



Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β 2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY)

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Title: Triple therapy in a single inhaler for COPD: The TRILOGY
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Abstract: Background

Limited data are available on the efficacy of 'triple therapy' with two long-acting bronchodilators and an inhaled corticosteroid in chronic obstructive pulmonary disease (COPD). This randomised, double-blind study examined the efficacy of single-inhaler combination of an extrafine formulation of beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide (BDP/FF/GB).

Methods

In the run-in, patients received BDP/FF 100/6µg, two actuations twice daily (BID); patients were then randomised to either continue BDP/FF or step-up to BDP/FF/GB 100/6/12.5µg two actuations BID for 52 weeks via pressurised metered-dose inhaler. Eligible COPD patients had post-bronchodilator forced expiratory volume in 1 second (FEV1) <50%, ≥1 moderate/severe COPD exacerbation in the previous 12 months, COPD Assessment Test total score ≥10 and Baseline Dyspnea Index focal score ≤10. The three co-primary objectives were superiority of BDP/FF/GB over BDP/FF for pre-dose and 2-h post-dose FEV1 and Transition Dyspnea Index (TDI) focal score, all at Week 26. Secondary endpoints included moderate/severe COPD exacerbation rate over 52 weeks.

ClinicalTrials.gov: NCT01917331.

Findings

The study ran from 21 March 2014 to 14 January 2016; 1368 patients were randomized (BDP/FF/GB=687; BDP/FF=681). At Week 26, BDP/FF/GB improved FEV1 pre-dose by 0.081L (95%CI 0.052, 0.109; p<0.001) and 2-h post-dose by 0.117L (0.086, 0.147; p<0.001) vs BDP/FF. Mean TDI focal scores at Week 26 were 1.71 for BDP/FF/GB and 1.50 for BDP/FF, with a difference of 0.21 (-0.08, 0.51; p=0.160). Adjusted annual moderate/severe exacerbation rates were 0.41 for BDP/FF/GB and 0.53 for BDP/FF; rate ratio 0.77 (0.65, 0.92; p=0.005), corresponding to a 23% reduction with BDP/FF/GB vs BDP/FF. Adverse events were reported by 53.6% patients with BDP/FF/GB and 55.7% with BDP/FF.

Interpretation

This study shows the additional bronchodilator benefit of BDP/FF/GB over BDP/FF and a significant reduction in exacerbations with triple therapy which, for the first time, is possible using a single inhaler.

Funding

Chiesi Farmaceutici SpA

Title

Triple therapy in a single inhaler for COPD: The TRILOGY randomised, double-blind study

Authors

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Summary

Background

Limited data are available on the efficacy of 'triple therapy' with two long-acting bronchodilators and an inhaled corticosteroid in chronic obstructive pulmonary disease (COPD). This randomised, double-blind study examined the efficacy of single-inhaler combination of an extrafine formulation of beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide (BDP/FF/GB).

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In the run-in, patients received BDP/FF 100/6 μ g, two actuations twice daily (BID); patients were then randomised to either continue BDP/FF or step-up to BDP/FF/GB 100/6/12.5 μ g two actuations BID for 52 weeks via pressurised metered-dose inhaler. Eligible COPD patients had post-bronchodilator forced expiratory volume in 1 second (FEV₁) <50%, ≥ 1 moderate/severe COPD exacerbation in the previous 12 months, COPD Assessment Test total score ≥ 10 and Baseline Dyspnea Index focal score ≤ 10 . The three co-primary objectives were superiority of BDP/FF/GB over BDP/FF for pre-dose and 2-h post-dose FEV₁ and Transition Dyspnea Index (TDI) focal score, all at Week 26. Secondary endpoints included moderate/severe COPD exacerbation rate over 52 weeks.

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BDP/FF. Adverse events were reported by 53.6% patients with BDP/FF/GB and 55.7% with BDP/FF.

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Funding

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Introduction

The goals of pharmacological treatment of chronic obstructive pulmonary disease (COPD) are to reduce current symptoms and to reduce the risk of future exacerbations.¹ COPD patients with a history of exacerbations are at increased risk of future exacerbations,^{2,3} and are more likely to suffer from a reduced quality of life,⁴ more rapid lung function decline,^{5,6} and increased mortality.⁷ To reduce the risk of future events the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has specific recommendations for these patients; the first choice treatment is a long-acting muscarinic antagonist (LAMA), or an inhaled corticosteroid plus a long-acting β_2 -agonist (ICS/LABA).¹ Both of these options have been shown to improve lung function, alleviate symptoms and reduce exacerbation rates.^{8,9}

Many COPD patients continue to exacerbate despite treatment with either a LAMA or ICS/LABA combination. In clinical practice, it is very common in this situation to step up treatment to 'triple therapy' combining an ICS/LABA with a LAMA.¹⁰ Short-term clinical trials have shown that this step up improves lung function and reduces symptoms.¹¹⁻¹⁶ However, GOLD recognises that there is a lack of evidence for this approach regarding exacerbation reduction.¹

Currently, COPD patients receiving triple therapy must use at least two inhalers, typically ICS/LABA in one inhaler and LAMA in a second, and often these inhalers are of different types and designs. A single ICS/LABA/LAMA inhaler combining extrafine formulations of beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (GB) has been developed in order to simplify this regime. In the TRILOGY study, we aimed to compare the efficacy and safety of triple therapy with BDP/FF/GB to that of BDP/FF in symptomatic COPD patients with severe or very severe airflow limitation and an exacerbation history. The recruitment of this patient group allowed us to evaluate treatment effects on lung function, symptoms and exacerbations.

Methods

Study design

This was a randomised, parallel group, double-blind, active-controlled study, conducted in 159 sites across 14 countries. The sites were a mixture of primary (18), secondary (99) and tertiary care (28) providers, and specialist investigation units (14).

Patients who met the inclusion and exclusion criteria at a screening visit (Visit 1) entered a 2-week open-label run-in period, during which they received an extrafine formulation of BDP/FF 100/6 µg, two actuations twice daily (BID) via pressurised metered dose inhaler (pMDI). At Visit 2, patients were randomised to one of two treatment groups, to either continue to receive BDP/FF, or to be stepped up to an extrafine formulation of BDP/FF/GB. Over the subsequent 52-week treatment period, patients attended visits at Weeks 4, 12, 26, 40 and 52. As rescue medication, patients were permitted to use salbutamol (100 µg per actuation, via pMDI), although not within 6 h prior to any spirometry assessment. Other than study treatments and rescue medication, for the duration of the study the following classes of medication were not permitted, from the indicated time prior to the screening visit: short-acting β₂-agonists (6 h); short-acting muscarinic antagonists (12 h); LABAs (12 h; 72 h for ultra-LABAs); LAMAs (72 h); ICSs (12 h); xanthine derivatives (7 days).

The study was approved by the ethics committee or institutional review board at each site, and was performed in accordance with the declaration of Helsinki, and the International Conference on Harmonisation Good Clinical Practice (ICH/CPMP/135/95). The protocol is included in the supplementary material. There were no substantial protocol amendments.

Patients

The main inclusion criteria were: ≥40 years of age; diagnosis of COPD, with post-bronchodilator forced expiratory volume in 1 second (FEV₁) <50% and a ratio of FEV₁ to forced vital capacity (FVC) <0.7; at least one moderate or severe COPD exacerbation in the previous 12 months (see the definition in the Outcomes section, below); and the use of ICS

plus LABA (as a free or fixed combination), ICS plus LAMA, LABA plus LAMA (as a free or fixed combination) or LAMA monotherapy for at least 2 months prior to screening (patients receiving triple therapy of ICS plus LABA plus LAMA were not eligible). In addition, all patients were to be symptomatic, with a COPD Assessment Test (CAT) total score ≥ 10 and a Baseline Dyspnea Index (BDI) focal score ≤ 10 at screening, with the BDI criterion also confirmed at the randomisation visit. All patients provided written informed consent prior to any study-related procedure.

The key criteria for exclusion were: a diagnosis of asthma, or history of allergic rhinitis or atopy; a COPD exacerbation in the 4 weeks prior to screening or during the run-in period; clinically significant cardiovascular conditions or laboratory abnormalities; or unstable concurrent disease that may have impacted efficacy or safety (as judged by the investigator). The full inclusion and exclusion criteria are listed in the supplementary material.

Randomisation and masking

Patients were randomised to treatment by investigators contacting an interactive response technology (IRT) system, which used a randomisation list generated by the IRT provider. Randomisation was stratified by country and severity of airflow limitation (in the post-bronchodilator FEV₁ categories $<30\%$ predicted, or 30 to $<50\%$ predicted). The two study treatments were provided in matching inhalers, with patients, investigators, site staff and sponsor personnel blinded to treatment assignment for the duration of the study.

Procedures

For the 52-week treatment period, patients were randomised 1:1 to either BDP/FF 100/6 μg or BDP/FF/GB 100/6/12.5 μg , both two actuations BID via pMDI. At Visit 2, baseline (pre-dose) data were collected for spirometry, BDI, and St George's Respiratory Questionnaire (SGRQ); spirometry was also performed at 2 h post-dose. At each subsequent visit, pre- and 2-h post-dose spirometry was conducted, and data were collected from the Transition

Dyspnea Index (TDI; which measures change from the BDI at Visit 2) and SGRQ.

Centralised spirometry was used to improve quality of the FEV₁ data. For the duration of the study, patients recorded daily symptoms using the EXACT-PRO questionnaire (EXAcerbations of Chronic pulmonary disease Tool Patient-Reported Outcome), together with treatment compliance and rescue medication use in an electronic diary; these data were reviewed by the investigator regularly, and at least at each visit.

Outcomes

There were three co-primary objectives: to demonstrate superiority of BDP/FF/GB over BDP/FF in terms of change from baseline in pre-dose (morning) FEV₁, change from baseline in 2-h post-dose FEV₁, and TDI focal score, all assessed at Week 26. The secondary efficacy variables were: pre-dose FEV₁ at all the other clinic visits and averaged over the treatment period; FEV₁ response (change from baseline in pre-dose FEV₁ ≥100 mL) at Weeks 26 and 52; 2-h post-dose FEV₁ at all the other clinic visits; TDI focal score at all the other clinic visits and TDI response (focal score ≥1; the minimal clinically important difference¹⁷) at Weeks 26 and 52; SGRQ total score at all clinic visits, and SGRQ response (decrease from baseline in total score ≥4 the minimal clinically important difference¹⁷) at Weeks 26 and 52; percentage of days without rescue medication use and average number of puffs/day; moderate/severe COPD exacerbation rate over 52 weeks of treatment; and the time to first moderate/severe COPD exacerbation.

A COPD exacerbation was defined as a worsening of the patient's respiratory symptoms that in the view of the patient's health care provider required treatment with systemic corticosteroids and/or antibiotics or hospitalisation.¹⁸ Events were classified as moderate or severe according to EMA/CHMP guidelines,¹⁸ with severe exacerbations being those requiring hospitalisation or resulting in death. Data from the EXACT-PRO questionnaire were used to optimise the recognition of potential exacerbations by programming the electronic diary to alert physicians and to advise patients to contact their investigator in the event of

worsening symptoms. EXACT-PRO data were also evaluated for the exploratory E-RS (Evaluating Respiratory Symptoms) Total Score endpoint.¹⁹

Treatment-emergent adverse events (TEAE) were captured throughout the study, with all events judged by the investigator as having reasonable causal relationship to a medical product considered to be treatment-related AEs. Blood pressure and ECG results were recorded pre-dose and at 10 min post-dose at each visit, with 24-h Holter recordings captured for a subset of approximately 10% of the patients at baseline and at Weeks 26 and 52. An independent Data Safety Monitoring Board (DSMB), composed of three independent clinicians and one independent biostatistician, provided a quarterly independent scrutiny of the study. Major adverse cardiovascular events (MACE) were adjudicated by an independent adjudication committee, comprising four cardiologists. The study is registered on ClinicalTrials.gov (NCT01917331).

Statistical analysis

It was estimated that a total of 1304 randomised patients (652 patients per group) would be required to reach a total of 1088 evaluable patients at Week 26 (544 patients per group), considering a non-evaluable rate of approximately 16.5% at this timepoint. Based on a two-sided significance level of 0.05, this sample size provided: 97.7% power to detect a mean difference of 60 mL in pre-dose FEV₁, assuming a standard deviation (SD) of 250 mL; 99.6% power to detect a mean difference of 70 mL in 2-h post-dose FEV₁, assuming a SD of 250 mL; and 87.1% power to detect a mean difference of 0.6 units in TDI focal score, assuming a SD of 3.2 units. An overall 85% study power for the primary efficacy analyses was therefore ensured.

The co-primary endpoints were all evaluated using a linear mixed model for repeated measures (MMRM), with data up to discontinuation included in the analysis for withdrawn patients. This model included treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status

at screening as fixed effects, and baseline value and baseline by visit interaction as covariates. Data are presented as the adjusted means (i.e. least squares means) and adjusted mean differences between treatment groups, together with their 95% confidence intervals (CIs). In order to deal with multiplicity, the primary efficacy variables were tested in the following pre-specified hierarchical order: 1) pre-dose FEV₁; 2) 2-h post-dose FEV₁; 3) TDI focal score. At each step of the procedure, no confirmatory claims were to be made unless the superiority of BDP/FF/GB over BDP/FF was demonstrated in the preceding steps. There was no multiplicity adjustment on the secondary analyses. Subgroup analyses of the co-primary endpoints were prespecified, with patients grouped according to severity of airflow limitation, smoking status, gender, reversibility to salbutamol, COPD phenotype (chronic bronchitis, emphysema, or mixed), blood eosinophil level at screening, and age, with TDI also analysed according to presence of cardiovascular comorbidities. Sensitivity analyses were performed on the three co-primary endpoints in order to assess the potential impact of missing data, as described in the supplementary material.

The majority of the secondary and exploratory endpoints were analysed using a similar MMRM to the co-primary endpoints. The responder analyses for FEV₁, TDI and SGRQ were conducted using a logistic model, the number of moderate/severe COPD exacerbations was analysed using a negative binomial model and the time to first moderate/severe COPD exacerbation was analysed using a Cox proportional hazards model. In these models, treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation, smoking status at screening and the baseline value (where available) were included as fixed effects. Log-time on study was also accounted for as an offset in the negative binomial model. *Post-hoc* subgroup analyses of the rate of moderate/severe exacerbations were conducted, with patients grouped as for the TDI co-primary endpoint, and also according to number of exacerbations in the previous 12 months.

The Intention-to-Treat (ITT) population was used for the efficacy evaluations. This included all randomised patients who received at least one dose of study treatment and with at least

one efficacy evaluation (primary or secondary efficacy variables). The Safety population, used for all safety analyses, was all randomised patients who received at least one dose of the study treatment. All analyses presented in this manuscript were conducted using Statistical Analysis System (SAS), Version 9.2.

Role of the funding source

The funder of the study, Chiesi Farmaceutici SpA was responsible for the design and analysis of the study, oversaw its conduct and was responsible for the study report preparation. All authors had full access to all of the data, with the lead author (DS) responsible for the decision to submit for publication.

Results

The first patient entered the study on 21 March 2014, with the last completing on 14 January 2016. Of the 1812 patients screened, 1368 were randomized to treatment (687 to BDP/FF/GB and 681 to BDP/FF; Figure 1), with 602 (87.6%) completing the study in the BDP/FF/GB group and 579 (85.0%) in the BDP/FF group. The Safety population was the same as the ITT population. Compliance to treatment was high, with a median of 95.6% and 95.0% of doses taken in the BDF/FF/GB and BDP/FF groups, respectively. The baseline characteristics of the recruited patients are shown in Table 1. More than 80% of patients had at least one concomitant disease, with at least one cardiac disorder reported by 35.5% of patients in the BDP/FF/GB group and 35.0% in the BDP/FF group.

Table 1. Baseline demographics, disease characteristics and most common concomitant diseases (≥5% in either group) (Safety population).

