



## LAUNCHING NEW STUDIES

# A trial of beclomethasone/formoterol in COPD using EXACT-PRO to measure exacerbations

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**ABSTRACT:** Combination inhalers containing corticosteroids and long-acting  $\beta$ -agonists are used to reduce exacerbation rates in patients with severe chronic obstructive pulmonary disease (COPD).

The FORWARD (Foster 48-week Trial to Reduce Exacerbations in COPD) clinical trial in severe COPD patients is a comparison of extrafine beclomethasone dipropionate and formoterol in a combination inhaler with extrafine formoterol; the co-primary end-points are exacerbation rates over 48 weeks and improvement in forced expiratory volume in 1 s over 12 weeks. The traditional physician diagnosis of exacerbations is a co-primary outcome, and the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) means of collecting patient-reported outcome data are also being used to enhance the detection of exacerbation events. EXACT data are being collected using a novel application of a digital platform technology.

FORWARD is therefore expected to provide information on the ability of EXACT to detect and measure exacerbations in a large clinical trial setting. The study design of FORWARD is described in this article.

**KEYWORDS:** Chronic obstructive pulmonary disease, corticosteroids

Chronic obstructive pulmonary disease (COPD) is a progressive condition characterised by airway inflammation and persistent airflow limitation. COPD patients often experience exacerbations, which are an acute worsening of symptoms beyond the normal day-to-day variation [1]. Exacerbations of COPD, which are associated with a worse quality of life [2] and increased mortality [3], are more frequent during the winter season [4, 5], being associated with an increased prevalence of infections with respiratory viruses [6]. These winter exacerbations have a greater impact on patients in terms of hospitalisations and recovery [5]. Recent work has described a subgroup of COPD patients who are susceptible to frequent exacerbations and that a prior history of exacerbations predicts the future risk of exacerbations [7].

An exacerbation is usually an event diagnosed by a physician after the patient has reported increased

symptoms/signs. However, many exacerbations are not reported by patients [2]. In clinical trials, this under-reporting leads to an under-estimate of exacerbation frequency [8]. Patient diaries can improve the standardisation of symptom collection and reduce the number of unreported events. The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a recently developed means of collecting patient-reported outcome (PRO) data, which helps to capture not only the frequency of exacerbations but also the severity and the time-course, *i.e.* onset, duration and recovery [9, 10]. This tool was developed and validated specifically to meet the standards required for PRO measurements in clinical trials. In an observational study, EXACT provided reproducible measurements in the stable state and was sensitive to changes in symptoms during exacerbations [11].

Long acting  $\beta$ -agonists (LABAs) are bronchodilators that are used to control symptoms in COPD

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patients [12]. The addition of inhaled corticosteroids (ICS) to LABAs is recommended in severe COPD patients with frequent exacerbations [12]. Single combination inhalers are frequently used to deliver ICS/LABA combinations, as this is a practical approach for patients, which enhances the possibility of synergistic interactions between the drugs after co-deposition in the airways [13]. Single combination inhalers containing fluticasone propionate/salmeterol (FP/S) and budesonide/formoterol (BUD/F) are licensed for use in COPD patients, as they both improve lung function and reduce exacerbation rates compared with the LABA component alone [14–16].

An ICS/LABA combination containing beclomethasone dipropionate and formoterol (BDP/F; Foster<sup>®</sup>; Chiesi Farmaceutici, Parma, Italy) has been developed in a pressurised metered dose inhaler (pMDI) using a hydrofluoralkane propellant to deliver an extrafine formulation capable of reaching the small airways [17]. This combination inhaler is licensed for use in patients with asthma, as it effectively improves pulmonary function and symptoms in subjects suffering from moderate-to-severe disease [18], with comparable efficacy compared to other fixed-dose ICS/LABA combinations achieved using a lower daily dose of inhaled corticosteroid (400 µg daily) [19, 20]. This lower daily dose is possible because of the optimised lung deposition characteristics of the extrafine formulation. A study in COPD patients has shown that the extrafine BDP/F and the BUD/F combinations cause similar improvements in forced expiratory volume in 1 s (FEV<sub>1</sub>) with both combinations being superior to formoterol alone [21]. However, neither of the combinations showed superiority compared to formoterol alone for the reduction of COPD exacerbations. 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 very stable at enrolment (*i.e.* free from exacerbations for ≥2 months before study screening and during a 4-week run-in period) and, therefore, less likely to exacerbate thereafter. The potentially beneficial effects of the BDP/F extrafine combination on exacerbation rates needs to be further investigated in patients with frequent exacerbations.

