and at Week 48 (or at early discontinuation).

Measurements

COPD exacerbations were defined according to GOLD guideline definition [11] and their recognition was enhanced by daily EXACT diary data transmission, although patients were allowed to seek medical advice directly, if needed. The EXACT, a 14-item questionnaire [10], was used to alert the physician about patients' symptom worsening but not to diagnose the exacerbation *per se* — that was performed on a clinical basis by the physician. The patient received regular reminders to contact the physician in case of symptoms worsening.

Spirometry was performed at each visit, following international recommendations [12], at approximately the same time of day and using the same spirometer throughout the course of the study. At screening, to verify the eligibility of the patient, spirometry was performed before and after the inhalation of 400 μg salbutamol (4 × 100 μg pMDI, ventolin®). At each clinical visits (from randomisation to Week 48), spirometry assessments were carried out prior to study drug administration and 2 h after dosing. Rescue medication (salbutamol) was withheld for at least 8 h and tiotropium for at least 72 h prior to the pre-dose assessment at each visit.

Health status was assessed at randomisation and Week 48 (or at early discontinuation) using the SGRQ [13].

Statistical analysis

551 randomised patients per group provided 82.6% power to detect a 20% reduction in exacerbation rate, assuming an annual rate of 0.8 with FOR, an overdispersion of 1.1 and 13.5% of patients discontinued at the end of study. 530 evaluable patients per group at Week 12 provided 80% power to detect a mean difference of 50 ml in pre-dose morning FEV_1 assuming an SD of 290 ml [5].

Efficacy variables were analysed on the Intent-to-Treat (ITT) population (all patients with efficacy data), while safety analysis included all treated patients. The number of COPD exacerbations was submitted to a Poisson regression model allowing for overdispersion and including country, smoking status, tiotropium use, number of exacerbations in the last year and post-salbutamol FEV_1 at Visit 1 as covariates. Pre-dose morning FEV_1 was analysed using a mixed model for repeated measures (MMRM) including country, smoking status, tiotropium use and the baseline value as covariates. Analyses of the primary variables were also performed on the Per Protocol (PP) population (ITT patients with no major deviations) stratifying by tiotropium use, smoking status and gender. A post-hoc sensitivity analysis of the exacerbations based on the negative binomial model was conducted [14]. The analysis of the average FEV_1 over the entire treatment period was also based on the MMRM above described, assuming equal weight for each visit. Time to first exacerbation was analysed using a Co_x proportional hazards model including the same covariates of the Poisson regression. The SGRQ total score was submitted to an ANCOVA model including the same covariates considered in the analysis of FEV_1. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics at baseline

Fig. 1 presents the flow diagram of the study. A total of 1693 patients were screened, of whom 1199 were randomised to BDP/FOR ($N = 602$) or FOR ($N = 597$) groups. The most common reasons for screen failure were failure to meet inclusion criteria and consent withdrawal ($n = 362$ and $n = 108$, respectively). The most common reason for early study discontinuation in both treatment groups was withdrawal of consent (4.2% and 6.0% in the BDP/FOR and FOR groups, respectively). A total of 7 randomised patients in the BDP/FOR group and 6 in the FOR group were not included in the ITT population due to the following reasons: violation of a major entry criterion (patients without COPD, $n = 5$ in the BDP/FOR group and $n = 4$ in the FOR group), lack of post-baseline efficacy data ($n = 1$ in each group) and no intake of study drug ($n = 1$ in each group, these patients were also not included in the analysis of safety).

Table 1 shows that the treatment groups were well-matched for demographic and functional characteristics at baseline. About 39% of the patients were current smokers, with a mean cumulative smoking exposure slightly above 40 pack-years. On average, about 1.5 exacerbations/year in the previous 12 months were reported in both