	BDP/FF/GB (N=687)	BDP/FF (N=680)
Gender, n (%)		
Male	509 (74.1)	527 (77.5)
Race, n (%)		
White	684 (99.6)	679 (99.9)
Other	3 (0.4)	1 (0.1)
Age (years), mean (SD)	63.3 (7.9)	63.8 (8.2)
Body mass index (kg/m ²), mean (SD)	26.3 (5.4)	26.4 (5.3)
Blood leukocytes (10 ⁹ /L), mean (SD)	8.02 (2.23)	8.13 (2.28)
Blood eosinophils (10 ⁹ /L), mean (SD)	0.25 (0.17)	0.24 (0.19)
Blood eosinophils (%), mean (SD)	3.12 (2.22)	3.06 (2.27)
Smoking status, n (%)		
Current smoker	323 (47.0)	318 (46.8)
Ex-smoker	364 (53.0)	362 (53.2)
Time since first COPD diagnosis (years), mean (SD)	7.7 (5.8)	7.7 (6.0)
FEV ₁ (L)*, mean (SD)	1.11 (0.32)	1.10 (0.33)
FEV ₁ % predicted*, mean (SD)	36.9 (8.4)	36.2 (8.6)
FEV ₁ % predicted*, n (%)		
30 to 50%	532 (77.4)	525 (77.2)
<30%	155 (22.6)	155 (22.8)

	BDP/FF/GB (N=687)	BDP/FF (N=680)
FVC (L)*, mean (SD)	2.73 (0.76)	2.75 (0.76)
FEV ₁ /FVC ratio*, mean (SD)	0.42 (0.11)	0.41 (0.11)
Reversibility (%), mean (SD)	10.4 (14.2)	10.4 (14.1)
Chronic bronchitis [†] , n (%)	450 (65.5)	463 (68.1)
Exacerbation rate in the previous year, mean (SD)	1.2 (0.5)	1.2 (0.5)
CAT total score, mean (SD)	20.8 (5.9)	20.8 (5.7)
COPD medication at study entry, n (%)		
ICS/LABA	506 (73.7)	487 (71.6)
ICS/LAMA	10 (1.5)	10 (1.5)
LABA/LAMA	95 (13.8)	107 (15.7)
LAMA	76 (11.1)	76 (11.2)
Spacer use during the study, n (%)	111 (16.2)	129 (19.0)
Patients with at least one concomitant disease, n (%)	590 (85.9)	563 (82.8)
Hypertension	404 (58.8)	382 (56.2)
Ischaemic heart disease	172 (25.0)	173 (25.4)
Myocardial ischaemia	91 (13.2)	92 (13.5)
Coronary artery disease	66 (9.6)	58 (8.5)
Angina pectoris	44 (6.4)	43 (6.3)
Ischaemic cardiomyopathy	3 (0.4)	6 (0.9)
Myocardial infarction	2 (0.3)	0
Diabetes mellitus	90 (13.1)	89 (13.1)
Cardiac failure	73 (10.6)	86 (12.6)
Hypercholesterolaemia	45 (6.6)	41 (6.0)
Respiratory failure	35 (5.1)	45 (6.6)
Gastritis	36 (5.2)	30 (4.4)
Benign prostatic hyperplasia	24 (3.5)	42 (6.2)
Cor pulmonale	39 (5.7)	25 (3.7)

* Post-salbutamol. [†] Includes patients with a mixed chronic bronchitis and emphysema phenotype. BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist.

In terms of the co-primary endpoints, BDP/FF/GB was superior to BDP/FF for both pre-dose and 2-h post-dose FEV₁ at Week 26, with mean differences of 0.081 L and 0.117 L, respectively (Table 2). There were improvements in TDI focal score at Week 26 in both groups; the mean difference between treatments (0.21 units) was not statistically significant. Subgroup analyses of the three co-primary endpoints (including by blood eosinophil levels)

were broadly consistent with the ITT analyses (Supplementary Figures 1, 2 and 3). An exception was for the subgroup with very severe airflow limitation; in these patients, statistical significance was not reached for the pre-dose FEV₁ evaluation.

Table 2. Baseline and changes from baseline at Weeks 26 and 52 for FEV₁ and TDI (ITT population).

Endpoint	BDP/FF/GB (N=687)	BDP/FF (N=680)	Adjusted mean difference between treatments
Baseline FEV ₁ (pre-dose, Week 0), L	1.096 (0.381)	1.094 (0.393)	
Pre-dose FEV₁, L			
Week 26	0.082 (0.062, 0.102)	0.001 (-0.019, 0.021)	0.081 (0.052, 0.109); p<0.001
Week 52	0.071 (0.050, 0.093)	0.008 (-0.014, 0.030)	0.063 (0.032, 0.094); p<0.001
2-h post-dose FEV₁, L			
Week 26	0.261 (0.240, 0.283)	0.145 (0.123, 0.166)	0.117 (0.086, 0.147); p<0.001
Week 52	0.249 (0.226, 0.273)	0.146 (0.122, 0.170)	0.103 (0.069, 0.137); p<0.001
BDI and TDI focal score			
BDI focal score*	5.27 (1.81)	5.45 (1.82)	
TDI focal score at	1.71	1.50	0.21
Week 26	(1.50, 1.92)	(1.29, 1.71)	(-0.08, 0.51); p=0.160
TDI focal score at	2.03	1.81	0.21
Week 52	(1.81, 2.25)	(1.59, 2.04)	(-0.10, 0.53); p=0.186

*BDI focal score is the baseline value from which TDI focal score is evaluated. Baseline data are mean (SD); post-baseline data are adjusted mean change from baseline (95% confidence interval). BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; FEV₁ = forced expiratory volume in 1 second; BDI = Baseline Dyspnea Index; TDI = Transition Dyspnea Index.

Compared to BDP/FF, BDP/FF/GB showed significantly greater improvements in both pre-dose and 2-h post-dose FEV₁ at all visits (Week 52 data are in Table 2 and other visits in Figures 2a and b), with a significantly higher proportion of patients responding to BDP/FF/GB (defined as ≥ 100 mL increase in pre-dose FEV₁) at Weeks 26 and 52 (Table 3).

The average pre-dose FEV₁ mean difference between treatments over the duration of the study was 0.072 L (95% CI 0.048, 0.096; p<0.001).

Table 3. FEV₁, TDI and SGRQ responder analyses at Weeks 26 and 52 (ITT population).

Endpoint	Number (%) of patients with a clinically relevant change from baseline		Odds ratio (95% CI); p value
	BDP/FF/GB	BDP/FF	
	(N=687)	(N=680)	
Pre-dose FEV₁ (≥100 mL increase from baseline)			
Week 26	287 (41.8)	165 (24.3)	2.30 (1.82, 2.91); p<0.001
Week 52	259 (37.7)	158 (23.2)	2.06 (1.62, 2.62); p<0.001
TDI (focal score ≥1)			
Week 26	394 (57.4)	352 (51.8)	1.28 (1.03, 1.59); p=0.027
Week 52	370 (53.9)	354 (52.1)	1.09 (0.88, 1.36); p=0.430
SGRQ (≥4 unit decrease from baseline in total score)			
Week 26	321 (46.7)	246 (36.2)	1.52 (1.21, 1.91); p<0.001
Week 52	297 (43.2)	244 (35.9)	1.33 (1.06, 1.66); p=0.014

BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; FEV₁ = forced expiratory volume in 1 second; BDI = Baseline Dyspnea Index; TDI = Transition Dyspnea Index; SGRQ = St George's Respiratory Questionnaire.

Increases in TDI focal score were observed in both groups at all visits, with a statistically significant difference between treatments favouring BDP/FF/GB at the two earliest visits (Weeks 4 and 12) (Figure 2c). More than 50% of patients in each group reported clinically relevant improvements (≥1 unit) in TDI focal score at Weeks 26 and 52; at Week 26 patients were significantly more likely to respond to BDP/FF/GB than BDP/FF (Table 3).

For SGRQ total score, there were clinically relevant improvements from baseline (decrease ≥ 4 units) for the BDP/FF/GB group at all visits from Week 12 onwards, with statistically significant differences between the two groups at Weeks 4, 12 and 52 (mean treatment difference at Week 52 of -1.69 [95% CI: $-3.20, -0.17$]; $p=0.029$; Figure 3a). Patients were significantly more likely to have a clinically relevant improvement in SGRQ total score with BDP/FF/GB than with BDP/FF at Weeks 26 and 52 (Table 3). The use of rescue medication in puffs/day was significantly lower with BDP/FF/GB than BDP/FF up to Week 26; patients in the BDP/FF/GB arm had a significantly greater percentage of days with no rescue use than those in the BDP/FF arm up to Week 12 (Supplementary Table 1). In addition, E-RS total scores (exploratory endpoint) were significantly lower with BDP/FF/GB than BDP/FF up to Week 26 (Supplementary Table 2).

The percentage of patients who experienced moderate/severe exacerbations was lower with BDP/FF/GB (31.1%) than with BDP/FF (35.3%). The adjusted annual rate of moderate/severe exacerbations was 0.41 for BDP/FF/GB and 0.53 for BDP/FF, with a rate ratio of 0.77 (95% CI 0.65, 0.92; $p=0.005$), indicating a significant 23% reduction in the rate with BDP/FF/GB. Subgroup analyses were broadly consistent with the ITT analysis, showing a reduction in the rate of moderate/severe exacerbations for BDP/FF/GB compared with BDP/FF (Supplementary Figure 4). Of note, there was a significant 33% reduction in the rate with BDP/FF/GB compared with BDP/FF in patients with a history of >1 exacerbation (rate ratio 0.67 [95% CI 0.48, 0.94]; $p=0.019$), whereas for patients with a history of 1 exacerbation the treatment reduction appeared to be slightly lower (0.83 [0.67, 1.02]; $p=0.074$). The adjusted exacerbation rates in patients with a history of 1 exacerbation were 0.37 and 0.44 for BDP/FF/GB and BDP/FF, respectively, and 0.65 and 0.97 in those with a history of >1 exacerbation. There was no influence of blood eosinophils on treatment effects (Supplementary Figure 4). The rate of both moderate and severe exacerbations was lower in the BDP/FF/GB group than the BDP/FF group (Figure 3b). Furthermore, as shown in Figure

3c, BDP/FF/GB significantly prolonged the time to first moderate/severe exacerbation, with a hazard ratio of 0.80 (95% CI 0.67, 0.97; p=0.020).

A similar proportion of patients experienced TEAEs in the two groups; the most common events are shown in Table 4. The majority of events were mild or moderate in severity. There was one treatment-related SAE – atrial fibrillation that occurred in a patient in the BDP/FF/GB group. This event resolved in 15 days, and did not cause study drug discontinuation. TEAEs resulted in death in a similar percentage of patients in the two groups. None of the deaths were assessed to be related to the study treatment.

Table 4. Treatment-emergent AEs and serious AEs (≥2% in either group for AEs and ≥0.5% in either group for serious AEs and treatment-related AEs) (Safety population).

Number (%) of patients	BDP/FF/GB N=687	BDP/FF N=680
TEAEs	368 (53.6)	379 (55.7)
COPD	214 (31.1)	240 (35.3)
Nasopharyngitis	39 (5.7)	38 (5.6)
Pneumonia	23 (3.3)	18 (2.6)
Hypertension	21 (3.1)	16 (2.4)
Headache	12 (1.7)	16 (2.4)
Ischaemic heart disease	10 (1.5)	16 (2.4)
Angina pectoris	5 (0.7)	3 (0.4)
Myocardial infarction	1 (0.1)	6 (0.9)
Myocardial ischaemia	1 (0.1)	6 (0.9)
Coronary artery disease	3 (0.4)	1 (0.1)
Respiratory tract infection viral	16 (2.3)	10 (1.5)
Oral candidiasis	15 (2.2)	4 (0.6)
Serious TEAEs	106 (15.4)	123 (18.1)
COPD	66 (9.6)	75 (11.0)
Pneumonia	15 (2.2)	7 (1.0)

Number (%) of patients	BDP/FF/GB	BDP/FF
	N=687	N=680
Ischaemic heart disease	2 (0.3)	11 (1.6)
Myocardial infarction	1 (0.1)	6 (0.9)
Myocardial ischaemia	0	4 (0.6)
Angina pectoris	1 (0.1)	1 (0.1)
Cardiac failure	5 (0.7)	5 (0.7)
Treatment-related TEAEs	26 (3.8)	14 (2.1)
Oral candidiasis	10 (1.5)	2 (0.3)
Muscle spasms	5 (0.7)	3 (0.4)
Dry mouth	4 (0.6)	2 (0.3)
Treatment-related serious TEAEs	1 (0.1)	0
Severe TEAEs	77 (11.2)	86 (12.6)
TEAEs leading to study drug discontinuation	35 (5.1)	33 (4.9)
TEAEs leading to death	15 (2.2)	16 (2.4)
MACEs	15 (2.2)	15 (2.2)

BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; TEAE = treatment-emergent adverse event; COPD = chronic obstructive pulmonary disease exacerbations; MACE = major adverse cardiovascular events, including acute myocardial infarction, arrhythmias, cardiovascular death, heart failure and stroke.

Mean changes from baseline in blood pressure, heart rate and QTcF interval were small, and similar in the two groups (Supplementary Tables 3–6, with the detail on blood pressure changes in Supplementary Appendix 1). The percentages of abnormal QTcF interval absolute values and changes were similar in both treatment groups (Supplementary Table 7). In the subgroup of patients with Holter assessments, changes from baseline in 24-h average heart rate to Week 26 and 52 were minimal and similar in both groups (Supplementary Table 8).

Discussion

This study shows that in symptomatic COPD patients with severe or very severe airflow limitation and an exacerbation history, triple therapy with BDP/FF/GB had a greater effect than BDP/FF on pre-dose and 2-h post-dose FEV₁. For the co-primary endpoint measuring breathlessness (TDI), superiority of BDP/FF/GB over BDP/FF was not demonstrated. The rate of moderate/severe COPD exacerbations was 23% lower with BDP/FF/GB compared to BDP/FF, with the time to first exacerbation significantly prolonged. Thus, the greater improvement in lung function with BDP/FF/GB compared to BDP/FF was more clearly accompanied by a reduction in exacerbations rather than an improvement in breathlessness in this group of patients. Furthermore, BDP/FF/GB had a greater effect on health-related quality of life than BDP/FF.

Clinical trials have previously tested the effectiveness of triple therapy delivered by two separate devices. Active comparators in these studies have included LAMA monotherapy, LAMA and LABA using separate inhalers, and combined ICS/LABA treatment. There is evidence from these studies of short-term superiority of triple therapy in terms of lung function and patient reported outcomes compared to LAMA monotherapy^{15,20,21} or ICS/LABA treatment.^{13,16,22} We chose ICS/LABA as the comparator arm due to its widespread use in clinical practice in the target population we studied, namely COPD patients with severe to very severe airflow limitation and an exacerbation history. We demonstrated that triple therapy had a greater effect on FEV₁ than ICS/LABA, with effect sizes similar to previous studies that were conducted using broader inclusion criteria.^{13,16,22}

There was a clinically relevant improvement in TDI focal score with both treatments, but the mean difference between treatments in TDI focal score at Week 26 was not statistically significant. A practical issue for TDI measurements that may have affected this outcome is the requirement for patients to recall their prior symptoms, which can be a problem in longer studies, as recently discussed by the FDA.²³ TDI responder analysis has been suggested as an alternative way to evaluate differences between active treatments;¹⁷ this analysis showed

a symptomatic benefit with BDP/FF/GB in a greater proportion of patients. Significant differences favouring BDP/FF/GB for SGRQ total score were also found at several timepoints (Weeks 4, 12 and 52) – results that were supported by the SGRQ responder analysis. Overall, these responder analyses indicate that the lung function improvement with BDP/FF/GB compared to BDP/FF causes a clinically meaningful improvement in patient reported outcomes in a proportion of patients.

The evidence for an effect of triple therapy on exacerbations is scarce, as studies have generally been of short duration, and have not specifically recruited COPD patients at risk of exacerbation events. In one of the few long-term studies, Aaron *et al.* evaluated exacerbation rates with LAMA alone or in combination with either LABA or ICS/LABA for 52 weeks;¹¹ although the rate was lower with triple therapy compared to LAMA monotherapy, the difference was not statistically significant. The study suffered with a small sample size and a high drop-out rate, which reduced the number of events, thereby reducing the statistical power. In contrast, a 12-week study showed a significant 62% reduction in the rate of severe exacerbations with triple therapy compared with LAMA monotherapy ($p < 0.001$), although the data on moderate/severe exacerbations were not reported.²¹

The design of TRILOGY ensured that patients had at least one exacerbation in the last year despite treatment, most commonly with ICS/LABA combination (which accounted for >70% of the study population). We specifically excluded patients who were previously on triple therapy, in order to avoid stepping down treatment in patients randomised to ICS/LABA. The inclusion criteria of $FEV_1 < 50\%$, CAT total score ≥ 10 and an exacerbation history means that all of the study population were in GOLD Group D.¹ For these patients, the GOLD strategy document states that triple therapy is an option. However, in real life triple therapy is not commonly prescribed as first-line treatment in such patients, but instead treatment is generally escalated from regimens of one or two long-acting bronchodilators or an ICS/LABA,¹⁰ although the evidence supporting this approach was previously limited. Since we used a run-in period during which all patients received BDP/FF (with >70% also receiving

ICS/LABA before entering the study), the study design therefore allows clinicians to better understand the consequences of escalation of maintenance therapy in COPD patients already treated with ICS/LABA.

Combination treatment with LABA/LAMA has been shown to have a greater effect on symptoms and exacerbations than LAMA monotherapy.²⁴ The current study did not address the benefit of escalation to triple therapy from a LABA/LAMA combination. This is an important point to examine in the future, especially given that a recent study suggested that LABA/LAMA treatment is more effective on a wide range of endpoints including exacerbations compared to an ICS/LABA combination.²⁵

The 23% reduction in the exacerbation rate, which is above the suggested minimal clinically important difference,¹⁷ can be attributed to the LAMA component of BDP/FF/GB. Most of this benefit was on moderate exacerbations – consistent with other studies that were mainly dominated by moderate events.^{11,20,26} Our results on exacerbations are broadly similar to a retrospective database review using UK National Health Service data to compare triple therapy with ICS/LABA in terms of exacerbations and mortality.²⁶ Over a mean follow-up of 4.65 years, triple therapy was associated with a significant 35% reduction in all-cause mortality ($p < 0.001$), 29% reduction in moderate exacerbations ($p < 0.001$) and 15% reduction in severe exacerbations ($p = 0.04$). We now show a clinically relevant effect on moderate/severe exacerbations in GOLD D patients of the LAMA component after escalation to triple therapy from ICS/LABA treatment.