The BDP/F extrafine combination has the potential to minimise long-term corticosteroid-related side-effects in COPD patients, as the corticosteroid dose used is lower than other fixed-dose ICS/LABA combinations [21]. However, it is necessary to demonstrate that this lower corticosteroid dose reduces exacerbation rates. We present the design of the FORWARD clinical trial (Foster 48-week Trial to Reduce Exacerbations in COPD), which investigates the effect of the extrafine BDP/F combination compared to extrafine formoterol alone on exacerbation rates in severe COPD patients with an exacerbation history. The trial design has been optimised to measure exacerbation rates; recruitment is in three winter waves across the globe in order to capture the winter seasonal peak of exacerbations, and EXACT is being used to enhance the detection of exacerbation events. This PRO is being collected using a digital platform technology to enhance the efficiency of data capture (HealthDiary, Inc., Toronto, Canada [22]); the physician will be able to monitor EXACT scores in real time on a daily basis. The traditional physician diagnosis of exacerbations is a primary outcome of this trial, but the trial is also expected to provide important information on the ability of EXACT to detect and measure exacerbations in a large clinical trial setting.

## METHODS

### Study objectives

The primary objective is to investigate whether the BDP/F combination twice daily is superior to formoterol twice daily in patients with severe COPD in terms of: 1) the reduction of exacerbation rates during 48 weeks of treatment; and 2) the improvement in pulmonary function, measured by the change in pre-dose morning FEV<sub>1</sub> from baseline to week 12. The main secondary objectives are to assess the efficacy of the BDP/F combination in terms of the change from baseline in morning pre-/post-dose lung function and the time to first COPD exacerbation. The safety of the treatments is also evaluated in terms of adverse events, vital signs and blood parameters. The end-points are listed fully in table 1.

### Subjects

Patients with severe COPD aged >40 yrs are being recruited. A minimum of 1,102 patients will be randomised in order that ≥952 patients complete the study (476 per treatment group) based on an estimated drop-out rate of 13.5%. The inclusion criteria are post-bronchodilator FEV<sub>1</sub> 30–50% of predicted value with FEV<sub>1</sub>/forced vital capacity (FVC) ratio <0.7, a smoking history of ≥10 pack-yrs, a documented history in the patient's medical records of one or more exacerbation within the previous 12 months that required healthcare utilisation (hospitalisation and/or emergency department admission) or treatment with antibiotics and/or oral corticosteroids and the ability to use

**TABLE 1** End-points of the FORWARD study

#### Co-primary end-points

- Comparison of Foster<sup>®</sup> versus formoterol alone in terms of:
  - COPD exacerbation rate
  - Change in pre-dose morning FEV<sub>1</sub> from baseline to week 12

#### Secondary end-points

- Change from baseline in morning pre-dose and 2-h post-dose FEV<sub>1</sub> and FVC at all clinic visits
- Change from baseline to the average pre-dose FEV<sub>1</sub> over the treatment period
- Change from pre-dose to 2-h post-dose FEV<sub>1</sub> and FVC at all clinic visits
- Pre-dose and 2-h post-dose FEV<sub>1</sub>/FVC
- Time to first COPD exacerbation
- Change from baseline to the end of treatment in the SGRQ total and component scores
- Change from baseline to the entire treatment period and to each inter-visit period in the percentage of rescue use-free days and in the average use of rescue medication (number of puffs per day)

#### Exploratory end-points

- Change from baseline to the entire randomised treatment period and to each inter-visit period in the EXACT-PRO total score and subscale scores