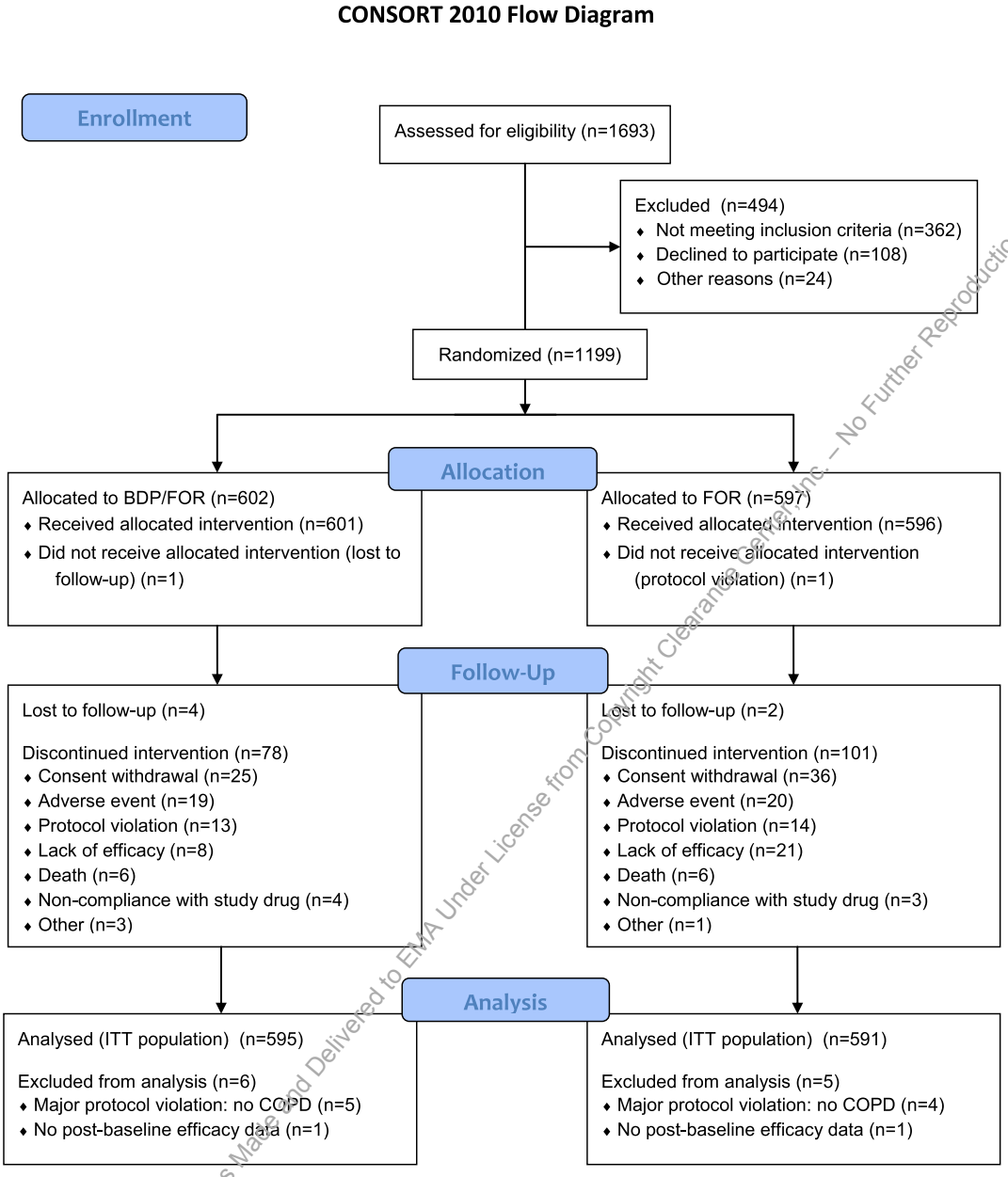

Figure 1 Flow diagram of the study.

groups and the mean SGRQ total score was approximately 48. Mean post-salbutamol FEV_1 at screening was 42% of the predicted value.

Efficacy endpoints

COPD exacerbation rate

The percentage of patients with exacerbations was lower in the BDP/FOR group (44.4%) than in the FOR group (49.7%, Table 2). The adjusted rate of exacerbations per patient per year was lower in the BDP/FOR arm (0.80 vs. 1.12), leading to a statistically significant adjusted rate ratio between the two treatment groups in favour of BDP/FOR of 0.72 (95% CI: 0.62, 0.84; $p < 0.001$) (Table 2), that corresponds to a 28% reduction in the exacerbation rate with BDP/FOR. These results were confirmed in the PP population and in the stratified analysis of the males, current smokers, ex-smokers and tiotropium and non—tiotropium users at randomisation. In female patients, a trend toward a lower exacerbation rate with BDP/FOR compared to FOR was found but did not reach statistical significance (Fig. 2). Consistent results were provided by the post-hoc sensitivity analysis using the negative binomial model.