There was a relatively low exacerbation rate during the 1-year follow-up, despite the requirement for patients to have a history of at least one exacerbation in the year prior to study entry (the exacerbation rate over this period was 1.2). The majority of patients were receiving ICS/LABA before study entry, so it would be reasonable to expect the exacerbation rate after randomisation to the ICS/LABA group to be similar to the historic rate, rather than the observed rate of 0.53. We believe that this could be explained by the more regular care received in a clinical trial setting, plus potentially improved compliance during a clinical trial.

The treatment difference between BDP/FF/GB and BDP/FF on exacerbations appeared to be even greater in patients with two or more exacerbations in the previous year. This is perhaps not surprising, showing a greater impact of triple therapy on exacerbations in patients who suffer with more of these events.

Patients in the BDP/FF group had no change in therapy when progressing from the run-in to the treatment period. It could be anticipated that this group would experience no change after randomisation (baseline) in patient reported outcomes. However, we observed a mean improvement in TDI focal score that exceeded the minimal clinically important difference threshold,¹⁷ and an improvement in SGRQ total score being close to the threshold,¹⁷ despite no change in treatment. A trial effect on patient reported outcomes has been observed in previous COPD clinical trials.^{27,28} We attempted to minimise this by using a run-in period where patients were established on ICS/LABA, and recruiting patients who previously were on background maintenance treatment; >70% were previously taking ICS/LABA. It is possible that a longer run in period would have reduced this effect. This apparent trial effect on patient reported outcomes in the BDP/FF group possibly reduced the likelihood of observing an overall group mean difference compared to BDP/FF/GB. Nevertheless, the responder analysis indicates a benefit for triple therapy on symptoms and health-related quality of life for a greater proportion of individuals in this GOLD D population.

There are a range of inhaler devices of various types (including pMDIs and dry powder systems) and of contrasting designs, which demand different patient manoeuvres to ensure correct dose delivery. This presents a particular challenge with triple therapy, since historically, in clinical practice its administration has required more than one inhaler device. The delivery of triple therapy using a single inhaler potentially has practical advantages in this respect, simplifying therapy in a patient population which includes the elderly.

This triple therapy approach did not result in any safety findings, with no relevant differences between treatments. Of particular note, few patients experienced pneumonia, an event that has been associated with ICS use in COPD.²⁹ The low incidence of pneumonia events was

within the range reported in a number of prior ICS/LABA studies (as summarised by Singh *et al.*³⁰). Notably, the incidence of pneumonia in this study was similar to that observed in the FLAME trial,²⁵ where the incidence of treatment emergent pneumonia was 3.2% in the group that received only dual bronchodilator treatment and 4.8% in those who received ICS/LABA. Furthermore, the 24-h Holter evaluation provides reassurance about the safety profile of GB when added to therapy with BDP/FF.

In conclusion, in this study, conducted in patients with symptomatic severe and very severe COPD at risk of exacerbations, extrafine BDP/FF/GB provided greater bronchodilation than BDP/FF, while superiority of BDP/FF/GB was not demonstrated by the analysis of the co-primary endpoint of dyspnoea. Triple therapy had greater effects on health-related quality of life and the prevention of moderate/severe exacerbations. This is the first study to provide evidence for the clinical benefits of stepping up COPD patients from ICS/LABA combination treatment to triple therapy using a single inhaler.

Research in context

Evidence before this study

We searched PubMed for articles published before 9 June 2016, using the search term *"Drug Therapy, Combination"[MeSH Terms] AND COPD*, with a limit applied of clinical trials. Of the 312 hits, 13 presented data from clinical trials evaluating the efficacy of triple therapy with an inhaled corticosteroid (ICS) plus a long-acting β_2 -agonist (LABA) plus a long-acting muscarinic antagonist (LAMA), with one further manuscript presenting data from a retrospective cohort analysis. Of these, four studies compared triple therapy with ICS/LABA therapy; three compared triple therapy with both LAMA and ICS/LABA. Triple therapy consistently provided improved bronchodilation (assessed using forced expiratory volume in 1 second; FEV₁) compared with ICS/LABA. However, results were more variable for the other endpoints, including health-related quality of life, breathlessness and exacerbations. Most studies were of short duration and had insufficient sample size to evaluate exacerbations.

Added value of this study

This is the first large, long-term study to compare a triple ICS/LABA/LAMA combination in a single inhaler with an ICS/LABA. All patients received ICS/LABA during the run-in period, and so the study provides an indication of the benefits of stepping-up treatment in COPD patients with both an exacerbation history and symptoms.

Implications of all the available evidence

Compared with ICS/LABA, triple therapy with ICS/LABA/LAMA provides additive bronchodilation. This study also shows that a reduction in exacerbations can be achieved through this approach using a single inhaler.

Contributors

Dave Singh contributed to the conception and design of this study, and the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Alberto Papi substantially contributed to the acquisition, analysis, and interpretation of data for the work. He contributed to drafting and revising the manuscript for intellectual content, and he provided approval of the version to be published.

Massimo Corradi, in his role as consultant for Chiesi and Clinical Research Physician for the study, contributed to the conception, design and medical data integrity of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Ilona Pavlišová substantially contributed to the acquisition, and interpretation of data for the work. She revised the manuscript for intellectual content, and provided approval of the version to be published.

Isabella Montagna, in her Chiesi Lead Data Manager role, contributed to the conception, design and data integrity of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Catherine Francisco, in her Chiesi Clinical Operation Project Manager role, contributed to the conception, design and conduct of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Géraldine Cohuet, in her Chiesi Clinical Operation Project Manager role, contributed to the conception, design and conduct of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Stefano Vezzoli, in his Chiesi Lead Statistician role, contributed to the conception and design of this study, and to the analyses and interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Mario Scuri, in his Chiesi Clinical Program Leader role, contributed to the conception and design of the study, to the interpretation of the data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Jørgen Vestbo contributed to the analysis and interpretation of data for the work. He contributed to drafting and revising the manuscript for intellectual content, and he provided approval of the version to be published.

Declaration of interests

Dave Singh received personal fees from Chiesi during the conduct of the study. Outside the submitted work, Dr Singh reports grants and personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Glenmark, Johnson and Johnson, Merck, NAPP, Novartis, Pfizer, Takeda, Teva, Theravance, and Verona, and personal fees from Genentech and Skyepharma.

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Ilona Pavlišová has no relevant declarations of interest.

Isabella Montagna is employed by Chiesi Farmaceutici SpA, the sponsor of the study

Catherine Francisco is employed by Chiesi SAS, affiliate of the sponsor of the study

Géraldine Cohuet is employed by Chiesi SAS, affiliate of the sponsor of the study

Stefano Vezzoli is employed by Chiesi Farmaceutici SpA, the sponsor of the study

Mario Scuri is employed by Chiesi Farmaceutici SpA, the sponsor of the study

Jørgen Vestbo reports personal fees from Chiesi Farmaceutici during the conduct of the study. Outside the submitted work, Dr Vestbo reports personal fees from GlaxoSmithKline, Chiesi Farmaceutici, Boehringer-Ingelheim, Novartis, and AstraZeneca.

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Figure legends

Figure 1. Trial profile.

*Figure 2. Adjusted mean change from baseline (and 95% confidence intervals) throughout the study (ITT population) for (a) Pre-dose FEV₁; (b) 2-h post-dose FEV₁ (note that the first datapoints are the Week 0 post-baseline evaluation); (c) TDI focal score **p<0.01 and ***p<0.001 for the difference between BDP/FF/GB and BDP/FF.*

BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; FEV₁ = forced expiratory volume in 1 second; TDI = Transition Dyspnea Index.

*Figure 3a. Adjusted mean change from baseline (and 95% confidence intervals) throughout the study for SGRQ total score (ITT population), *p<0.05 and **p<0.01 for the difference between BDP/FF/GB and BDP/FF; Figure 3b. Unadjusted annual rate of COPD exacerbations of different severities (ITT population); Figure 3c. Time to first moderate/severe COPD exacerbation (ITT population).*

BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; SGRQ = St George's Respiratory Questionnaire; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

Title

Triple therapy in a single inhaler for COPD: The TRILOGY randomised, double-blind study

~~Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist in COPD: The TRILOGY randomised, double-blind study~~

Authors

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Summary

Background

Limited data are available on the efficacy of 'triple therapy' with two long-acting bronchodilators and an inhaled corticosteroid in chronic obstructive pulmonary disease (COPD). This randomised, double-blind study examined the efficacy of single-inhaler combination of an extrafine formulation of beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide (BDP/FF/GB).

Methods

In the run-in, patients received BDP/FF 100/6 μ g, two actuations twice daily (BID); patients were then randomised to either continue BDP/FF or step-up to BDP/FF/GB 100/6/12.5 μ g two actuations BID for 52 weeks via pressurised metered-dose inhaler. Eligible COPD patients had post-bronchodilator forced expiratory volume in 1 second (FEV₁) <50%, ≥ 1 moderate/severe COPD exacerbation in the previous 12 months, COPD Assessment Test total score ≥ 10 and Baseline Dyspnea Index focal score ≤ 10 . The three co-primary objectives were superiority of BDP/FF/GB over BDP/FF for pre-dose and 2-h post-dose FEV₁ and Transition Dyspnea Index (TDI) focal score, all at Week 26. Secondary endpoints included moderate/severe COPD exacerbation rate over 52 weeks.

ClinicalTrials.gov: NCT01917331.

Findings

The study ran from 21 March 2014 to 14 January 2016; 1368 patients were randomized (BDP/FF/GB=687; BDP/FF=681). At Week 26, BDP/FF/GB improved FEV₁ pre-dose by 0.081L (95%CI 0.052, 0.109; $p < 0.001$) and 2-h post-dose by 0.117L (0.086, 0.147;

$p < 0.001$) vs BDP/FF. Mean TDI focal scores at Week 26 were 1.71 for BDP/FF/GB and 1.50 for BDP/FF, with a difference of 0.21 (-0.08, 0.51; $p = 0.160$) Both groups had clinically relevant improvements in TDI at Week 26; the improvement was larger with BDP/FF/GB, although the treatment difference was not statistically significant. Adjusted annual

moderate/severe exacerbation rates were 0.41 for BDP/FF/GB and 0.53 for BDP/FF; rate ratio 0.77 (0.65, 0.92; $p=0.005$), corresponding to a 23% reduction with BDP/FF/GB vs BDP/FF. Adverse events were reported by 53.6% patients with BDP/FF/GB and 55.7% with BDP/FF.

Interpretation

This study shows the additional bronchodilator benefit of BDP/FF/GB over BDP/FF and a significant reduction in exacerbations with triple therapy which, for the first time, is possible using a single inhaler.

Funding

Chiesi Farmaceutici SpA

Introduction

The goals of pharmacological treatment of chronic obstructive pulmonary disease (COPD) are to reduce current symptoms and to reduce the risk of future exacerbations.¹ COPD patients with a history of exacerbations are at increased risk of future exacerbations,^{2,3} and are more likely to suffer from a reduced quality of life,⁴ more rapid lung function decline,^{5,6} and increased mortality.⁷ To reduce the risk of future events the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has specific recommendations for these patients; the first choice treatment is a long-acting muscarinic antagonist (LAMA), or an inhaled corticosteroid plus a long-acting β_2 -agonist (ICS/LABA).¹ Both of these options have been shown to improve lung function, alleviate symptoms and reduce exacerbation rates.^{8,9}

Many COPD patients continue to exacerbate despite treatment with either a LAMA or ICS/LABA combination. In clinical practice, it is very common in this situation to step up treatment to 'triple therapy' combining an ICS/LABA with a LAMA.¹⁰ Short-term clinical trials have shown that this step up improves lung function and reduces symptoms.¹¹⁻¹⁶ However, GOLD recognises that there is a lack of evidence for this approach regarding exacerbation reduction.¹

Currently, COPD patients receiving triple therapy must use at least two inhalers, typically ICS/LABA in one inhaler and LAMA in a second, and often these inhalers are of different types and designs. A single ICS/LABA/LAMA inhaler combining extrafine formulations of beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (GB) has been developed in order to simplify this regime. In the TRILOGY study, we aimed to compare the efficacy and safety of triple therapy with BDP/FF/GB to that of BDP/FF in symptomatic COPD patients with severe or very severe airflow limitation and an exacerbation history. The recruitment of this patient group allowed us to evaluate treatment effects on lung function, symptoms and exacerbations.

Methods

Study design

This was a randomised, parallel group, double-blind, active-controlled study, conducted in 159 sites across 14 countries. The sites were a mixture of primary (18), secondary (99) and tertiary care (28) providers, and specialist investigation units (14).

Patients who met the inclusion and exclusion criteria at a screening visit (Visit 1) entered a 2-week open-label run-in period, during which they received an extrafine formulation of BDP/FF 100/6 µg, two actuations twice daily (BID) via pressurised metered dose inhaler (pMDI). At Visit 2, patients were randomised to one of two treatment groups, to either continue to receive BDP/FF, or to be stepped up to an extrafine formulation of BDP/FF/GB. Over the subsequent 52-week treatment period, patients attended visits at Weeks 4, 12, 26, 40 and 52. As rescue medication, patients were permitted to use salbutamol (100 µg per actuation, via pMDI), although not within 6 h prior to any spirometry assessment. Other than study treatments and rescue medication, for the duration of the study the following classes of medication were not permitted, from the indicated time prior to the screening visit: short-acting β_2 -agonists (6 h); short-acting muscarinic antagonists (12 h); LABAs (12 h; 72 h for ultra-LABAs); LAMAs (72 h); ICSs (12 h); xanthine derivatives (7 days).

The study was approved by the ethics committee or institutional review board at each site, and was performed in accordance with the declaration of Helsinki, and the International Conference on Harmonisation Good Clinical Practice (ICH/CPMP/135/95). The protocol is included in the supplementary material. There were no substantial protocol amendments.

Patients

The main inclusion criteria were: ≥ 40 years of age; diagnosis of COPD, with post-bronchodilator forced expiratory volume in 1 second (FEV_1) $< 50\%$ and a ratio of FEV_1 to forced vital capacity (FVC) < 0.7 ; at least one moderate or severe COPD exacerbation in the previous 12 months ([see the definition in the Outcomes section, below](#)); and the use of ICS

plus LABA (as a free or fixed combination), ICS plus LAMA, LABA plus LAMA (as a free or fixed combination) or LAMA monotherapy for at least 2 months prior to screening (patients receiving triple therapy of ICS plus LABA plus LAMA were not eligible). In addition, all patients were to be symptomatic, with a COPD Assessment Test (CAT) total score ≥ 10 and a Baseline Dyspnea Index (BDI) focal score ≤ 10 at screening, with the BDI criterion also confirmed at the randomisation visit. All patients provided written informed consent prior to any study-related procedure.

The key criteria for exclusion were: a diagnosis of asthma, or history of allergic rhinitis or atopy; a COPD exacerbation in the 4 weeks prior to screening or during the run-in period; clinically significant cardiovascular conditions or laboratory abnormalities; or unstable concurrent disease that may have impacted efficacy or safety (as judged by the investigator). The full inclusion and exclusion criteria are listed in the supplementary material.

Randomisation and masking

Patients were randomised to treatment by investigators contacting an interactive response technology (IRT) system, which used a randomisation list generated by the IRT provider. Randomisation was stratified by country and severity of airflow limitation (in the post-bronchodilator FEV₁ categories $<30\%$ predicted, or 30 to $<50\%$ predicted). The two study treatments were provided in matching inhalers, with patients, investigators, site staff and sponsor personnel blinded to treatment assignment for the duration of the study.

Procedures

For the 52-week treatment period, patients were randomised 1:1 to either BDP/FF 100/6 μg or BDP/FF/GB 100/6/12.5 μg , both two actuations BID via pMDI. At Visit 2, baseline (pre-dose) data were collected for spirometry, BDI, and St George's Respiratory Questionnaire (SGRQ); spirometry was also performed at 2 h post-dose. At each subsequent visit, pre- and 2-h post-dose spirometry was conducted, and data were collected from the Transition

Dyspnea Index (TDI; which measures change from the BDI at Visit 2) and SGRQ.

Centralised spirometry was used to improve quality of the FEV₁ data. For the duration of the study, patients recorded daily symptoms using the EXACT-PRO questionnaire (EXAcerbations of Chronic pulmonary disease Tool Patient-Reported Outcome), together with treatment compliance and rescue medication use in an electronic diary; these data were reviewed by the investigator regularly, and at least at each visit.

Outcomes

There were three co-primary objectives: to demonstrate superiority of BDP/FF/GB over BDP/FF in terms of change from baseline in pre-dose (morning) FEV₁, change from baseline in 2-h post-dose FEV₁, and TDI focal score, all assessed at Week 26. The secondary efficacy variables were: pre-dose FEV₁ at all the other clinic visits and averaged over the treatment period; FEV₁ response (change from baseline in pre-dose FEV₁ ≥100 mL) at Weeks 26 and 52; 2-h post-dose FEV₁ at all the other clinic visits; TDI focal score at all the other clinic visits and TDI response (focal score ≥1; the minimal clinically important difference¹⁷) at Weeks 26 and 52; SGRQ total score at all clinic visits, and SGRQ response (decrease from baseline in total score ≥4 the minimal clinically important difference¹⁷) at Weeks 26 and 52; percentage of days without rescue medication use and average number of puffs/day; moderate/severe COPD exacerbation rate over 52 weeks of treatment; and the time to first moderate/severe COPD exacerbation.