#### Safety end-points

- Adverse events
- Adverse drug reactions
- Vital signs
- Haematology and blood biochemistry, including potassium and glucose

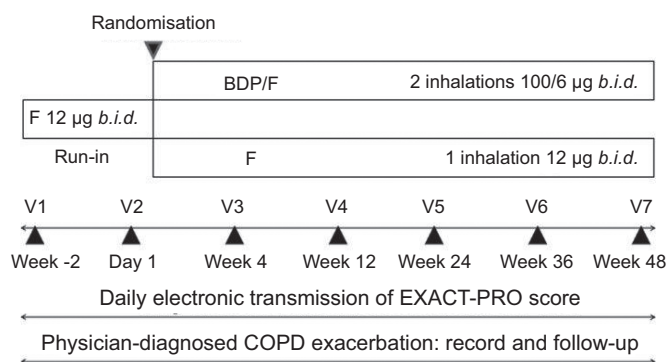
FORWARD: Foster 48-week Trial to Reduce Exacerbations in COPD; COPD: chronic obstructive pulmonary disease; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity; SGRQ: St George's Respiratory Questionnaire; EXACT: Exacerbations of Chronic Pulmonary Disease Tool; PRO: patient-recorded outcome.

EXACT questionnaire loaded onto a BlackBerry® (Research In Motion, Waterloo, Canada) digital platform. Exclusion criteria are a previous diagnosis of asthma, allergic rhinitis or atopic diseases such as eczema, obstructive symptoms in childhood, unstable concurrent diseases, significant hepatic or renal impairment, significant concurrent pulmonary diseases such as tuberculosis or lung cancer, serum potassium levels  $<3.5 \text{ mmol}\cdot\text{L}^{-1}$ , a history of antibiotic and/or oral corticosteroid treatment for an exacerbation of COPD in the 4 weeks before screening and during the run-in, oxygen therapy for  $>12 \text{ h}\cdot\text{day}^{-1}$  or the use of mechanical noninvasive ventilation. Additionally, the following patients are excluded: those treated with depot corticosteroids or long-acting antihistamines in the 2 months preceding the screening visit and those treated with  $\beta$ -blockers in the week preceding the screening visit. Patients treated with tiotropium or theophylline are allowed to enter the study and continue these medications, provided that there are no changes in the dose, schedule or formulation of these drugs within 3 and 2 months, respectively, before the screening visit. All patients provide written informed consent, and the study is ethically approved. The study is registered at clinicaltrials.gov (NCT00929851).

Recruitment is being performed in three waves capturing the winter exacerbation season; the first wave was held in Western Europe (Austria, Czech Republic, Germany and the UK) starting in October 2009. The second wave recruited patients in the southern hemisphere (Argentina, Australia, Chile, New Zealand and South Africa) starting in April 2010. The third wave was held in Europe starting in October 2010 (Bulgaria, Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Spain, Turkey and the UK).

### Study design

This is a 48-week, double-blind, randomised, multinational, multicentre, two-arm, parallel-group clinical trial of a fixed combination of BDP/F administered *via* pMDI (Foster®) versus formoterol alone (Atimos®; Chiesi Farmaceutici). The study design is shown in figure 1, with patients undergoing eight clinic visits. At visit 0 (V0), consent is gained and the study visits explained. At V1 (screening visit), the eligibility of patients is



**FIGURE 1.** The double-blind parallel group randomised study design is shown. At screening, each patient receives a BlackBerry® (Research In Motion, Waterloo, Canada), configured to receive the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) means of collecting patient-reported outcome (PRO) questionnaire daily. During the 48 weeks of the randomised period, healthcare utilisations due to exacerbations of chronic obstructive pulmonary disease (COPD) are recorded. BDP: beclomethasone dipropionate; F: formoterol; V: visit.

assessed, including spirometry before and after the administration of 400 µg inhaled salbutamol. There follows a 2-week run-in period when all patients receive formoterol 12 µg twice a day plus salbutamol as required. The randomisation visit (V2) is followed by a 48-week treatment period with patients randomly allocated to receive either BDP/F combination or formoterol alone. Patients take either two inhalations of BDP/F 100/6 µg twice per day, or one inhalation of formoterol 12 µg twice per day. The double-blind design is ensured by the addition, in the formoterol arm, of a placebo canister following the same administration pattern as formoterol, *i.e.* one inhalation twice per day. Salbutamol is used as a rescue medication throughout the study. Patients taking tiotropium are required to stop this medication for 72 h before each visit to the clinic (V1–V7) and are then allowed to restart after the visit.