Change in pre-dose morning FEV1 from baseline to Week 12

The adjusted mean FEV_1 change at Week 12 was larger in the BDP/FOR group than in the FOR group (0.081 L vs. 0.012 L), with a statistically significant difference between treatment groups in favour of BDP/FOR (0.069 L [95% CI: 0.043, 0.095]; $p < 0.001$) (Table 2). This was confirmed in the PP population and in all subgroups analyzed (Fig. 3).

Table 1 Demographic and baseline clinical characteristics of patients (ITT population).

	BDP/FOR ($N = 595$)	FOR ($N = 595$)
Males, *n* (%)	408 (69%)	410 (69%)
Age, years, mean ± SD	64.6 ± 8.6	63.9 ± 8.6
BMI, Kg/m^2, mean ± SD	26.5 ± 5.4	26.5 ± 5.3
Current smokers, *n* (%)	231 (39%)	237 (40%)
Packs/year, mean ± SD	43.1 ± 23.5	42.7 ± 22.9
SGRQ total score, mean ± SD	47.3 ± 17.9	48.0 ± 17.2
Number of exacerbations in past year, mean ± SD	1.5 ± 0.9	1.4 ± 0.9
Tiotropium users, *n* (%)	318 (53%)	298 (50%)
Post-bronchodilator FEV_1, % of predicted, mean ± SD	41.9 ± 6.0	41.6 ± 6.0
Post-bronchodilator FEV_1, L, mean ± SD	1.15 ± 0.30	1.16 ± 0.30
Post-bronchodilator FEV_1/FVC, mean ± SD	0.48 ± 0.10	0.48 ± 0.10
Reversibility, L, mean ± SD	0.10 ± 0.12	0.10 ± 0.13
Reversibility, %, mean ± SD	10.8 ± 12.9	10.7 ± 14.1

Note: lung function data are from Visit 1 (screening visit). Reversibility in L was calculated as post-bronchodilator FEV_1 minus pre-bronchodilator FEV_1, while reversibility in percentage was calculated as (reversibility in L/pre-bronchodilator FEV_1)*100.

Secondary endpoints

Analysis of time to first COPD exacerbation showed a significantly lower even risk in the BDP/FOR group compared to the FOR group, with a hazard ratio of 0.80 (95% CI: 0.68, 0.95; $p = 0.010$) (Fig. 4).

Fig. 5 presents the adjusted mean change from baseline in pre-dose morning FEV_1 at all post-randomisation visits. Differences between groups were statistically significant in favour of BDP/FOR at all visits. The average FEV_1 change over the treatment period was also significantly higher in the BDP/FOR arm (adjusted mean difference between treatments: 0.062 L [95% CI: 0.040, 0.084]; $p < 0.001$).

Likewise, the decrease (i.e. improvement) from baseline to end of treatment in the SGRQ total score was statistically significant only in the BDP/FOR group ($p < 0.001$), and the adjusted mean difference of −2.78 units (95%: −4.51, −1.05) between treatments was statistically significant ($p = 0.002$) (Table 2).

Safety endpoints

The incidence of AEs, SAEs, adverse drug reactions (ADRs) and withdrawals due to AEs were similar in the two treatment groups (Table 3). Pneumonia was reported by 23 patients (3.8%) in the BDP/FOR group and 11 patients (1.8%) in the FOR group (Table 4).

Treatment-emergent SAEs and ADRs are listed in on-line supplement (Table 5). The most commonly reported ADR was oral candidiasis (2.2% and 0.3% respectively in the BDP/FOR and FOR groups). Two ADRs (1 in each treatment arm) were considered serious (atrial fibrillation), a known AE associated with FOR treatment (Table 5 on-line supplement). Changes in vital signs and 12-lead ECG did not raise any unexpected safety concern. Eleven patients (1.8%) in the BDP/FOR group and 8 patients (1.3%) in the FOR group died. Four out of the 11 patients' deaths in the BDP/FOR group were due to events started after treatment discontinuation. None of the deaths reported during the trial were classified as related to the study treatment.

Table 2 COPD exacerbations during the study: change from baseline to Week 12 in FEV_1 and change from baseline to the end of treatment in the SGRQ total score.