A COPD exacerbation was defined as a worsening of the patient's respiratory symptoms that in the view of the patient's health care provider required treatment with systemic corticosteroids and/or antibiotics or hospitalisation~~a sustained worsening of dyspnea, cough and/or sputum production/purulence requiring systemic steroids and/or antibiotics, or need for hospitalisation~~.¹⁸ Events were classified as moderate or severe according to EMA/CHMP guidelines,¹⁸ with severe exacerbations being those requiring hospitalisation or resulting in death. Data from the EXACT-PRO questionnaire were used ~~To~~ to optimise the recognition of potential exacerbations, by programming the electronic diary ~~was programmed~~ to alert

physicians and to advise patients to contact their investigator in the event of worsening symptoms. EXACT-PRO data were also evaluated for the exploratory E-RS (Evaluating Respiratory Symptoms) Total Score endpoint.¹⁹

Treatment-emergent adverse events (TEAE) were captured throughout the study, with all events judged by the investigator as having reasonable causal relationship to a medical product considered to be treatment-related AEs. Blood pressure and ECG results were recorded pre-dose and at 10 min post-dose at each visit, with 24-h Holter recordings captured for a subset of approximately 10% of the patients at baseline and at Weeks 26 and 52. An independent Data Safety Monitoring Board (DSMB), composed of three independent clinicians and one independent biostatistician, provided a quarterly independent scrutiny of the study. Major adverse cardiovascular events (MACE) were adjudicated by an independent adjudication committee, comprising four cardiologists. The study is registered on ClinicalTrials.gov (NCT01917331).

Statistical analysis

It was estimated that a total of 1304 randomised patients (652 patients per group) would be required to reach a total of 1088 evaluable patients at Week 26 (544 patients per group), considering a non-evaluable rate of approximately 16.5% at this timepoint. Based on a two-sided significance level of 0.05, this sample size provided: 97.7% power to detect a mean difference of 60 mL in pre-dose FEV₁, assuming a standard deviation (SD) of 250 mL; 99.6% power to detect a mean difference of 70 mL in 2-h post-dose FEV₁, assuming a SD of 250 mL; and 87.1% power to detect a mean difference of 0.6 units in TDI focal score, assuming a SD of 3.2 units. An overall 85% study power for the primary efficacy analyses was therefore ensured.

The co-primary endpoints were all evaluated using a linear mixed model for repeated measures (MMRM), with data up to discontinuation included in the analysis for withdrawn patients. ~~with~~ This model included treatment, visit, treatment by visit interaction, country,

number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates. Data are presented as the adjusted means (i.e. least squares means) and adjusted mean differences between treatment groups, together with their 95% confidence intervals (CIs). In order to deal with multiplicity, the primary efficacy variables were tested in the following pre-specified hierarchical order: 1) pre-dose FEV₁; 2) 2-h post-dose FEV₁; 3) TDI focal score. At each step of the procedure, no confirmatory claims were to be made unless the superiority of BDP/FF/GB over BDP/FF was demonstrated in the preceding steps. There was no multiplicity adjustment on the secondary analyses. Subgroup analyses of the co-primary endpoints were prespecified, with patients grouped according to severity of airflow limitation, smoking status, gender, reversibility to salbutamol, COPD phenotype (chronic bronchitis, emphysema, or mixed), blood eosinophil level at screening, and age, with TDI also analysed according to presence of cardiovascular comorbidities.

Sensitivity analyses were performed on the three co-primary endpoints in order to assess the potential impact of missing data, as described in the supplementary material.

The majority of the secondary and exploratory endpoints were analysed using a similar MMRM to the co-primary endpoints. The responder analyses for FEV₁, TDI and SGRQ were conducted using a logistic model, the number of moderate/severe COPD exacerbations was analysed using a negative binomial model and the time to first moderate/severe COPD exacerbation was analysed using a Cox proportional hazards model. In these models, treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation, smoking status at screening and the baseline value (where available) were included as fixed effects. Log-time on study was also accounted for as an offset in the negative binomial model. The responder analyses for FEV₁, TDI and SGRQ were conducted using a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors, and the baseline value as a covariate. The number of moderate/severe COPD exacerbations

~~was analysed using a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as fixed effects, and log-time on study as an offset. The time to first moderate/severe COPD exacerbation was analysed using a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as factors.~~ *Post-hoc* subgroup analyses of the rate of moderate/severe exacerbations were conducted, with patients grouped as for the TDI co-primary endpoint, and also according to number of exacerbations in the previous 12 months.

The Intention-to-Treat (ITT) population was used for the efficacy evaluations. This included all randomised patients who received at least one dose of study treatment and with at least one efficacy evaluation (primary or secondary efficacy variables). The Safety population, used for all safety analyses, was all randomised patients who received at least one dose of the study treatment. All analyses presented in this manuscript were conducted using Statistical Analysis System (SAS), Version 9.2.

Role of the funding source

The funder of the study, Chiesi Farmaceutici SpA was responsible for the design and analysis of the study, oversaw its conduct and was responsible for the study report preparation. All authors had full access to all of the data, with the lead author (DS) responsible for the decision to submit for publication.

Results

The first patient entered the study on 21 March 2014, with the last completing on 14 January 2016. Of the 1812 patients screened, 1368 were randomized to treatment (687 to BDP/FF/GB and 681 to BDP/FF; Figure 1), with 602 (87.6%) completing the study in the BDP/FF/GB group and 579 (85.0%) in the BDP/FF group. The Safety population was the same as the ITT population. Compliance to treatment was high, with a median of 95.6% and 95.0% of doses taken in the BDF/FF/GB and BDP/FF groups, respectively. The baseline characteristics of the recruited patients are shown in Table 1. More than 80% of patients had at least one concomitant disease, with at least one cardiac disorder reported by 35.5% of patients in the BDP/FF/GB group and 35.0% in the BDP/FF group.

Table 1. Baseline demographics, disease characteristics and most common concomitant diseases (≥5% in either group) (Safety population).

	BDP/FF/GB (N=687)	BDP/FF (N=680)
Gender, n (%)		
Male	509 (74.1)	527 (77.5)
Race, n (%)		
White	684 (99.6)	679 (99.9)
Other	3 (0.4)	1 (0.1)
Age (years), mean (SD)	63.3 (7.9)	63.8 (8.2)
Body mass index (kg/m ²), mean (SD)	26.3 (5.4)	26.4 (5.3)
<u>Blood leukocytes (10⁹/L), mean (SD)</u>	<u>8.02 (2.23)</u>	<u>8.13 (2.28)</u>
<u>Blood eosinophils (10⁹/L), mean (SD)</u>	<u>0.25 (0.17)</u>	<u>0.24 (0.19)</u>
<u>Blood eosinophils (%), mean (SD)</u>	<u>3.12 (2.22)</u>	<u>3.06 (2.27)</u>
Smoking status, n (%)		
Current smoker	323 (47.0)	318 (46.8)
Ex-smoker	364 (53.0)	362 (53.2)
Time since first COPD diagnosis (years), mean (SD)	7.7 (5.8)	7.7 (6.0)
FEV ₁ (L)*, mean (SD)	1.11 (0.32)	1.10 (0.33)
FEV ₁ % predicted*, mean (SD)	36.9 (8.4)	36.2 (8.6)
FEV ₁ % predicted*, n (%)		
30 to 50%	532 (77.4)	525 (77.2)
<30%	155 (22.6)	155 (22.8)

	BDP/FF/GB (N=687)	BDP/FF (N=680)
<u>FVC (L)*, mean (SD)</u>	<u>2.73 (0.76)</u>	<u>2.75 (0.76)</u>
FEV ₁ /FVC ratio*, mean (SD)	0.42 (0.11)	0.41 (0.11)
Reversibility (%), mean (SD)	10.4 (14.2)	10.4 (14.1)
<u>Chronic bronchitis[†], n (%)</u>	<u>450 (65.5)</u>	<u>463 (68.1)</u>
Exacerbation rate in the previous year, mean (SD)	1.2 (0.5)	1.2 (0.5)
<u>CAT total score, mean (SD)</u>	<u>20.8 (5.9)</u>	<u>20.8 (5.7)</u>
COPD medication at study entry, n (%)		
ICS/LABA	506 (73.7)	487 (71.6)
ICS/LAMA	10 (1.5)	10 (1.5)
LABA/LAMA	95 (13.8)	107 (15.7)
LAMA	76 (11.1)	76 (11.2)
<u>Spacer use during the study, n (%)</u>	<u>111 (16.2)</u>	<u>129 (19.0)</u>
Patients with at least one concomitant disease, n (%)	590 (85.9)	563 (82.8)
Hypertension	404 (58.8)	382 (56.2)
<u>Ischaemic heart disease</u>	<u>172 (25.0)</u>	<u>173 (25.4)</u>
<u>Myocardial ischaemia</u>	<u>91 (13.2)</u>	<u>92 (13.5)</u>
<u>Coronary artery disease</u>	<u>66 (9.6)</u>	<u>58 (8.5)</u>
<u>Angina pectoris</u>	<u>44 (6.4)</u>	<u>43 (6.3)</u>
<u>Ischaemic cardiomyopathy</u>	<u>3 (0.4)</u>	<u>6 (0.9)</u>
<u>Myocardial infarction</u>	<u>2 (0.3)</u>	<u>0</u>
<u>Myocardial ischaemia</u>	<u>91 (13.2)</u>	<u>92 (13.5)</u>
Diabetes mellitus	90 (13.1)	89 (13.1)
Cardiac failure	73 (10.6)	86 (12.6)
<u>Coronary artery disease</u>	<u>66 (9.6)</u>	<u>58 (8.5)</u>
<u>Angina pectoris</u>	<u>44 (6.4)</u>	<u>43 (6.3)</u>
Hypercholesterolaemia	45 (6.6)	41 (6.0)
Respiratory failure	35 (5.1)	45 (6.6)
Gastritis	36 (5.2)	30 (4.4)
Benign prostatic hyperplasia	24 (3.5)	42 (6.2)
Cor pulmonale	39 (5.7)	25 (3.7)

* Post-salbutamol. [†]Includes patients with a mixed chronic bronchitis and emphysema phenotype. BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist.

In terms of the co-primary endpoints, BDP/FF/GB was superior to BDP/FF for both pre-dose and 2-h post-dose FEV₁ at Week 26, with mean differences of 0.081 L (-95% CI 0.052,

~~0.109~~ and 0.117 ~~(0.086, 0.147)~~, respectively (Table 2). There were improvements in TDI focal score at Week 26 in both groups, ~~and although the improvement was numerically greater with BDP/FF/GB~~ the mean difference between treatments (0.21 units) was not statistically significant. Subgroup analyses of the three co-primary endpoints (including by blood eosinophil levels) were broadly consistent with the ITT analyses (Supplementary Figures 1, 2 and 3). An exception was for the subgroup with very severe airflow limitation; in these patients, statistical significance was not reached for ~~although superiority was not reached for patients with very severe airflow limitation in~~ the pre-dose FEV₁ evaluation (Supplementary Figures 1, 2 and 3).

Table 2. Baseline and changes from baseline at Weeks 26 and 52 for FEV₁ and TDI the primary and secondary endpoints (ITT population).

Endpoint	BDP/FF/GB (N=687)	BDP/FF (N=680)	Adjusted mean difference between treatments
Baseline FEV ₁ (pre-dose, Week 0), L	1.096 (0.381)	1.094 (0.393)	
Pre-dose FEV₁, L			
Primary endpoint:	0.082	0.001	0.081
Week 26	(0.062, 0.102)	(-0.019, 0.021)	(0.052, 0.109); p<0.001
Week 52	0.071 (0.050, 0.093)	0.008 (-0.014, 0.030)	0.063 (0.032, 0.094); p<0.001
2-h post-dose FEV₁, L			
Primary endpoint:	0.261	0.145	0.117
Week 26	(0.240, 0.283)	(0.123, 0.166)	(0.086, 0.147); p<0.001
Week 52	0.249 (0.226, 0.273)	0.146 (0.122, 0.170)	0.103 (0.069, 0.137); p<0.001
BDI and TDI focal score			
BDI focal score*	5.27 (1.81)	5.45 (1.82)	
Primary endpoint:	1.71	1.50	0.21
TDI <u>focal score</u> at	(1.50, 1.92)	(1.29, 1.71)	(-0.08, 0.51); p=0.160
Week 26			
TDI <u>focal score</u> at	2.03	1.81	0.21
Week 52	(1.81, 2.25)	(1.59, 2.04)	(-0.10, 0.53); p=0.186
SGRQ total score			
Baseline	52.29 (16.84)	50.32 (16.50)	
Week 26	-4.76 (-5.69, -3.83)	-3.43 (-4.38, -2.47)	-1.33 (-2.66, 0.01); p=0.051
Week 52	-5.12 (-6.18, -4.06)	-3.43 (-4.51, -2.35)	-1.69 (-3.20, -0.17); p=0.029

*BDI focal score is the baseline value from which TDI focal score is evaluated. Baseline data are mean (SD); post-baseline data are adjusted mean change from baseline (95% confidence interval). BDP = beclometasone dipropionate; FF = formoterol

fumarate; GB = glycopyrronium bromide; FEV₁ = forced expiratory volume in 1 second; BDI = Baseline Dyspnea Index; TDI = Transition Dyspnea Index; SGRQ = St George's Respiratory Questionnaire.

Compared to BDP/FF, BDP/FF/GB showed significantly greater improvements in both pre-dose and 2-h post-dose FEV₁ at all visits (Week 52 data are in Table 2 and other visits in Figures 2a and b), with a significantly higher proportion of patients responding to BDP/FF/GB (defined as ≥ 100 mL increase in pre-dose FEV₁) at Weeks 26 and 52 (Table 3). The average pre-dose FEV₁ mean difference between treatments over the duration of the study was 0.072 L (95% CI 0.048, 0.096; $p < 0.001$).

Table 3. FEV₁, TDI and SGRQ responder analyses at Weeks 26 and 52 (ITT population).

Endpoint	Number (%) of patients with a clinically relevant change from baseline		Odds ratio (95% CI); p value
	BDP/FF/GB (N=687)	BDP/FF (N=680)	
	Pre-dose FEV₁ (≥ 100 mL increase from baseline)		
Week 26	287 (41.8)	165 (24.3)	2.30 (1.82, 2.91); p<0.001
Week 52	259 (37.7)	158 (23.2)	2.06 (1.62, 2.62); p<0.001
TDI (focal score ≥ 1)			
Week 26	394 (57.4)	352 (51.8)	1.28 (1.03, 1.59); p=0.027
Week 52	370 (53.9)	354 (52.1)	1.09 (0.88, 1.36); p=0.430
SGRQ (≥ 4 unit decrease from baseline in total score)			
Week 26	321 (46.7)	246 (36.2)	1.52 (1.21, 1.91); p<0.001
Week 52	297 (43.2)	244 (35.9)	1.33 (1.06, 1.66); p=0.014

BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; FEV₁ = forced expiratory volume in 1 second; BDI = Baseline Dyspnea Index; TDI = Transition Dyspnea Index; SGRQ = St George's Respiratory Questionnaire.

Increases in TDI focal score were observed in both groups at all visits, with a statistically significant difference between treatments favouring BDP/FF/GB at the two earliest visits (Weeks 4 and 12) (Figure 2c). More than 50% of patients in each group reported clinically relevant improvements (≥ 1 unit) in TDI focal score at Weeks 26 and 52; at Week 26 patients were significantly more likely to respond to BDP/FF/GB than BDP/FF (Table 3).

For SGRQ total score, there were clinically relevant improvements from baseline (decrease ≥ 4 units) for the BDP/FF/GB group at all visits from Week 12 onwards, with statistically significant differences between the two groups at Weeks 4, 12 and 52 (mean treatment difference at Week 52 of -1.69 [95% CI $-3.20, -0.17$]; $p=0.029$ Table 2 and; Figure 2d3a).

Patients were significantly more likely to have a clinically relevant improvement in SGRQ total score with BDP/FF/GB than with BDP/FF at Weeks 26 and 52 (Table 3). The use of rescue medication in puffs/day was significantly lower with BDP/FF/GB than BDP/FF up to Week 26; patients in the BDP/FF/GB arm had a significantly greater percentage of days with no rescue use than those in the BDP/FF arm up to Week 12 (Supplementary Table 1). In addition, E-RS total scores (exploratory endpoint) were significantly lower with BDP/FF/GB than BDP/FF up to Week 26 (Supplementary Table 2).

The percentage of patients who experienced moderate/severe exacerbations was lower with BDP/FF/GB (31.1%) than with BDP/FF (35.3%). The adjusted annual rate of moderate/severe exacerbations was 0.41 for BDP/FF/GB and 0.53 for BDP/FF, with a rate ratio of 0.77 (95% CI: 0.65, 0.92; $p=0.005$), indicating a significant 23% reduction in the rate with BDP/FF/GB. Subgroup analyses were broadly consistent with the ITT analysis, showing a reduction in the rate of moderate/severe exacerbations for BDP/FF/GB compared with BDP/FF (Supplementary Figure 4). Of note, there was a significant 33% reduction in the rate with BDP/FF/GB compared with BDP/FF in patients with a history of >1 exacerbation (rate ratio 0.67 [95% CI 0.48, 0.94]; $p=0.019$), whereas for patients with a history of 1

exacerbation the treatment reduction appeared to be slightly lower (0.83 [0.67, 1.02]; p=0.074). The adjusted exacerbation rates in patients with a history of 1 exacerbation were 0.37 and 0.44 for BDP/FF/GB and BDP/FF, respectively, and 0.65 and 0.97 in those with a history of >1 exacerbation. There was no influence of blood eosinophils on treatment effects (Supplementary Figure 4). The rate of both moderate and severe exacerbations was lower in the BDP/FF/GB group than the BDP/FF group (Figure 3b). Furthermore, as shown in Figure 43c, BDP/FF/GB significantly prolonged the time to first moderate/severe exacerbation, with a hazard ratio of 0.80 (95% CI 0.67, 0.97; p=0.020).