Clinic visits occur at 4, 12, 24, 36 and 48 weeks after randomisation. At these visits, FEV<sub>1</sub> and FVC (pre-dose and 2 h post-dose) and vital signs are measured. COPD exacerbations and adverse events are recorded throughout the study. The St George's Respiratory Questionnaire (SGRQ) is administered at V2 and V7, and the evaluation of haematology and blood biochemistry and ECG are performed at V1 and V7. In case of early discontinuation, V7 assessments should be performed. The use of rescue medication and the EXACT scores are recorded daily by the patient using the BlackBerry® and transmitted daily as encrypted data to centralised database servers.

### Measurement of exacerbations

A COPD exacerbation is defined as a sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence) from the stable state and beyond normal day-to-day variations that is acute in onset and requires unscheduled medical intervention, leading to prescriptions of systemic corticosteroids and/or antibiotics or the need for a visit to an emergency department or hospitalisation [23]. The physician-diagnosed COPD exacerbations that fit the above criteria, corresponding to HealthCare Resource Utilisation (HCRU) exacerbations, will be used for the analysis of the exacerbation rate as the co-primary end-point.

EXACT assesses breathlessness, cough and sputum, chest symptoms, and quality of life using a 14-item questionnaire with a total score ranging from 0 to 100. In the FORWARD study, the baseline EXACT total score for each patient will be calculated based on the first 14 days' scores after the screening visit. Each investigator can review individual EXACT scores *via* the web. During the treatment period, a change in the total score of  $>12$  compared with baseline on two consecutive days automatically triggers an alert to the investigator, through the digital platform, that a significant change in symptoms has occurred. Simultaneously, the BlackBerry® also delivers the individualised message ("Please remember to call your doctor if your symptoms worsen") when this worsening of symptoms has occurred. This message is also delivered to the patient at regular intervals during the study. Upon the 12-point increase alert, the investigator then checks the patient's clinical status by a telephone call, and makes the decision whether to arrange a clinic visit to further assess the symptoms. The EXACT score will be used to assess exacerbation patterns in the study as an exploratory outcome; the co-primary end-point of HCRU exacerbations will be compared to the exploratory outcome of EXACT-detected events.



### Statistics

The sample size has been calculated to demonstrate the superiority of BDP/F compared to formoterol for COPD exacerbation rates and change in pre-dose morning FEV<sub>1</sub> from baseline to week 12. With 551 randomised patients per group, assuming 0.64 exacerbations per patient per year in the BDP/F group and 0.8 in the formoterol group, an exponential distribution of dropouts with a cumulative percentage of 13.5% at the end of the study, an overdispersion factor of 10% (*i.e.* variance of number of exacerbations =  $1.1 \times$  mean number of exacerbations) and a two-sided significance level of 0.05, simulations suggest that the power using Poisson regression will be 82.6%. With 530 evaluable patients at week 12 in each group, the study will have 80% power to detect a mean difference of 50 mL in change in pre-dose morning FEV<sub>1</sub>, assuming a standard deviation of 290 mL, using an unpaired t-test with two-sided significance level of 0.05. The difference of 50 mL was chosen based on previous long-term clinical trials showing that ICS/LABA combinations show this level of superiority over LABA alone, and this is associated with differences in health status and exacerbation rates [14, 15, 16, 21]. Further statistical analysis details are in the online supplementary material.