	ITT population		PP population	
	BDP/FOR $N = 595$	FOR $N = 591$	BDP/FOR $N = 517$	FOR $N = 515$
COPD exacerbations during the study				
Number (%) of patients with at least one exacerbation	264 (44.4%)	294 (49.7%)	222 (42.9%)	257 (49.9%)
Adjusted rate per patient per year (95% CI)	0.804 (0.713, 0.907)	1.118 (1.006, 1.242)	0.774 (0.679, 0.881)	1.073 (0.959, 1.200)
Adjusted rate ratio BDP/FOR vs. FOR (95% CI)	0.719 (0.619, 0.837) $p < 0.001$		0.721 (0.613, 0.848) $p < 0.001$	
Change from baseline to Week 12 in FEV_1 (L)				
Adjusted mean change from baseline (95% CI)	0.081 (0.062, 0.100) $p < 0.001$	0.012 (−0.007, 0.030) $p = 0.218$	0.080 (0.060, 0.100) $p < 0.001$	0.015 (−0.005, 0.035) $p = 0.152$
Adjusted mean difference BDP/FOR vs. FOR (95% CI)	0.069 (0.043, 0.095) $p < 0.001$		0.065 (0.037, 0.093) $p < 0.001$	
Change from baseline to the end of treatment in the SGRQ total score				
Adjusted mean change from baseline (95% CI)	−3.55 (−4.80, −2.29) $p < 0.001$	−0.77 (−2.01, 0.47) $p = 0.222$	–	–
Adjusted mean difference BDP/FOR vs. FOR (95% CI)	−2.78 (−4.51, −1.05) $p = 0.002$		–	–

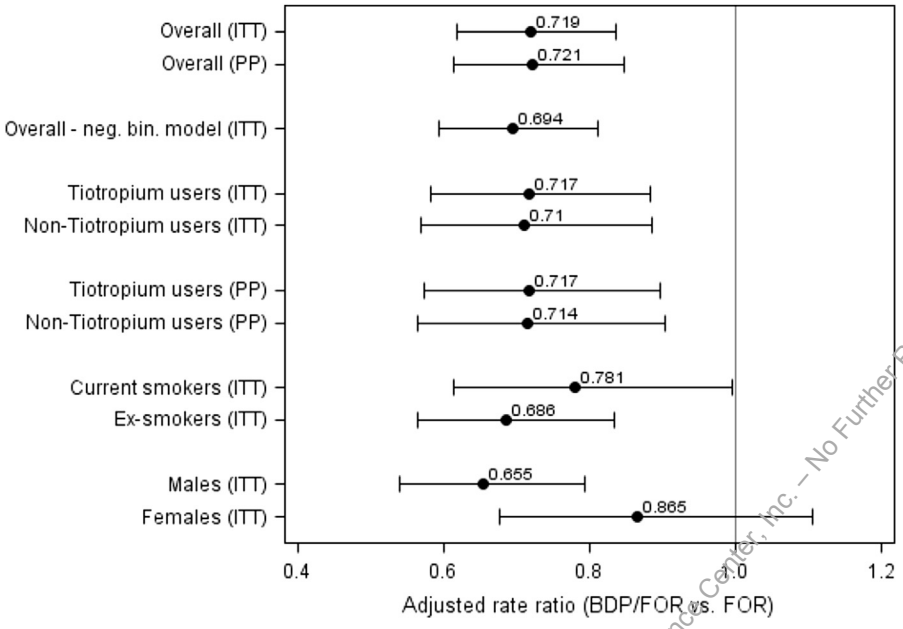

Figure 2 Summary of the analyses of COPD exacerbations during the study. Legend: Bars represent the 95% CI.

Discussion

The result of the FORWARD study shows that, compared to FOR, BDP/FOR significantly reduces the exacerbation rate and improves lung function in patients with severe COPD and history of exacerbations. This data further confirms the beneficial effects of ICS combined to a bronchodilator in preventing exacerbations in COPD patients. Moreover, the exacerbation rate in the BDP/FOR group was reduced regardless of whether patients were receiving chronically tiotropium, suggesting that the effects on preventing exacerbations is independent from other bronchodilation background therapy.