A similar proportion of patients experienced TEAEs in the two groups; the most common events are shown in Table 4. The majority of events were mild or moderate in severity. There was one treatment-related SAE – atrial fibrillation that occurred in a patient in the BDP/FF/GB group. This event resolved in 15 days, and did not cause study drug discontinuation. TEAEs resulted in death in a similar percentage of patients in the two groups. None of the deaths were assessed to be related to the study treatment.

Table 4. Treatment-emergent AEs and serious AEs (≥2% in either group for AEs and ≥0.5% in either group for serious AEs and treatment-related AEs) (Safety population).

Number (%) of patients	BDP/FF/GB N=687	BDP/FF N=680
TEAEs	368 (53.6)	379 (55.7)
COPD	214 (31.1)	240 (35.3)
Nasopharyngitis	39 (5.7)	38 (5.6)
Pneumonia	23 (3.3)	18 (2.6)
Hypertension	21 (3.1)	16 (2.4)
<u>Headache</u>	<u>12 (1.7)</u>	<u>16 (2.4)</u>
<u>Ischaemic heart disease</u>	<u>10 (1.5)</u>	<u>16 (2.4)</u>
<u>Angina pectoris</u>	<u>5 (0.7)</u>	<u>3 (0.4)</u>
<u>Myocardial infarction</u>	<u>1 (0.1)</u>	<u>6 (0.9)</u>
<u>Myocardial ischaemia</u>	<u>1 (0.1)</u>	<u>6 (0.9)</u>

Number (%) of patients	BDP/FF/GB	BDP/FF
	N=687	N=680
<u>Coronary artery disease</u>	<u>3 (0.4)</u>	<u>1 (0.1)</u>
Respiratory tract infection viral	16 (2.3)	10 (1.5)
Headache	12 (1.7)	16 (2.4)
Oral candidiasis	15 (2.2)	4 (0.6)
Serious TEAEs	106 (15.4)	123 (18.1)
COPD	66 (9.6)	75 (11.0)
Pneumonia	15 (2.2)	7 (1.0)
<u>Ischaemic heart disease</u>	<u>2 (0.3)</u>	<u>11 (1.6)</u>
<u>Myocardial infarction</u>	<u>1 (0.1)</u>	<u>6 (0.9)</u>
<u>Myocardial ischaemia</u>	<u>0</u>	<u>4 (0.6)</u>
<u>Angina pectoris</u>	<u>1 (0.1)</u>	<u>1 (0.1)</u>
Cardiac failure	5 (0.7)	5 (0.7)
Myocardial infarction	1 (0.1)	6 (0.9)
Myocardial ischaemia	0 (0.0)	4 (0.6)
Treatment-related TEAEs	26 (3.8)	14 (2.1)
Oral candidiasis	10 (1.5)	2 (0.3)
Muscle spasms	5 (0.7)	3 (0.4)
Dry mouth	4 (0.6)	2 (0.3)
Treatment-related serious TEAEs	1 (0.1)	0
Severe TEAEs	77 (11.2)	86 (12.6)
TEAEs leading to study drug discontinuation	35 (5.1)	33 (4.9)
TEAEs leading to death	15 (2.2)	16 (2.4)
MACEs	15 (2.2)	15 (2.2)

BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; TEAE = treatment-emergent adverse event; COPD = chronic obstructive pulmonary disease exacerbations; MACE = major adverse cardiovascular events, including acute myocardial infarction, arrhythmias, cardiovascular death, heart failure and stroke.

Mean changes from baseline in blood pressure, heart rate and QTcF interval were small, and similar in the two groups ([Supplementary Tables 3–6, with the detail on blood pressure changes in Supplementary Appendix 1](#)). The percentages of abnormal QTcF interval absolute values and changes were similar in both treatment groups ([Supplementary Table 7](#)). In the subgroup of patients with Holter assessments, changes from baseline in 24-h average heart rate to Week 26 and 52 were minimal and similar in both groups, ~~with adjusted mean changes ranging from –0.49 to 0.08 bpm~~ ([Supplementary Table 8](#)).

Discussion

~~This is the first study showing that in patients with severe to very severe COPD who were at risk of exacerbations, BDP/FF/GB was superior to BDP/FF in terms of lung function. Specifically, for the FEV₁ co-primary endpoints at Week 26, the mean treatment differences were 0.081 and 0.117 L for pre-dose (morning) trough and 2-h post-dose measurements, respectively. Similar superiority of BDP/FF/GB was consistently observed throughout the 52-week treatment period. For the co-primary endpoint measuring breathlessness (TDI), superiority of BDP/FF/GB over BDP/FF was not demonstrated, although there was a clinically relevant improvement in TDI focal score with both treatments. This study shows that in symptomatic COPD patients with severe or very severe airflow limitation and an exacerbation history, triple therapy with BDP/FF/GB had a greater effect than BDP/FF on pre-dose and 2-h post-dose FEV₁. For the co-primary endpoint measuring breathlessness (TDI), superiority of BDP/FF/GB over BDP/FF was not demonstrated. The rate of moderate/severe COPD exacerbations was 23% lower with BDP/FF/GB compared to BDP/FF, with the time to first exacerbation significantly prolonged. Thus, the greater improvement in lung function with BDP/FF/GB compared to BDP/FF was more clearly accompanied by a reduction in exacerbations rather than an improvement in breathlessness in this group of patients. Furthermore, BDP/FF/GB had a greater effect on health-related quality of life than BDP/FF.~~

Clinical trials have previously tested the effectiveness of triple therapy delivered by two separate devices. Active comparators in these studies have included LAMA monotherapy, LAMA and LABA using separate inhalers, and combined ICS/LABA treatment. There is evidence from these studies of short-term superiority of triple therapy in terms of lung function and patient reported outcomes compared to LAMA monotherapy^{15,20,21} or ICS/LABA treatment.^{13,16,22} We chose ICS/LABA as the comparator arm due to its widespread use in clinical practice in the target population we studied, namely COPD patients with severe to very severe airflow limitation and an exacerbation history. We demonstrated that triple

therapy had a greater effect on FEV₁ than ICS/LABA, with effect sizes similar to previous studies that were conducted using broader inclusion criteria.^{13,16,22}

There was a clinically relevant improvement in TDI focal score with both treatments, but tThe mean difference between treatments in TDI focal score at Week 26 was not statistically significant. A practical issue for TDI measurements that may have affected this outcome is the requirement for patients to recall their prior symptoms, which can be a problem in longer studies, as recently discussed by the FDA.²³ but the TDI responder analysis has been suggested as an alternative way to evaluate differences between active treatments;¹⁷ this analysis showed indicated a symptomatic benefit with BDP/FF/GB in a greater proportion of patients. Significant differences favouring BDP/FF/GB in terms of for SGRQ total score were also found at several timepoints (Weeks 4, 12 and 52) – results that were supported by the SGRQ responder analysis. Overall, these responder analyses indicate that the lung function improvement with BDP/FF/GB compared to BDP/FF causes a clinically meaningful improvement in patient reported outcomes in a proportion of patients.

The evidence for an effect of triple therapy on exacerbations is scarce, as studies have generally been of short duration, and have not specifically recruited COPD patients at risk of exacerbation events. In one of the few long-term studies, Aaron *et al.* evaluated exacerbation rates with LAMA alone or in combination with either LABA or ICS/LABA for 52 weeks;¹¹ although the rate was lower with triple therapy compared to LAMA monotherapy, the difference was not statistically significant. The study suffered with a small sample size and a high drop-out rate, which reduced the number of events, thereby reducing the statistical power. In contrast, a 12-week study showed a significant 62% reduction in the rate of severe exacerbations with triple therapy compared with LAMA monotherapy ($p < 0.001$), although the data on moderate/severe exacerbations were not reported.²¹

The design of TRILOGY ensured that patients had at least one exacerbation in the last year despite treatment, most commonly with ICS/LABA combination (which accounted for >70% of the study population). We specifically excluded patients who were previously on triple

therapy, in order to avoid stepping down treatment in patients randomised to ICS/LABA. The inclusion criteria of FEV₁ <50%, CAT total score ≥10 and an exacerbation history means that all of the study population were in GOLD Group D.¹ For these patients, the GOLD strategy document states that triple therapy is an option. However, in real life triple therapy is not commonly prescribed as first-line treatment in such patients, but instead treatment is generally escalated from regimens of one or two long-acting bronchodilators or an ICS/LABA,¹⁰ although the evidence supporting this approach was previously limited. Since we used a run-in period during which all patients received BDP/FF (with >70% also receiving ICS/LABA before entering the study), the study design therefore allows clinicians to better understand the consequences of escalation of maintenance therapy in COPD patients already treated with ICS/LABA.

Combination treatment with LABA/LAMA has been shown to have a greater effect on symptoms and exacerbations than LAMA monotherapy.²⁴ The current study did not address the benefit of escalation to triple therapy from a LABA/LAMA combination. This is an important point to examine in the future, especially given that a recent study suggested that LABA/LAMA treatment is more effective on a wide range of endpoints including exacerbations compared to an ICS/LABA combination.²⁵

~~In particular, t~~he 23% reduction in the exacerbation rate, which is above the suggested minimal clinically important difference,¹⁷ can be attributed to the LAMA component of BDP/FF/GB. Most of this benefit was on moderate exacerbations – consistent with other studies that were mainly dominated by moderate events.^{11,20,26} Our results on exacerbations are broadly similar to a retrospective database review using UK National Health Service data to compare triple therapy with ICS/LABA in terms of exacerbations and mortality.²⁶ Over a mean follow-up of 4.65 years, triple therapy was associated with a significant 35% reduction in all-cause mortality (p<0.001), 29% reduction in moderate exacerbations (p<0.001) and 15% reduction in severe exacerbations (p=0.04). We now show a clinically relevant effect on

moderate ~~and~~/severe exacerbations in GOLD D patients of the LAMA component after escalation to triple therapy from ICS/LABA treatment.

There was a relatively low exacerbation rate during the 1-year follow-up, despite the requirement for patients to have a history of at least one exacerbation in the year prior to study entry (the exacerbation rate over this period was 1.2). The majority of patients were receiving ICS/LABA before study entry, so it would be reasonable to expect the exacerbation rate after randomisation to the ICS/LABA group to be similar to the historic rate, rather than the observed rate of 0.53. We believe that this could be explained by the more regular care received in a clinical trial setting, plus potentially improved compliance during a clinical trial. The treatment difference between BDP/FF/GB and BDP/FF on exacerbations appeared to be even greater in patients with two or more exacerbations in the previous year. This is perhaps not surprising, showing a greater impact of triple therapy on exacerbations in patients who suffer with more of these events.

Patients in the BDP/FF group had no change in therapy when progressing from the run-in to the treatment period. It could be anticipated that this group would experience no change after randomisation (baseline) in patient reported outcomes. However, we observed a mean improvement in TDI focal score that exceeded the minimal clinically important difference threshold,¹⁷ and an improvement in SGRQ total score being close to the threshold,¹⁷ despite no change in treatment. A trial effect on patient reported outcomes has been observed in previous COPD clinical trials.^{27,28} We attempted to minimise this by using a run-in period where patients were established on ICS/LABA, and recruiting patients who previously were on background maintenance treatment; >70% were previously taking ICS/LABA. It is possible that a longer run in period would have reduced this effect. This apparent trial effect on patient reported outcomes in the BDP/FF group possibly reduced the likelihood of observing an overall group mean difference compared to BDP/FF/GB. Nevertheless, the responder analysis indicates a benefit for triple therapy on symptoms and health ~~status-~~ related quality of life for a greater proportion of individuals in this GOLD D population.

There are a range of inhaler devices of various types (including pMDIs and dry powder systems) and of contrasting designs, which demand different patient manoeuvres to ensure correct dose delivery. This presents a particular challenge with triple therapy, since historically, in clinical practice its administration has required more than one inhaler device.

The delivery of triple therapy using a single inhaler potentially has practical advantages in this respect, simplifying therapy in a patient population which includes the elderly. ~~Moreover, BDP/FF/GB is an extrafine formulation designed to maximise delivery to the lungs, not only in the large but also in the small airways where significant inflammation and obstruction is often present.~~²⁸

This triple therapy approach did not result in any safety findings, with no relevant differences between treatments. Of particular note, few patients experienced pneumonia, an event that has been associated with ICS use in COPD.²⁹ The low incidence of pneumonia events was within the range reported in a number of prior ICS/LABA studies (as summarised by Singh et al.³⁰). Notably, the incidence of pneumonia in this study was similar to that observed in the FLAME trial,²⁵ where the incidence of treatment emergent pneumonia was 3.2% in the group that received only dual bronchodilator treatment and 4.8% in those who received ICS/LABA.

Furthermore, the 24-h Holter evaluation provides reassurance about the safety profile of GB when added to therapy with BDP/FF.

In conclusion, in this 52-week study, conducted in patients with symptomatic severe and very severe COPD at risk of exacerbations, demonstrated that extrafine BDP/FF/GB provided greater bronchodilation than BDP/FF, while superiority of BDP/FF/GB was not demonstrated by the analysis of the co-primary endpoint of dyspnoea. Triple therapy had greater effects on health-related quality of life and ~~Importantly, this was associated with a clinically relevant reduction in the prevention of~~ moderate/severe exacerbations. This is the first study to study design provides evidence for the clinical benefits of stepping up COPD patients from ICS/LABA combination treatment to triple therapy using a single inhaler.

Research in context

Evidence before this study

We searched PubMed for articles published before 9 June 2016, using the search term *"Drug Therapy, Combination"[MeSH Terms] AND COPD*, with a limit applied of clinical trials. Of the 312 hits, 13 presented data from clinical trials evaluating the efficacy of triple therapy with an inhaled corticosteroid (ICS) plus a long-acting β_2 -agonist (LABA) plus a long-acting muscarinic antagonist (LAMA), with one further manuscript presenting data from a retrospective cohort analysis. Of these, four studies compared triple therapy with ICS/LABA therapy; three compared triple therapy with both LAMA and ICS/LABA. Triple therapy consistently provided improved bronchodilation (assessed using forced expiratory volume in 1 second; FEV₁) compared with ICS/LABA. However, results were more variable for the other endpoints, including health-related quality of life, breathlessness and exacerbations. Most studies were of short duration and had insufficient sample size to evaluate exacerbations.

Added value of this study

This is the first large, long-term study to compare a triple ICS/LABA/LAMA combination in a single inhaler with an ICS/LABA. All patients received ICS/LABA during the run-in period, and so the study provides an indication of the benefits of stepping-up treatment in COPD patients with both an exacerbation history and symptoms.

Implications of all the available evidence

Compared with ICS/LABA, triple therapy with ICS/LABA/LAMA provides additive bronchodilation. This study also shows that a reduction in exacerbations can be achieved through this approach using a single inhaler.

Contributors

Dave Singh contributed to the conception and design of this study, and the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Alberto Papi substantially contributed to the acquisition, analysis, and interpretation of data for the work. He contributed to drafting and revising the manuscript for intellectual content, and he provided approval of the version to be published.

Massimo Corradi, in his role as consultant for Chiesi and Clinical Research Physician for the study, contributed to the conception, design and medical data integrity of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Ilona Pavlišová substantially contributed to the acquisition, and interpretation of data for the work. She revised the manuscript for intellectual content, and provided approval of the version to be published.

Isabella Montagna, in her Chiesi Lead Data Manager role, contributed to the conception, design and data integrity of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Catherine Francisco, in her Chiesi Clinical Operation Project Manager role, contributed to the conception, design and conduct of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Géraldine Cohuet, in her Chiesi Clinical Operation Project Manager role, contributed to the conception, design and conduct of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Stefano Vezzoli, in his Chiesi Lead Statistician role, contributed to the conception and design of this study, and to the analyses and interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Mario Scuri, in his Chiesi Clinical Program Leader role, contributed to the conception and design of the study, to the interpretation of the data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Jørgen Vestbo contributed to the analysis and interpretation of data for the work. He contributed to drafting and revising the manuscript for intellectual content, and he provided approval of the version to be published.

Declaration of interests

Dave Singh received personal fees from Chiesi during the conduct of the study. Outside the submitted work, Dr Singh reports grants and personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Glenmark, Johnson and Johnson, Merck, NAPP, Novartis, Pfizer, Takeda, Teva, Theravance, and Verona, and personal fees from Genentech and Skyepharma.

Alberto Papi received grants from Chiesi Farmaceutici during the conduct of the study. Outside the submitted work, Dr Papi reports grants, personal fees and non-financial support from Chiesi Farmaceutici, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Takeda, Mundipharma and TEVA, and personal fees and non-financial support from Menarini, Novartis and Zambon.

Massimo Corradi received a research contract from Chiesi Farmaceutici SpA during the conduct of the study.

Ilona Pavlišová has no relevant declarations of interest.