The frequency distribution of adverse events and adverse drug reactions will be presented for each treatment group. The mean and 95% confidence intervals for the changes from baseline in vital signs will be calculated within each treatment group. Shift tables from baseline to the end of treatment, with regard to normal ranges, will be provided for the laboratory parameters for each treatment group.

### DISCUSSION

The FORWARD study will evaluate the potential benefits of the extrafine BDP/F combination inhaler compared to extrafine formoterol on exacerbation rate and lung function in COPD patients. The study design allows the effects of the ICS component of the extrafine BDP/F combination to be determined in the specific subgroup of patients who are at most risk of future exacerbations. The recruitment approach employed in the study was specifically designed to enrich the patient population by ensuring the recruitment of patients prone to exacerbations. The frequency and severity of COPD exacerbations is worse during the winter season [4, 5] and the study design is optimised to capture such seasonal events by randomising patients immediately before the winter peak of exacerbations. Furthermore, the use of EXACT scores transmitted digitally on a daily basis may provide a sensitive way to detect and monitor exacerbation events, and thus enable differences between the study treatments to be accurately determined.

The co-primary end-points of the FORWARD study are the reduction of exacerbation rate during 48 weeks of treatment and the improvement in FEV<sub>1</sub> from baseline to week 12. Exacerbation rate and lung function were investigated in the previous study comparing the effects of extrafine BDP/F, BUD/F and formoterol alone in COPD patients [21]. It was observed that both combination therapies were superior to formoterol in terms of FEV<sub>1</sub> improvement, and a similar result is expected in the FORWARD study. The lack of superiority over formoterol of both extrafine BDP/F and BUD/F in terms of exacerbation rate was unexpected and in contrast with results from previous studies

showing superiority of BUD/F and FP/S over LABA alone [14–16]. The low exacerbation rate detected in the previous study with extrafine BDP/F (~0.42 per patient-year) as compared to previous studies (>0.8 per patient-year in TORCH (Towards a Revolution in COPD Health) [14] and  $\leq 1.6$  per patient-year in INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations) [24]) might have masked the beneficial effect of extrafine BDP/F on reduction of exacerbations. FORWARD has therefore been designed to recruit a COPD population with a higher exacerbation frequency in order to evaluate the efficacy of BDP/F combination on this end-point.

The daily EXACT score transmission enhances the contact between patients and physicians. The automatic alert to the physician, whenever the score of a specific patient increases by  $\geq 12$  points for two consecutive days, may increase the number of physician-diagnosed exacerbations requiring HCRU. EXACT may therefore reduce the proportion of unreported exacerbation events and at the same time increase HCRU.

In addition to studying the rate of exacerbations requiring additional treatment, the FORWARD study will include a series of exploratory analyses on symptom patterns and exacerbations evaluated using EXACT [9, 10]. This may include, but is not limited to, frequency, severity and duration of exacerbations. The EXACT questionnaire seems able to consistently quantify the symptoms associated with an exacerbation [11] and may provide a useful tool for quantifying exacerbations in clinical trials.

In our study, all patients fill out their EXACT questionnaire on a mobile device and it will be possible to compare this symptom-based approach with the event-based calculation of exacerbation rates. The daily questionnaire, duly completed, is transmitted, anonymously and encrypted, to the digital platform developed specifically for the FORWARD study. The study design is unique in providing the investigator with daily information of the patients' clinical status from the reports of the EXACT focused on COPD exacerbations. This is an essential part of the study design, promoting early detection of events to allow an immediate response to the patients' change in symptoms. There is a known under-reporting of exacerbations that will lead to conservative estimates of exacerbation rate when the more conventional definition of exacerbations based on additional treatments is used [8]. Using EXACT can tell us more about the degree of under-reporting as well as the distribution of this phenomenon in a clinical trial setting. Also, treatment with inhaled corticosteroids not only reduces exacerbation rates, since they have also been shown to reduce the severity of exacerbations [25]. Using EXACT scores in the FORWARD study may enable us to compare exacerbation severity by the assessment of symptoms in the two treatment groups. It has recently been shown that COPD exacerbations follow distinct patterns of onset and recovery [26], and EXACT has the potential to accurately measure the whether the randomised treatments change such patterns in this clinical trial.