In this study both co-primary endpoints were met: *(1)* compared to FOR, BDP/FOR reduced the adjusted exacerbation rate ratio by 28%. This reduction compares favourably with that estimated by a recent systematic meta-analysis for the effects of an ICS/LABA combination vs. LABA alone (24%) [15]; and, *(2)* the pre-dose morning FEV_1 increase from baseline to Week 12 was significantly larger in the BDP/FOR group. This improvement in FEV_1 was found in patients who were both tiotropium and non-tiotropium

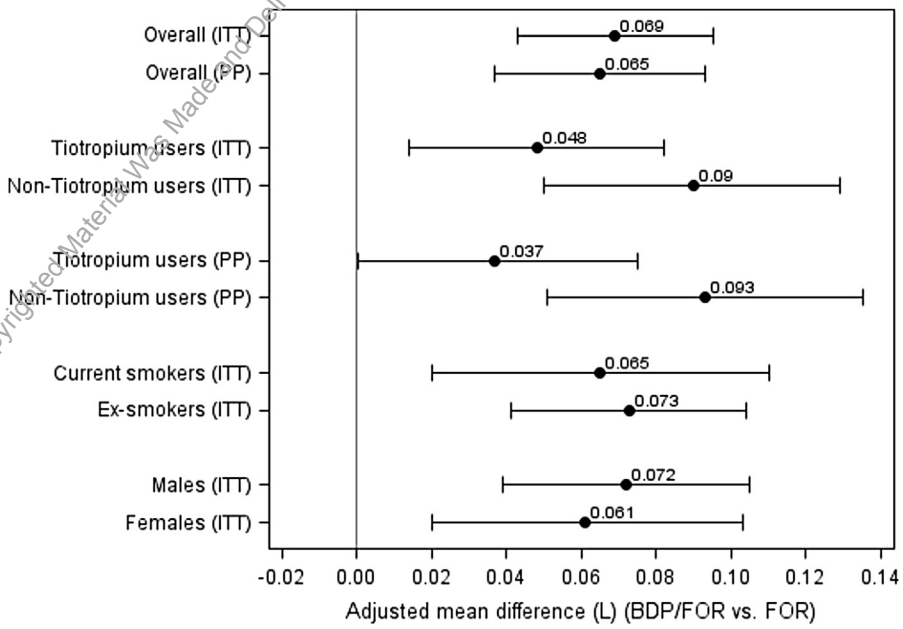

Figure 3 Summary of the analyses of change in pre-dose morning FEV_1 (L) from baseline to Week 12. Legend: Bars represent the 95% CI.

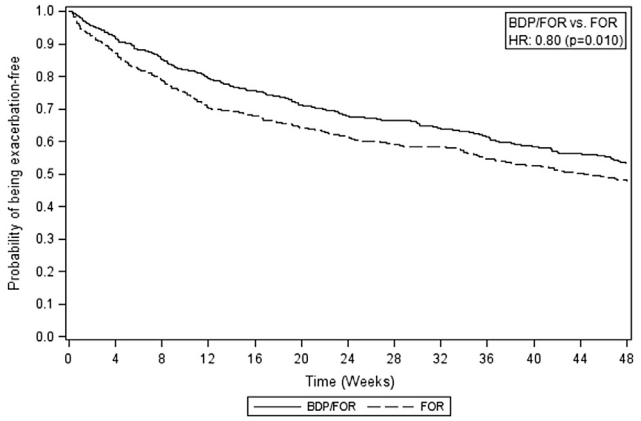

Figure 4 Kaplan–Meier plot of time to first COPD exacerbation (ITT population).

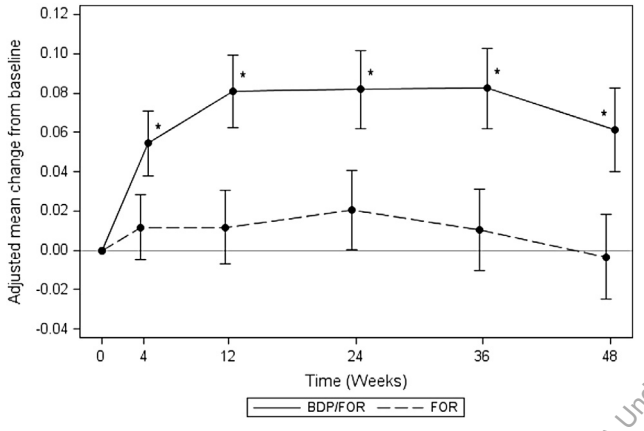

Figure 5 Adjusted mean change from baseline in pre-dose morning FEV_1 (L) (ITT population). Legend: Bars represent 95% CI. Asterisk indicate a statistically significant difference ($p < 0.05$) between treatment groups.