Isabella Montagna is employed by Chiesi Farmaceutici SpA, the sponsor of the study

Catherine Francisco is employed by Chiesi SAS, affiliate of the sponsor of the study

Géraldine Cohuet is employed by Chiesi SAS, affiliate of the sponsor of the study

Stefano Vezzoli is employed by Chiesi Farmaceutici SpA, the sponsor of the study

Mario Scuri is employed by Chiesi Farmaceutici SpA, the sponsor of the study

Jørgen Vestbo reports personal fees from Chiesi Farmaceutici during the conduct of the study. Outside the submitted work, Dr Vestbo reports personal fees from GlaxoSmithKline, Chiesi Farmaceutici, Boehringer-Ingelheim, Novartis, and AstraZeneca.

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Figure legends

Figure 1. Trial profile.

Figure 2. Adjusted mean change from baseline (and 95% confidence intervals) throughout the study (ITT population) for (a) Pre-dose FEV₁; (b) 2-h post-dose FEV₁ (note that the first datapoints are the Week 0 post-baseline evaluation); (c) TDI focal score; ~~(d) SGRQ total score (ITT population); *p<0.05, **p<0.01 and ***p<0.001 for the difference between BDP/FF/GB and BDP/FF.~~

BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; FEV₁ = forced expiratory volume in 1 second; TDI = Transition Dyspnea Index; ~~SGRQ = St George's Respiratory Questionnaire.~~

Figure 3a. Adjusted mean change from baseline (and 95% confidence intervals) throughout the study for SGRQ total score (ITT population), *p<0.05 and **p<0.01 for the difference between BDP/FF/GB and BDP/FF; Figure 3b. Unadjusted annual rate of COPD exacerbations of different severities (ITT population).

~~BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; COPD = chronic obstructive pulmonary disease.~~

Figure 43c. Time to first moderate/severe COPD exacerbation (ITT population).

BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide; SGRQ = St George's Respiratory Questionnaire; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

Comment	Response
<p>Reviewer #1:</p> <p>These authors report the results of a large well conducted comparison of twice daily beclomethasone-formoterol and twice daily beclomethasone-formoterol- glycopyrronium in a metered dose inhaler in patients with severe COPD who would be classed as having stage D COPD using the GOLD system. As would be expected from many other shorter studies including the paper in Thorax cited using these drugs adding LAMA increased the FEV1 significantly but rather disappointingly failed to increase the TDI by the 0.6 units anticipated in the power calculation. As the authors state the study had 3 co-primary endpoints and although it met the 2 closely related FEV1 outcomes the failure to achieve the TDI change means that it should be viewed as a negative trial. This is not apparent from the way the paper is written especially given the focus on the exacerbation end point (which does not seem to have had a prior power calculation) and which properly speaking should be considered to show differences of only nominal significance. I am sure the Lancet statistical editor will have a view on the proper way to express this key issue. Hopefully a form of words can be found which will let you fairly present the results of this potentially important study.</p>	<p>As pre-specified in the protocol (section 12.3.4) and stated in the paper (“Statistical analysis” section), the co-primary endpoints were tested in the following hierarchical order: 1) pre-dose FEV₁; 2) 2-h post-dose FEV₁; 3) TDI focal score. Since in this sequence TDI focal score was the last co-primary variable to be tested, the absence of a significant treatment difference for this endpoint did not affect the conclusion of superiority of BDP/FF/GB vs. BDP/FF in terms of pre-dose and 2-hour post-dose FEV₁. Therefore, it is not appropriate to view the trial as negative. Also, significant differences between treatments in favour of BDP/FF/GB were found on several secondary endpoints, including a clinically relevant reduction in moderate/severe COPD exacerbation rate. We agree with the reviewer that these results on secondary endpoints only provide supportive evidence and they cannot serve as a basis for confirmatory claims. The wording of the paper was refined in order to better reflect this concept.</p> <p>We have amended the way that the TDI data are presented – avoiding any mention of numerical improvement in the abstract or results. We have also expanded on the paragraph in the discussion on the TDI to make it clearer that statistical significance was not met for this co-primary endpoint.</p>
<p>In general I thought that the presentation was clear although I prefer a results section with subheadings rather than the continuous narrative presented here.</p>	<p>Many thanks for your feedback. The Lancet author guidelines specify that subheadings should not be used in the results or discussion sections, so we have not added these.</p>

Comment	Response
<p>1. The patients recruited were spirometrically severe and reported prior exacerbations yet the observed rate was relatively low, certainly compared with the recent FLAME data. Have you any explanation for this - where there geographic differences with some countries contributing patient who did not exacerbate in either arm of the study or was this a generalised effect?</p>	<p>Patients were required to have a history of at least one exacerbation in the year prior to entry, most of whom were receiving ICS/LABA during this period. During the study, patients were treated with ICS/LABA or ICS/LABA/LAMA, and compliance to therapy was high (much higher than is typically achieved outside the clinical trial environment) – please see our response to Comment 6, where we suggest some explanations for this high compliance. The low rate of exacerbations during the study could therefore be explained by the combination of similar or increased pharmacotherapy plus potentially improved compliance.</p> <p>We have added some text to the discussion.</p> <p>There were exacerbations observed in each geographic region, although there was variability in the rate between regions (which one would expect). In particular, this variability was due to the regions with the lowest numbers of patients enrolled, and this limited sample size may contribute in explaining this heterogeneity.</p>
<p>2. It would help to say that patients using triple therapy were excluded. This is evident if you read the methods carefully but is not really obvious till you discuss it much later</p>	<p>We have added this to the 'Patients' section in the methods</p>
<p>3. You talk about the numerical difference in TDI scores but the p value is nowhere near significant.</p>	<p>We have removed all descriptions of 'numerical difference' from the results, only including this in the discussion.</p>
<p>You report a responder analysis for SGRQ and FEV1 which is significant but this appears to have been done post hoc as it is not mentioned in the methods or the study protocol which was not amended.</p>	<p>Both of these analyses were prespecified. They are mentioned in the protocol in Sections 8 (page 43) and 12.3.5 (page 53), and in the manuscript methods under 'Outcomes' (first paragraph) and 'Statistical analysis' (third paragraph).</p>

Comment	Response
<p>4. You have a very long list of secondary outcomes but focus on exacerbation (2 figures) which happily showed a positive effect. Whilst I think this is likely to be correct I suspect you were lucky given the low overall event rate. You did not correct for multiplicity or indicate that exacerbations were a key secondary outcome (they are last in your list of endpoints) so perhaps some more cautious wording would be appropriate.</p>	<p>Many thanks for your comments.</p> <p>The moderate/severe COPD exacerbation rate was defined in the protocol as a secondary endpoint. The inclusion of this secondary variable was intended to yield supportive evidence related to the primary objectives, and no confirmatory conclusions were needed. Therefore, no adjustment for multiplicity was required (EMA Points to Consider on Multiplicity Issues in Clinical Trials, section 2).</p> <p>In this context, we believe that it is valid to discuss the effect of BDP/FF/GB on the clinically significant endpoint of exacerbations to corroborate the treatment effect observed on the primary endpoints and to provide additional information on the treatment.</p> <p>Regarding the comment on the low exacerbation rate, it should be noted that the lower the overall rate, the more difficult the demonstration of a statistically significant difference between treatments (Keene et al. <i>Pharm Stat</i> 2007; 6:89-97). This further enhances the relevance of the results on exacerbations.</p>
<p>5. You talk about data you do not present - the EXACT-PRO. Presumably this was an exploratory outcome that will be presented subsequently?</p> <p>You mention spacer use in the protocol but you give no indication of how often this as needed and if it was balanced between the groups.</p>	<p>The electronic diary used in the study contained the EXACT-PRO questionnaire in order to daily collect data on symptoms. The reviewer is correct that the data from the EXACT-PRO are an exploratory endpoint, and so for the sake of space had not been included. Data have been added to the supplement from the E-RS, which are derived from the EXACT-PRO.</p> <p>16.2% of patients in the BDP/FF/GB group and 19.0% in the BDP/FF used a spacer device. Only patients who needed to take their previous COPD medication with a spacer were asked to use it throughout the run-in and treatment periods. We have added these data to the manuscript.</p>

Comment	Response
<p>6. Your inhaler adherence is based on self-report in the e-diary rather than any more objective assessment. Is this why it is so high?</p>	<p>We believe that this could be due to inclusion in a clinical trial, with regular (frequent) visits. In addition, the patient electronic diary included reminders, and if the patient did not transmit/report any intake of the study medication for several days an alert was sent to the site.</p> <p>In the TORCH trial, where adherence was evaluated using the dose counter on the device, 79.8% of the study population had a compliance >80% (Vestbo et al. <i>Thorax</i> 2009; 64(11): 939-43). In the TRILOGY study, compliance was above this threshold for the 86.8% of the patients overall. Considering the longer duration of the TORCH study (3 years), our findings on compliance seems in line with the scientific literature.</p>
<p>7. It would be reasonable to mention the Wedzicha paper in Lancet Respiratory Medicine comparing once daily glycopyrronium with glyco+indacaterol - the magnitude of change in lung function and exacerbations here is similar to that study I think. While you have addressed the benefits of one pathway of treatment escalation it is worth pointing out the need to look at others such as LABA-LAMA going to triple therapy.</p>	<p>Many thanks for the suggestion. We have added this to the discussion.</p>
<p>Reviewer #2: Statistical review</p>	
<p>This paper reports a RCT comparing two treatment regimens for COPD. Of three co-primary endpoints, two are found to be significantly improved in the experimental arm.</p> <p>Generally I found this to be a very good report of a RCT. The analysis is appropriate and well reported. I have a few minor comments to make which are listed below.</p>	<p>Many thanks for the positive feedback.</p>
<p>1) Abstract - please report the results of the third primary endpoint in the same way as the other two, even if it isn't significant.</p>	<p>Amended, as requested</p>

Comment	Response
<p>2) Please clarify in the methods how loss to follow-up was dealt with. I presume withdrawn individuals were included in the mixed effects model until withdrawn, which is valid under a missing at random assumption.</p> <p>The protocol mentions sensitivity analyses - were any of these done? There wasn't a huge difference in loss to follow up within arms so probably these are not needed.</p>	<p>Primary efficacy analyses were based on mixed models for repeated measurements (MMRM), with data up to discontinuation included in the analysis for withdrawn patients. As correctly pointed out, this is a valid approach under the missing at random (MAR) assumption.</p> <p>In order to assess the potential impact of missing data on the results of the primary efficacy analyses, the following sensitivity analyses were performed on all randomised patients:</p> <ul style="list-style-type: none"> • change from baseline in pre-dose morning FEV1: missing at random (MAR), copy reference (BDP/FF/GB) and baseline observation carried forward (BOCF) – like multiple imputation (MI); • change from baseline in 2-hour post-dose FEV1 and TDI focal score: MAR and copy reference MI, single imputation BOCF. <p>Of note, the analysis using MI under MAR is based on the same assumption behind the MMRM used for the primary efficacy analysis, however it allowed the inclusion in the analysis of all randomised patients (this is not always possible with the MMRM). Also, for 2-hour post-dose FEV1 and TDI focal score it was not feasible to conduct a proper BOCF-like imputation since a real baseline value was not available. For this reason, this sensitivity analysis was based on a single imputation BOCF, even though the risk of biasing the standard error downwards by ignoring the uncertainty of imputed values is acknowledged.</p> <p>Statistical Analysis System (SAS), Version 9.4 was used for the analyses based on MI.</p> <p>The results of the above sensitivity analyses have been added to Supplementary Figures 1, 2 and 3. These provided similar results to the co-primary analyses (as expected, considering the very low drop-out rate).</p>

Comment	Response
3) Results, page 12 - please add p-values to the text here.	Reviewer 5 has asked for duplication of data (tables and text) to be removed. As the addition of p values (which are already in Table 2) would mean further duplication, we have not incorporated this amend.
4) Table 1 - the alignment of the rows seemed like it was a bit off - it wasn't clear to me what the 'primary endpoint' rows means. For the BDI and TDI focal score part of the table, is the first row baseline?	The 'Primary endpoint' text was to indicate the three co-primary endpoints; this has been deleted. Yes, BDI is the baseline value from which TDI is evaluated. We have added a footnote for clarity.
5) Page 15 - if there is space, I would recommend adding the estimated odds ratios and confidence intervals/ p-values to the results on this page.	As per the response to Point 5, this would mean duplication of data reported in Table 3. We have therefore not included this text.
6) Page 17 - I think the results given in the final paragraph of the results should be provided more fully in the supplementary material.	Added to the supplementary material, as suggested.
7) Page 17 'with adjusted mean changes ranging from -0.49 to 0.08' - it is not clear to me over what groups or times this range is.	A table has been added to the supplement, and this test has been deleted from the manuscript.
8) Figure 3 - it would be useful if it could be stated whether these differences are significant or not (either in the text or a suitable symbol give in the figure.	Unfortunately the only prespecified analysis was on moderate/severe exacerbations, and not separately on moderate and severe (due to the limited number of event included in each category, these were expected to lead to a very low power). Figure 3b is included mainly to show the relative contribution of both severities of exacerbation to the overall moderate/severe rate.
9) The authors should provide a completed CONSORT checklist, which is required for Lancet reports of RCTs.	This has been uploaded.
Reviewer #4:	
Page 5, patients: eosinophils are not mentioned. Have they been analyzed and if so, what do they look like?	The three co-primary endpoints and the exacerbation rates were analysed according to blood eosinophil levels at screening (both percentage and absolute), with the results included in the supplement. This analysis (including the thresholds to be considered) was pre-specified in the Statistical Analysis Plan. The results were consistent in the low and high eosinophil subgroups (as expected, since both the combinations compared included an ICS). We have included a brief mention of these data.

Comment	Response
Page 5, patients: "...at least one moderate or severe COPD exacerbation in the previous 12 months...". How were these historical exacerbations defined? I know that this is stated in the online supplement, but I would suggest to mention it here.	We have added text to refer the reader to the Outcomes section.
Page 6, patients: "...with a COPD Assessment Test (CAT) total score ≥ 10 and a Baseline Dyspnea Index (BDI) focal score ≤ 10 at screening...". Why did the authors CAT analyse only at baseline and then continue with the SGRQ?	We used CAT as an inclusion criterion to ensure that patients were symptomatic, as specified in the GOLD strategy document. SGRQ has been established as it is a validated endpoint for intervention. Importantly, SGRQ is recognised as an endpoint in COPD for regulatory purposes (For example in the EMA's <i>Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease</i>) – and this study was conducted as part of the regulatory development of BDP/FF/GB.
Page 6, patients: "...The key criteria for exclusion were: a diagnosis of asthma, or history of allergic rhinitis or atopy...". Why did the authors chose these exclusion criteria? I think it would make perfect sense to use triple in particular (also) in patients that may suffer from	This comment appears to be truncated. If the reviewer is asking about asthma/COPD overlap, although the recruitment of such patients may be useful in evaluating the effect of an ICS component, this is perhaps less valid when evaluating the LAMA component. Furthermore, as this study was conducted in part to support regulatory approval of BDP/FF/GB, the patient population needed to be relatively homogenous.
Table 1: respiratory failure? What does that mean?	'Respiratory failure' or 'respiratory insufficiency' is the exact wording investigators have reported for any case associated with "difficulty breathing".