The early detection of a change in symptoms due to the information provided by EXACT should occur equally in both treatment arms, so we do not expect that the use of EXACT will cause a bias towards increased detection of exacerbation events in one treatment arm only. It could be argued that the administration of EXACT through the BlackBerry® device will be difficult

for certain subjects, such as those who are not competent with the use of mobile telephones. However, the operation of the BlackBerry® has been simplified to administer EXACT, and this technique has been developed and validated in COPD patients [9–11], so we do not expect this to be a major issue.

SGRQ scores and rescue medication usage will be measured as secondary end-points to assess quality of life and breathlessness, respectively. These measurements are commonly used in COPD clinical trials [14–16, 24]. We have limited the number of other secondary end-point measurements performed in order to focus on achieving quality in the primary end-point measurements, and also for practical reasons to not overload patients with clinical procedures.

Previous studies of ICS/LABA combinations in COPD have either not permitted the widely prescribed long-acting anticholinergic tiotropium to be used, or were performed before tiotropium was licensed for use [14–16]. We have allowed patients who are taking tiotropium to continue with this medication during the FORWARD study, as it allows the comparison of extrafine BDP/F to extrafine formoterol to be performed with the patients taking their normal and recommended COPD medications. This is different to previous ICS/LABA studies in COPD [14, 21] and, arguably, is a more “real-life” study design. Furthermore, there are ethical issues in asking severe COPD patients to withhold an effective medication over a year for research purposes and to be treated with formoterol only. Tiotropium will not be used for 72 h prior to the measurement of pulmonary function, so that the potential difference between the study treatments can be evaluated without the bronchodilator effect of concurrent tiotropium administration which may cause difficulty in interpretation.

The combination inhalers containing FP/S (Seretide®; GlaxoSmithKline, Uxbridge, UK) and BUD/F (Symbicort®; AstraZeneca, London, UK) are already widely used for the treatment of COPD. The key COPD studies with these combinations have been performed with dry powder inhalers (Diskus® (GlaxoSmithKline) and the Turbohaler® (AstraZeneca) respectively) [14–16]. Many patients prefer using pMDI devices; extrafine BDP/F pMDI therefore offers an alternative device for such patients. Furthermore, the pMDI extrafine formulation enhances deposition in small airways, which is an important site of airway inflammation in COPD patients [27]. The delivery of treatment to the small airways may be important for reducing the progression of inflammation and obstruction at this site. Indeed, it has been demonstrated that BDP/F causes a greater improvement in FVC compared to either BUD/F or formoterol in patients with COPD, indicating an effective reduction of air trapping associated with small airway patency [21]. Moreover, the extrafine formulation of Foster® offers the benefit of a reduced efficacious dose of inhaled corticosteroid (400 µg daily) compared to other fixed-dose combinations of ICS and LABAs. This lower daily dose may reduce the rate of ICS side-effects, including the increased frequency of pneumonia observed in TORCH [14].

In conclusion, the FORWARD study will evaluate the effect of the ICS component of the extrafine BDP/F combination on exacerbation rate and pulmonary function in severe COPD patients with a history of frequent exacerbations. The FORWARD study

will also provide data on the use of EXACT in a large clinical trial. Changes in EXACT scores during physician-diagnosed exacerbations will be explored, and the ability of quantitative scores from the EXACT to add additional information on impact of treatment on features of exacerbations will be explored. The use of EXACT scores, coupled with the capture of winter exacerbation peaks across the globe, may provide a sensitive study design for investigating the effects of pharmacotherapies on exacerbation rates in COPD patients.

#### SUPPORT STATEMENT

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#### CLINICAL TRIAL

This study is registered at clinicaltrials.gov with identifier number NCT00929851.

#### STATEMENT OF INTEREST

Statements of interest for all authors and for the study itself can be found at [www.erj.ersjournals.com/site/misc/statements.xhtml](http://www.erj.ersjournals.com/site/misc/statements.xhtml)

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