users at randomisation (adjusted mean differences found of 48 and 90 ml, respectively). Prior studies of twice-daily ICS/LABA combinations have shown a significant improvement of the combination over the LABA component alone for pre-dose morning FEV_1 of about 50 ml at 3 months [16–18]. These results were confirmed in other clinically relevant subgroups such as current smokers and ex-smokers, although women had a smaller difference in exacerbation rate between treatments compared to men. This might be due, at least partially, to the greater proportion of current smokers in women (45%) than in men (37%), as active smoking reduces the sensitivity to steroids [19]. The effects on lung function and COPD exacerbations were also associated with an improvement in health status as measured by the SGRQ. This is expected as changes in COPD exacerbation rates are closely related to changes in health status [7,20]. SGRQ changes did not reach the MCID and this could be due to the long study duration, since the largest SGRQ effect, compared with placebo, occurs at around 6 months with long-acting bronchodilators and, subsequently, improvement in SGRQ, scores may subsequently return to the baseline level (or worse) due to disease progression.

The results confirm that ICS/LABA combination therapy is more effecting in reducing exacerbation in severe COPD patients over LABA alone; this demonstrates the anti-inflammatory effect of ICS, suggesting also a complementary and synergistic interaction at the molecular level.

This study also had a number of novel methodological approaches to enhance exacerbation reporting. Many studies of exacerbation therapy have reported lower exacerbation rates than expected even though patients have been enriched for an exacerbation history [21–23]. A previous study evaluating exacerbation rates with BDP/FOR compared to FOR was not able to show a difference between treatments, but there was a very low rate of exacerbations in the study population, despite the subjects to be enrolled were required to have at least one exacerbation in the previous year [4]. The current study took a number of steps to avoid such an occurrence. COPD exacerbations have been shown to peak in incidence during the winter season [24,25] and thus patient recruitment was initiated before the end of winter in three waves across the globe to optimally capture exacerbations, two in the Northern (waves 1 and 3) and one in the Southern Hemisphere (wave 2). COPD exacerbations that occur during the winter months are more likely to have a viral aetiology and have been shown to be longer in duration [24–27] and thus

Table 3 Summary of treatment-emergent adverse events (safety population).

	BDP/FOR $N = 601$		FOR $N = 596$	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Adverse events	313 (52.1)	903	293 (49.2)	840
Serious adverse events	106 (17.6)	189	94 (15.8)	158
Adverse drug reactions (ADRs)	42 (7.0)	49	26 (4.4)	37
Serious ADRs	1 (0.2)	1	1 (0.2)	1
Severe adverse events	75 (12.5)	115	62 (10.4)	94
Adverse events leading to discontinuation	26 (4.3)	30	28 (4.7)	38
Adverse events leading to death	11 (1.8)	14	8 (1.3)	10

Table 4 Treatment-emergent adverse events reported in ≥1% of patients in any treatment group (safety population).