Comment	Response
<p>Page 15, results: "...The adjusted annual rate of moderate/severe exacerbations was 0*41 for BDP/FF/GB and 0*53 for BDP/FF..." This is a very low exacerbation rate compared to the rate in the year before the trial. Do the authors have any explanation for this phenomenon?</p>	<p>As per the response to Comment 1 of Reviewer 1, patients were required to have a history of at least one exacerbation in the year prior to entry, most of whom were receiving ICS/LABA during this period. During the study, patients were treated with ICS/LABA or ICS/LABA/LAMA, and compliance to therapy was high (much higher than is typically achieved outside the clinical trial environment) – please see our response to Comment 6, where we suggest some explanations for this compliance rate. The low rate of exacerbations during the study could therefore be explained by the combination of similar or increased pharmacotherapy plus potentially improved compliance.</p> <p>We have added some text to the discussion.</p>
<p>Table 4: The given incidence of pneumonia is very low. Do the authors have an explanation for this observation?</p>	<p>The incidence of pneumonia in this study is consistent with the incidence in a number of ICS/LABA studies, as summarised in <i>Singh et al npj Prim Care Respir Med 2016;26:16030</i>.</p> <p>We have added this reference to the discussion.</p>
<p>Discussion, general: Wedzicha et al. NEJM 2016 - LABA/LAMA vs ICS/LABA is not mentioned! I think it would be important to discuss this study. The main reason is that the basis of TRILOGY (ICS/LABA) from my perspective is not the standard of care any more for COPD patients with a considerable exacerbation risk. Thus, a comparison of LABA/LAMA with LABA/LAMA/ICS would be appropriate.</p>	<p>Many thanks for the suggestion. We have added this to the discussion.</p>
<p>Page 19, discussion: "... Aaron et al. evaluated exacerbation rates with LAMA alone or in combination with either LABA or ICS/LABA for 52 weeks;14 although the rate was lower with triple therapy compared to LAMA monotherapy, the difference was not statistically significant. The study suffered with a high drop-out rate, which reduced the number of events, thereby reducing the statistical power. .." This was not the only problem of Aaron et al. The authors should mention that the study was far too small to come to any relevant conclusions.</p>	<p>Again, many thanks for the suggestion. We have added this caveat to the discussion.</p>

Comment	Response
<p>Page 19, discussion: "...Since we used a run-in period during which all patients received BDP/FF, the study design therefore allows clinicians to better understand the consequences of escalation of maintenance therapy in COPD patients already treated with ICS/LABA..." I think that this is quite a bold statement considering the fact that run-in was only 2 weeks. I would suggest that the authors rephrase this.</p>	<p>Although the BDP/FF run-in period was only 2 weeks, we specifically sought to recruit patients already receiving ICS+LABA, ICS+LAMA, LABA+LAMA or LAMA monotherapy – and in fact more than 70% were receiving ICS+LABA. We therefore believe that the statement is appropriate. We have added some text on the prior medication.</p>
<p>Page 20, discussion: "...Moreover, BDP/FF/GB is an extrafine formulation designed to maximise delivery to the lungs, not only in the large but also in the small airways where significant inflammation and obstruction is often present...". The reference (28) that the authors give is not a reference for the triple drug! This needs to be corrected.</p>	<p>We have deleted this sentence.</p>
<p>Reviewer #5: TRYLOGY</p>	

Comment	Response
<p>The Authors of this paper examined in a 26-52 weeks randomized double blind study the efficacy and safety of single-inhaler combination of an extrafine formulation of beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide (BDP/FF/GB) in patients with severe COPD at risk of exacerbations (Severity grade DE). They found that, in comparison with BDP/FF BDP/FF/GB improved significantly 2 of the 3 co-primary outcomes, ie FEV1 pre-dose and 2-h post-dose, but not the dyspnea index. Interestingly for these kind of patients, they also found a significant reduction of the important secondary outcome moderate/severe exacerbation. No relevant adverse events. Interpretation. They conclude that this triple combination is effective and safe.</p> <p>General comments This is an interesting and important study conducted by company scientists supported by academic investigators with solid experience in the field. The study is properly designed and adequately powered to provide valid answers on efficacy and safety of BDP/FF/GB on functional and symptomatic outcomes (6 months) and exacerbations (12 months).</p> <p>Strengths The strengths of the study are: 1) it focussed in the most difficult COPD patients (100% grade D, even if most due to low lung function rather than exacerbations), 2) it investigates for the first time efficacy and safety of a triple LABA/ICS/LAMA combination, 3) it is the first study ever demonstrating conclusively that the triple LABA/ICS/LAMA combination in a single inhaler is superior to one of the 2 currently recommended treatments (LABA/ICS combination, the other being LAMA alone), and 4) that safety is not a problem in these severe complex patients.</p>	<p>Many thanks for your positive comments.</p>
<p>Weaknesses</p>	

Comment	Response
<p>The major limitations of the study are the</p> <ol style="list-style-type: none"> 1) it was powered mainly on lung function (again!!!!) that is not an aim of treatment of COPD (ref 30), 2) it failed to show an effect on dyspnoea, even if I have to say that in GOLD D the major concern is exacerbations) 3) the lack of LAMA (tiotropium arm) control arm; and 4) surprisingly no stratification for eosinophils and/or frequent exacerbators! Best data are to be included in the primary manuscript, the Authors have these data, they should include them here!!!! 	<ol style="list-style-type: none"> 1) As this is a regulatory study of a bronchodilator in COPD, FEV₁ is required as one of the primary endpoints. The overall power calculation actually took into account also the TDI co-primary (as highlighted in the 'Statistical analysis' section in the methods). We agree that lung function is not an aim of treatment in COPD – and indeed we highlight symptoms and exacerbations as treatment goals in the first sentence of the introduction. In recognition of this, we specifically recruited patients with symptoms and exacerbations. 2) We have expanded the section in the discussion on the lack of statistical significance for the co-primary endpoint (in response to a number of comments from the reviewers), and trust this is clearer now? It is important to note that there was a benefit of BDP/FF/GB over BDP/FF in the TDI responder analysis. 3) This is a very reasonable question but such comparison would serve different objectives. We sought to evaluate stepping up from ICS/LABA to triple therapy, not the benefits of the addition of ICS/LABA to a LAMA. This is a question that is being evaluated in a different study (NCT01911364). 4) Subgroup analyses of the three co-primary endpoints were pre-specified in the Statistical Analysis Plan by blood eosinophil levels at screening, and are reported in the supplement (Supplementary Figures 1-4). In addition the rate of moderate/severe exacerbations was analysed stratifying by blood eosinophil levels at screening, and historic numbers of exacerbations, and the results are again reported in the supplement (Supplementary Figure 4). We have included a brief mention of these data.

Comment	Response
<p>Considering that no triple or double has ever been convincingly shown to be superior to tiotropium alone, I believe that the lack of a tiotropium arm should be at least explained; in addition, in the conclusions the need for such a comparative study the Authors should emphasize that LAMA (ie tiotropium) remain first choice initial treatment for GOLD D patients: in fact no need to start with double or triple if single treatment is equivalent or non inferior, right?)</p>	<p>As highlighted in the conclusion paragraph, this study evaluated the efficacy of stepping up from ICS/LABA to triple – and as the reviewer correctly points out cannot answer any questions as to the relative efficacy of triple therapy and mono-LAMA. This is a question that is being evaluated in a different study (NCT01911364).</p>
<i>Specific comments</i>	
<p>TITLE</p> <p>I do not like the title. Considering the target journal LANCET, in my opinion it should read either:</p> <p>TRIPLE THERAPY IN A SINGLE INHALER FOR SEVERE COPD</p> <p>or</p> <p>BECLOMETHASONE-FORMOTEROL-GLYCOPYRRONIUM IN A SINGLE INHALER FOR SEVERE COPD</p>	<p>Many thanks for the suggestion. We have changed the title to:</p> <p>Triple therapy in a single inhaler for COPD: The TRILOGY randomised, double-blind study</p>
<p>ABSTRACT</p> <p>The abstract starts too general (I'd rather start mentioning that The triple therapy recommended by guidelines for severe COPD (grade3 D) is not supported by evidence.</p> <p>Also the abstract contains unnecessary details, eg the study ran from ... to....</p> <p>Finally I'd rather make stronger conclusions, ie This study shows that the triple BDP/FF/GB therapy in a single inhaler provide additional benefits in severe COPD patients treated with BDP/FF without safety concerns</p>	<p>Many thanks for the suggestion. There are some data on triple therapy – albeit limited and not from a single inhaler (as highlighted in the introduction and research in context sections), and so we prefer to retain the current sentence.</p> <p>Our thanks for the suggestion, but this is a Lancet requirement.</p> <p>Again, our thanks for the suggestion. The stronger text that you have suggested is perhaps a bit too strong, though. The main benefits of BDP/FF/GB in this study were on bronchodilation and exacerbations, and so we feel more comfortable retaining the current text.</p>

Comment	Response
Page 2, para 3: I would recommend to write simply that BDP/FF/GB therapy did not reduce dyspnea compared to BDP/FF.	Many thanks for the suggestion. We have revised this sentence to address feedback from Reviewer 2, which hopefully now also addresses this comment?
<p>INTERPRETATION</p> <p>The statement is not supported by evidence: the Authors provided no evidence that the effect on exacerbations was due to improvement in lung function!!!!!! By the way, I believe that nobody ever showed that, and in fact improvement of lung function is NOT an aim of treatment of COPD(1, 20)</p>	We fully agree. We are not saying that the improvement in bronchodilation is the reason for the improvement in exacerbations – only that we saw both.
Page 7, para 3: definition of exacerbations: please be more specific, and describe whether dyspnoea alone was considered sufficient to define an exacerbations, and/or the Anthonisen criteria were used at all	We have rephrased the definition.
Page 10, Table 1: I would recommend to add: absolute and %predicted values of FVC, VC (if available), prevalence of chronic bronchitis, CAT (including table with specific values for single components, maybe in the supplementaruyy appendix), total leucocytes, and particularly eosinophils	We have added absolute FVC, prevalence of chronic bronchitis, CAT total score, leukocyte and eosinophil values to Table 1. Unfortunately the CAT component scores have not been analysed, since CAT was used only at screening, and we do not have FVC percent predicted or VC data.
<p>Page 11, Table 1: why and how separating Myocardial ischaemia, Coronary Artery Disease, and Angina Pectoris? If necessary to mention all 3, then put them under Ischaemic Heart Disease. Also, it would be important to mention the percentage of patients who had at least 1 cardiac disease (MI, CF, CAD, AP, CP).</p> <p>BPH seems to be pretty low considering age and > 75% males, please check-</p> <p>By the way, useful to emphasize that > 80% patients had one or more concomitant chronic diseases)</p>	<p>The relevant conditions have been grouped under “Ischemic Heart Disease” in Tables 1 and 4, and we have added text presenting the overall prevalence of cardiac disease.</p> <p>We confirm the data are correct. This might be explained by Exclusion Criterion 12 – patients were excluded with a medical diagnosis of prostatic hypertrophy that in the opinion of the investigator would have prevented the use of anti-cholinergics.</p> <p>We have added a sentence, as requested.</p>

Comment	Response
<p>Page 11, last 4 lines: The sentence "Subgroup analyses of the three co-primary endpoints were broadly consistent with the ITT analyses, although superiority was not reached for patients with very severe airflow limitation in the predose FEV₁ evaluation (Supplementary Figures 1, 2 and 3)" is unclear to me</p>	<p>The subgroups are listed in the methods (in the statistical analysis section on Page 9). We have amended the text to read:</p> <p>Subgroup analyses of the three co-primary endpoints (including by blood eosinophil levels at screening) were broadly consistent with the ITT analyses (Supplementary Figures 1, 2 and 3). An exception was for the subgroup with very severe airflow limitation; in these patients, statistical significance was not reached for the predose FEV₁ evaluation (Supplementary Figures 1, 2 and 3).</p> <p>We trust that this makes the rest of the text clearer?</p>
<p>Page 13, Table 2: This table should include only the 3 co-primary outcomes data, and thus NOT SGRQ! Also some data are repeated 3 times, ie here in the table, in the text of results, and in figures</p>	<p>SGRQ has been deleted from this table and the repetitions have been deleted from the text (we have retained only the mean treatment differences in the text, and trust this is acceptable).</p>
<p>Figures: the figures are poorly prepared and too many. I would recommend to group the figures in 3 figures, ie 1) Figure 1 (CONSORT) could be moved to supplementary appendix; Figure 1 could then group only primary outcomes (Panel a: FEV₁, Panel b: 2H FEV₁, Panel c: TDI); Figure 3 could then group most relevant secondary outcomes (Panel a: SGRQ; Panel b: Moderate to severe exacerbations; Panel c: Time to first exacerbation modified like in the example to amplify the signal following the example from the POET study (NEJM, 2011; 364: 1093; Figure 3)</p>	<p>We are happy to move the CONSORT figure to the supplement, but leave this decision to the editor.</p> <p>We have grouped the figures as suggested, but respectfully prefer to retain the Kaplan-Meier curve as it is, rather than follow the example given.</p>
<p><i>Discussion</i></p>	

Comment	Response
<p>The question of the study (end of introduction) was "we aimed to compare the efficacy and safety of triple therapy with BDP/FF/GB to that of BDP/FF in symptomatic COPD patients with severe or very severe airflow limitation and an exacerbation history. The recruitment of this patient group allowed us to evaluate treatment effects on lung function, symptoms and exacerbations". The first sentence of the discussion should answer this question, and thus something like "This study shows that in symptomatic COPD patients with severe or very severe airflow limitation and an exacerbation history triple therapy with BDP/FF/GB is equally safe and more effective than BDP/FF in improving lung function but not dyspnea, and in improving quality of life and in reducing moderate to severe exacerbations".</p>	<p>Many thanks for the suggestion. We have modified the first paragraph in the discussion accordingly.</p>
<p>No need to repeat for the forth time the absolute differences in FEV1, and statistical levels.</p>	<p>We have deleted this text, as suggested.</p>
<p>I miss 2 most important sentence, ie 1) Even if GOLD recommends triple therapy in GOLD D patients not controlled by LAMA or LABA/ICS, this recommendation is not supported by any evidence;</p> <p>2) This is the first study that firmly shows that triple LABA/ICS/LAMA therapy in a single inhaler is superior to the double LABA/ICS recommended initial treatment for GOLD D patients.</p>	<p>This is covered by the final sentence of the second paragraph in the introduction, and by the opening sentence of the third paragraph of the discussion.</p> <p>Our thanks for the suggestion. The conclusion has been rewritten to include this point.</p>
<p>Page 21, Para 1: Because of the speculative nature of the content, the lack of data supporting it, and more importantly the weakness of the supporting reference 28, I would recommend to delete the sentence "Moreover, BDP/FF/GB is an extrafine formulation designed to maximise delivery to the lungs, not only in the large but also in the small airways where significant inflammation and obstruction is often present.28</p>	<p>We have deleted this sentence.</p>
<p><i>I would strongly recommend also:</i></p>	

Comment	Response
1. look again at eosinophilic (eg >300) and/or frequent exacerbators (both historic in the previous year (eg ≥ 2) and prospective (eg ≥ 2), as you may find additional positive results there, particularly for severe exacerbations; I noticed that frequent exacerbators and chronic bronchitics have larger effect on exacerbations).	Many thanks for this suggestion. The three co-primary endpoints have been analysed stratifying by blood eosinophil levels at screening, and the rate of moderate/severe exacerbations has been analysed stratifying by both eosinophil levels and history of exacerbations. These data are reported in the supplement, and some text has now been added to the manuscript.
2. to state that the only drug that was convincently shown to further improve lung function in patients treated with double LABA/ICS was roflumilast, even if patients included in that study were more severe (ie ≥ 2 exacerbations and had chronic bronchitis) and ≥70% were already on triple therapy, excluded in this study)	Many thanks for the suggestion. Although we agree that this is an interesting point, this is outside the scope of the manuscript – and we are limited for space.
3. that the prevalence of pneumonia was low, no different between arms, and anyway lower than most previous studies with ICS alone or in combination	The rate is actually similar to rates observed in prior ICS/LABA studies, as summarised in <i>Singh et al npj Prim Care Respir Med 2016;26:16030</i> . We have added this reference to the discussion.
<i>Minor comments</i>	
Reference 1 is incomplete, eg www.goldcopd.org , last consulted	As we were citing the document, and not the website, we hadn't included these details. However, we have now added the requested information.
Reference 21 is incomplete,	We have expanded the citation.
Page 25, line 6: Vestbobo should read Vestbo	Many thanks – this has been corrected.
Reviewer #6	

Comment	Response
<p>Singh et al present the results of the TRILOGY randomized control trial comparing ICS/LABA (BDP/FF) to ICS/LABA/LAMA (BDP/FF/GB) in patients with severe COPD and at risk for exacerbations. The trial is among the first to adequately test the benefits of triple therapy compared with dual therapy including an ICS. It is of particular interest because of the delivery of both combinations with a single inhaler which is not possible clinically at present. The co-primary endpoints included pre and post bronchodilator FEV1 (for which the triple combination demonstrated superiority) and dyspnea as assessed by the TDI focal score (for which the triple combination was numerically but not statistically superior) each at 26 weeks. The triple combination also reduced the risk of moderate and severe exacerbations by 23% compared with the dual combination and also modestly greater improvements in health status. Some of these differences were more pronounced when responder analyses were employed. Follow up was quite good with more patients completing the study than in many comparable trials. Adverse events were comparable. The paper is clear and well written.</p>	<p>Our thanks for the overall summary.</p>
<p>1. The majority of the population had been treated previously with ICS/LABA (>70% in both arms) and thus for most patients the study was a comparison of continued same therapy to an add-on bronchodilator (LAMA). In addition to the almost certain benefit on FEV1 that would be expected with the LAMA, it seems that this may introduce bias as it relates to other outcomes. It seems likely that a patient who had been on ICS/LABA for some time and had a new class of drug introduced that the chances of a symptomatic benefit would be greater. This warrants comment.</p>	<p>We agree with the reviewer that for the majority of patients this is a comparison between continuation and escalation of therapy – and we believe that this is a strength of this study, rather than a weakness. We therefore respectfully disagree, and do not consider this to be a source of bias. A similar approach (not washing out medication prior to study entry) has been used in other studies – including UPLIFT (Decramer et al COPD 2004;1:303–12).</p>

Comment	Response
<p>2. Why was the exacerbation rate so low in this population with severe disease, most of whom had events on maintenance therapy in the past year and remained symptomatic?</p>	<p>As per the response to Comment 1 of Reviewer 1, patients were required to have a history of at least one exacerbation in the year prior to entry, most of whom were receiving ICS/LABA during this period. During the study, patients were treated with ICS/LABA or ICS/LABA/LAMA, and compliance to therapy was high (much higher than is typically achieved outside the clinical trial environment) – please see our response to Reviewer 1 Comment 6, where we suggest some explanations for this compliance rate. The low rate of exacerbations during the study could therefore be explained by the combination of similar or increased pharmacotherapy plus potentially improved compliance.</p> <p>We have added some text to the discussion.</p>
<p>3. How were the exact pro data used? could these data be put together to give an estimate of mild exacerbations?</p>	<p>The EXACT-PRO data were used to collect symptoms, worsening of which was then used to alert physicians and to prompt patients to contact their investigator, so improving the quality of the exacerbations data. This has been clarified in the second paragraph of the 'Outcomes' section in the methods.</p> <p>As suggested by Reviewer 1, we have added data for the E-RS to the supplement.</p> <p>An analysis of mild exacerbations was not planned, since moderate/severe exacerbations were considered more relevant due to the regulatory purpose of the study. This is an interesting suggestion, however, and is worth further exploration.</p>
<p>4. The authors have addressed the issue of multiplicity as it relates to the primary endpoints. That said, does the failure of the third co-primary (TDI score) allow authors to claim superiority for exacerbations (key secondary)? The approach warrants a comment given the small numerical difference in exacerbation rates between the two arms.</p>	<p>See the response to Reviewer 1 (Comment 4).</p> <p>It is important to recognise that the 23% reduction in the exacerbation rate is above the suggested minimal clinically important difference, and so the superiority is not just statistical, but potentially clinically relevant.</p>
<p>5. The statistics section is very thorough but could likely be shortened with some details moved to the supplement.</p>	<p>The text has been edited down, as suggested by the reviewer.</p>

Comment	Response
6. The primary driver of the exacerbation benefit was a reduction in moderate events. This is not unexpected but warrants comment.	We have added some text to the discussion
7. The details of comorbid illness in Table 1 seems to have duplicate categories - for example CAD, angina and myocardial ischemia are all listed separately. These should be collapsed. Also, what is respiratory failure?	As per the response to Reviewer 5, Comment 4, the relevant conditions have been grouped under "Ischemic Heart Disease" in Tables 1 and 4. 'Respiratory failure' or 'respiratory insufficiency' is the exact wording investigators have reported for any case associated with "difficulty breathing".
8. Can the authors clarify the number of subjects lost in run in?	From the patients who successfully performed the screening visit (and therefore met the inclusion criteria), 52 patients were actually lost during the run-in. The breakdown is as follows: 22 withdrawals of consent, 15 for adverse events, 11 for failure to comply to protocol procedures/requirements, 1 for lack of efficacy, 2 on the sole decision of the investigator and 1 lost to follow up. Please note that these patients are included in the 'Excluded' box in the CONSORT diagram (Figure 1).
9. I am not certain there is data to support the statement that small airways inflammation would be treated better by ultrafine formulations such as those used in the trial.	This sentence has been deleted.