	BDP/FOR $N = 601$		FOR $N = 596$	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Infections and infestations				
Nasopharyngitis	17 (2.8)	21	21 (3.5)	24
Pneumonia	23 (3.8)	26	11 (1.8)	11
Bronchopneumonia	*3 (0.5)*	*3*	*1 (0.2)*	*1*
Lobar pneumonia	*1 (0.2)*	*1*	*0*	*0*
Pneumonia	*19 (3.2)*	*22*	*10 (1.7)*	*10*
Upper respiratory tract infection	17 (2.8)	17	13 (2.2)	15
Oral candidiasis	18 (3.0)	22	4 (0.7)	5
Pharyngitis	11 (1.8)	13	7 (1.2)	7
Influenza	8 (1.3)	8	7 (1.2)	8
Lower respiratory tract infection	9 (1.5)	10	4 (0.7)	5
Urinary tract infection	11 (1.8)	14	2 (0.3)	2
Gastroenteritis	5 (0.8)	5	6 (1.0)	6
Sinusitis	6 (1.0)	6	0	0
Respiratory, thoracic and mediastinal disorders[a]				
Dyspnoea	9 (1.5)	11	19 (3.2)	23
Cough	5 (0.8)	6	15 (2.5)	16
Gastrointestinal disorders				
Diarrhoea	8 (1.3)	9	11 (1.8)	11
Constipation	8 (1.3)	9	6 (1.0)	6
Gastritis	5 (0.8)	5	8 (1.3)	9
Nausea	2 (0.3)	2	6 (1.0)	7
Musculoskeletal and connective tissue disorders				
Back pain	12 (2.0)	13	16 (2.7)	18
Arthralgia	9 (1.5)	9	7 (1.2)	7
Muscle spasms	11 (1.8)	12	3 (0.5)	3
Vascular disorders				
Hypertension	26 (4.3)	26	27 (4.5)	28
Metabolism and nutrition disorders				
Hyperglycaemia	7 (1.2)	7	6 (1.0)	6
Hypercholesterolemia	6 (1.0)	6	6 (1.0)	6
Cardiac disorders				
Cardiac failure	11 (1.8)	13	6 (1.0)	7
Atrial fibrillation	7 (1.2)	7	2 (0.3)	3
Nervous system disorders				
Headache	10 (1.7)	11	12 (2.0)	13
General disorders and administration site conditions				
Chest pain	7 (1.2)	8	9 (1.5)	9
Oedema peripheral	3 (0.5)	3	11 (1.8)	12
Investigations				
Gamma-glutamyltransferase increased	2 (0.3)	2	7 (1.2)	7
Weight decreased	2 (0.3)	2	6 (1.0)	6
Psychiatric disorders				
Insomnia	8 (1.3)	8	10 (1.7)	14
Skin and subcutaneous tissue disorders				
Dermatitis	9 (1.5)	9	2 (0.3)	2
Reproductive system and breast disorders				
Benign prostatic hyperplasia	6 (1.0)	6	5 (0.8)	5

[a] COPD exacerbation are not listed, described in Table 2.

associated with increased airway and systemic inflammation and thus more likely to be reduced in severity and frequency by anti-inflammatory therapy. Thus by recruiting patients in waves before the winter season ends, exacerbations will be more commonly detected early in the course of the study and before patient withdrawals from the study are observed the most, potentially enhancing the exacerbation rate.

The second technique was a novel application of the EXACT diary, using telemonitoring, to raise the awareness of physician to the possibility that an exacerbation may have been occurring. In this study the standard healthcare resource use definition of a COPD exacerbation was used, however it is known that COPD patients often under report their exacerbations and over 50% of exacerbation events may be unreported [7,9]. It is also recognised that unreported exacerbations may also affect health status and thus patients must be encouraged to treat these events [8,25]. In this study, the EXACT daily diary was administered using the Blackberry® mobile device as an aid to detection of events [26]. There was very good compliance with e-diary completion (mean compliance 90.7% in BDP/FOR and 90% in FOR group). When the pre-specified criteria for symptoms' worsening were met [10], an alert was generated that a possible exacerbation had occurred prompting early patient reporting. Early reporting of exacerbations will lead to more homogeneous exacerbation events especially as airway inflammatory changes during COPD exacerbations occur early in the time course of these events. This study showed that the EXACT can be used to aid detection, but despite this, only 47% of patients with severe COPD and an exacerbation history reported an exacerbation over the 48 week study period. Further analyses of the EXACT diaries from this study will be reported in due course, although as an exploratory outcome. Two novel methodological approaches were used in this study; recruiting before the winter months and using a COPD diary to increase exacerbation reporting rates. Thus this study will also inform future trials of exacerbation preventative therapies in COPD.

The most common adverse drug reaction that was reported during the study period was oral candidiasis, which was not unexpected because of the presence of the ICS in the combination therapy [15]. The BDP/FOR treatment arm was also associated with a higher incidence of pneumonia. This is in line with recent studies [22,28—30], showing a 2—3 fold excess of pneumonia in the ICS/LABA treatment arms of studies compared to the corresponding monotherapy. However although there is an increased risk of pneumonia with BDP/FOR therapy, the number of pneumonia events relative to the number of exacerbations during the study was small and consistent with previous observations suggesting that the benefit of an ICS/LABA combination outweighs the potential risks.

In conclusion, the results of the FORWARD study show that BDP/FOR is superior to FOR in the reduction of COPD exacerbations and improvement in pre-dose morning FEV_1 as well as for the symptom-based parameters, thus supporting the positioning of BDP/FOR among the appropriate therapeutic options for this category of patients.

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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.2014.05.013.

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