Figure 1

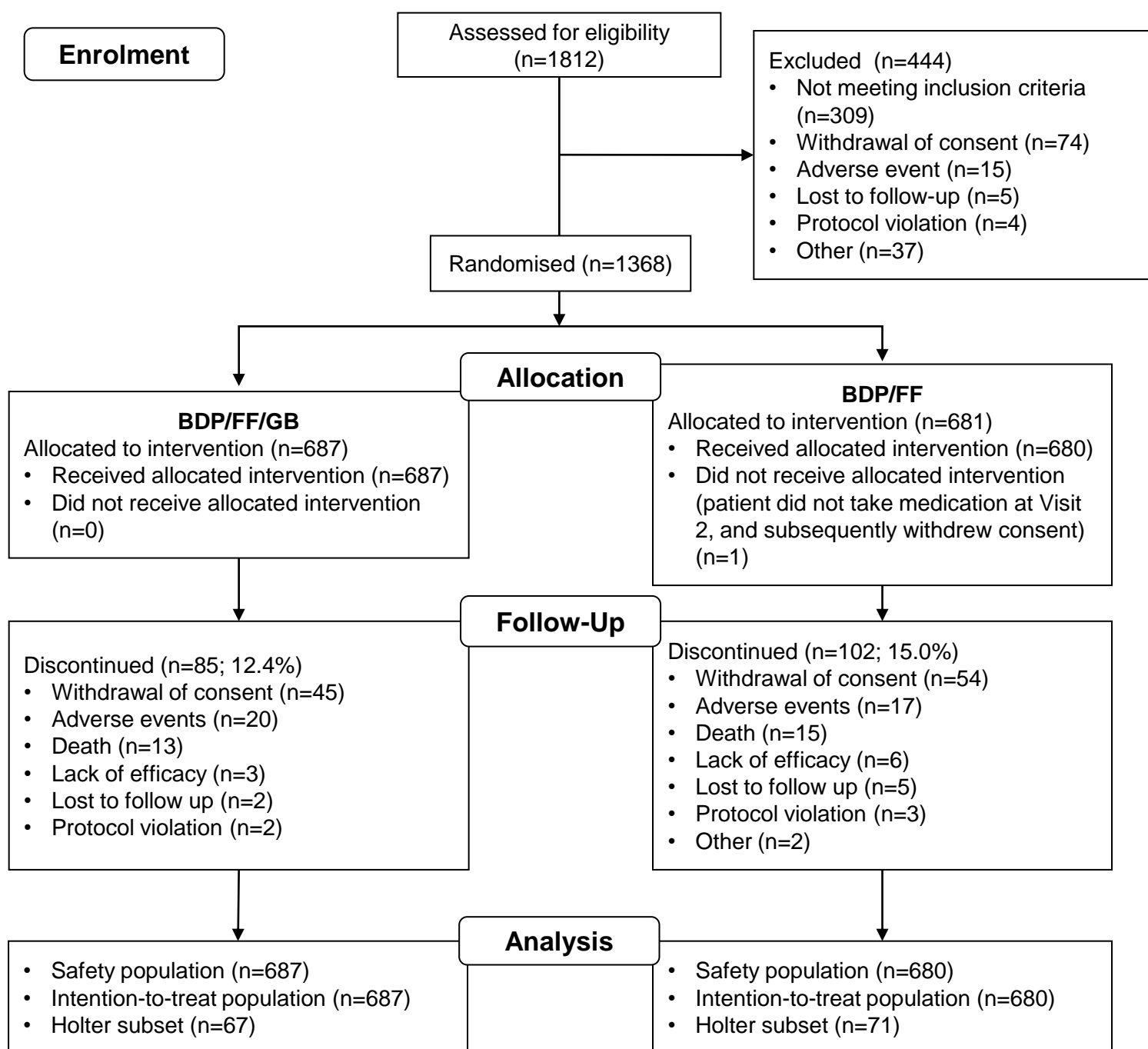
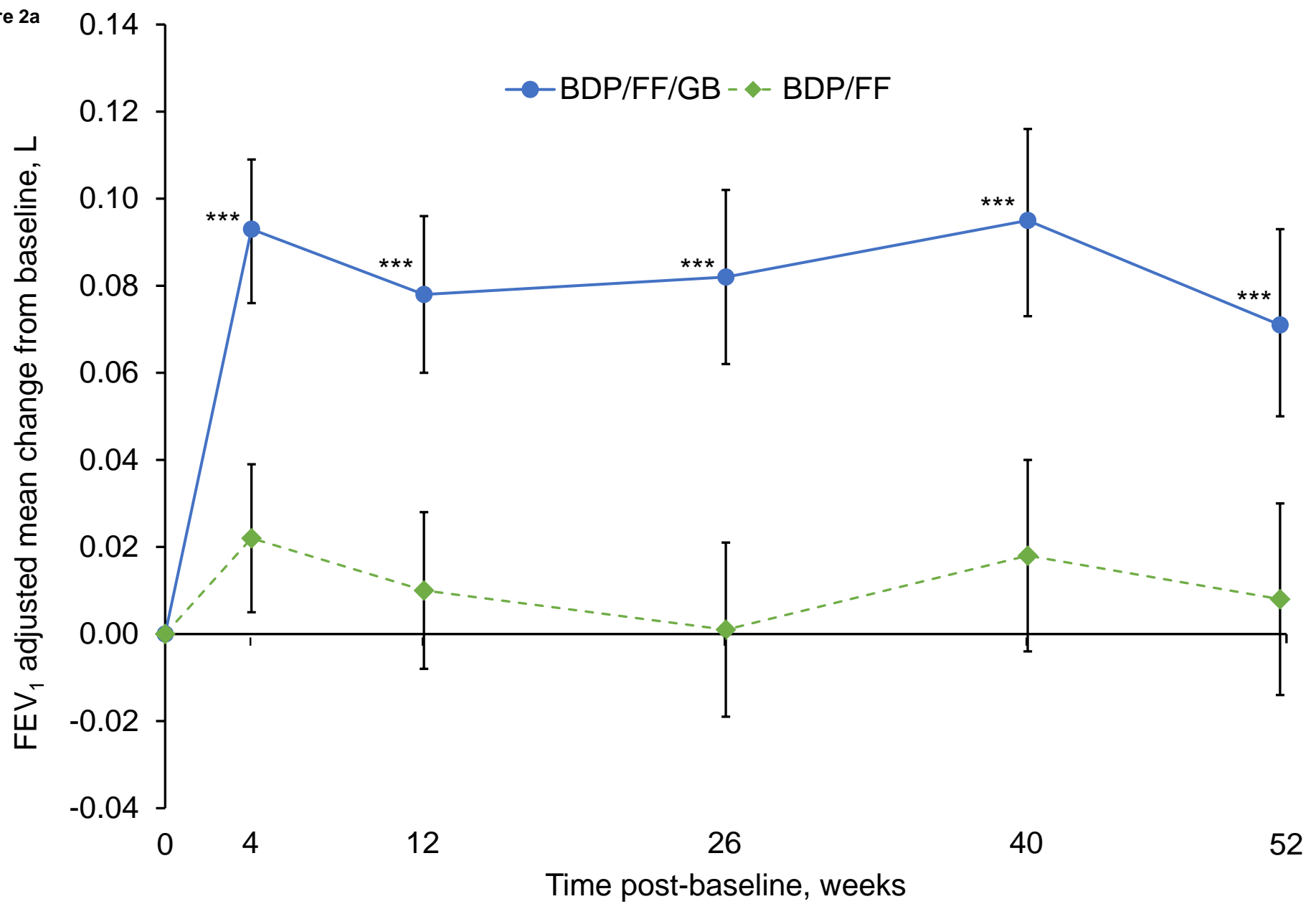
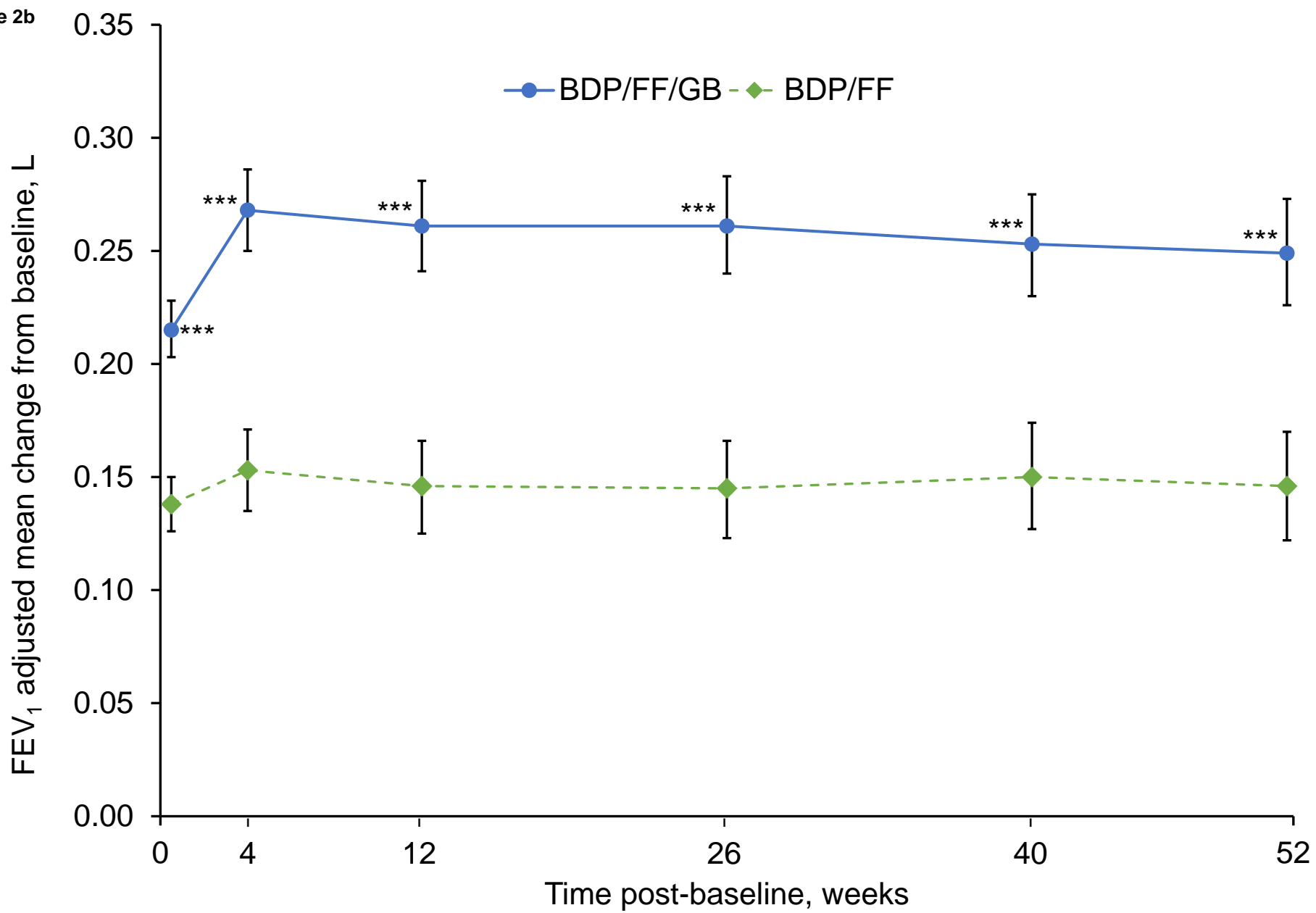


Figure 2a



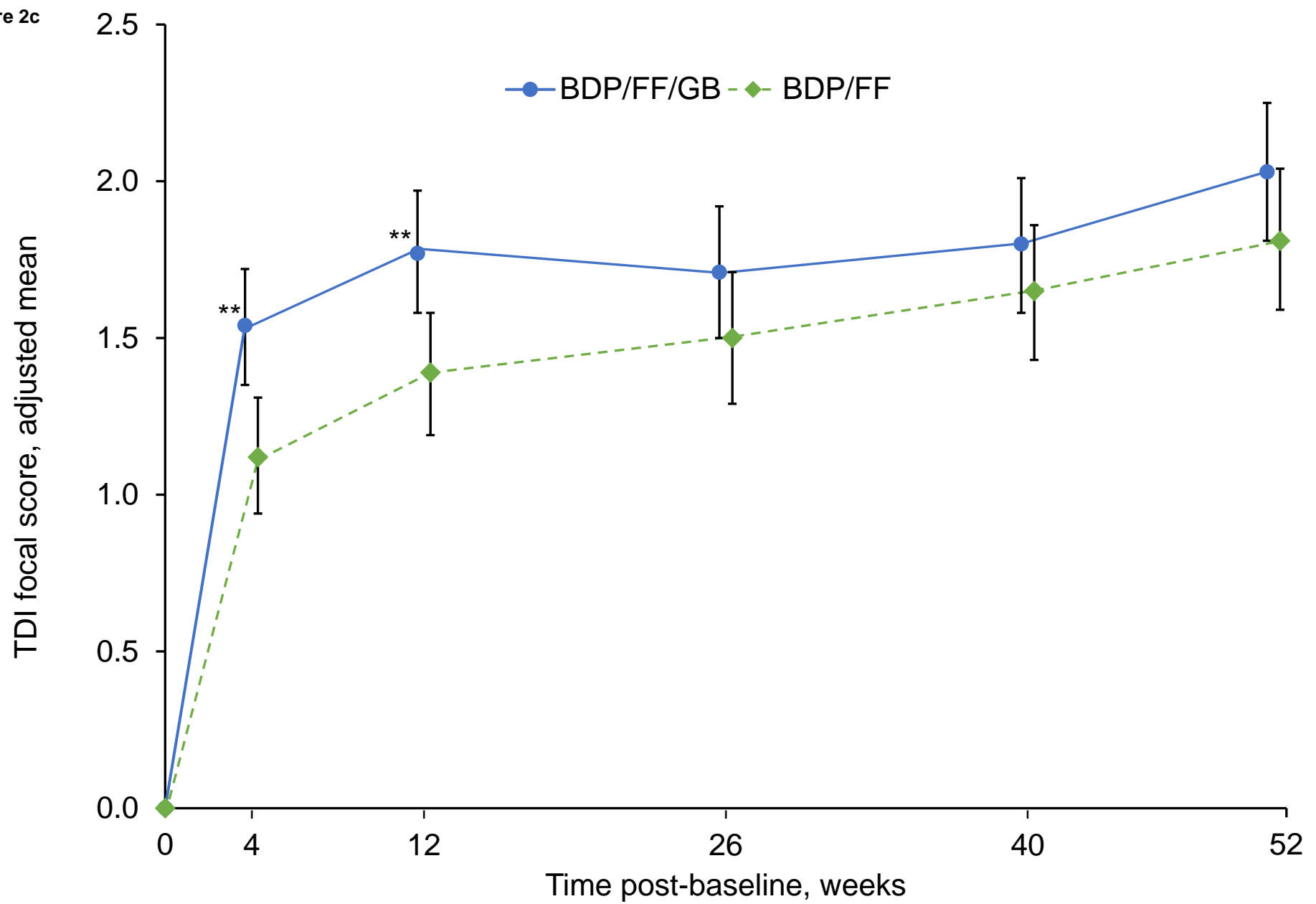
BDP/FF/GB	n=686	679	660	642	622	606
BDP/FF	n=679	669	654	616	597	578

Figure 2b



BDP/FF/GB	n=683	675	657	631	615	598
BDP/FF	n=674	660	648	609	590	575

Figure 2c



BDP/FF/GB	n=687	680	661	642	622	608
BDP/FF	n=680	672	651	619	596	579

Figure 3a

BDP/FF/GB	n=658	628	601	594	572	559
BDP/FF	n=644	607	597	558	545	532

Time post-baseline, weeks

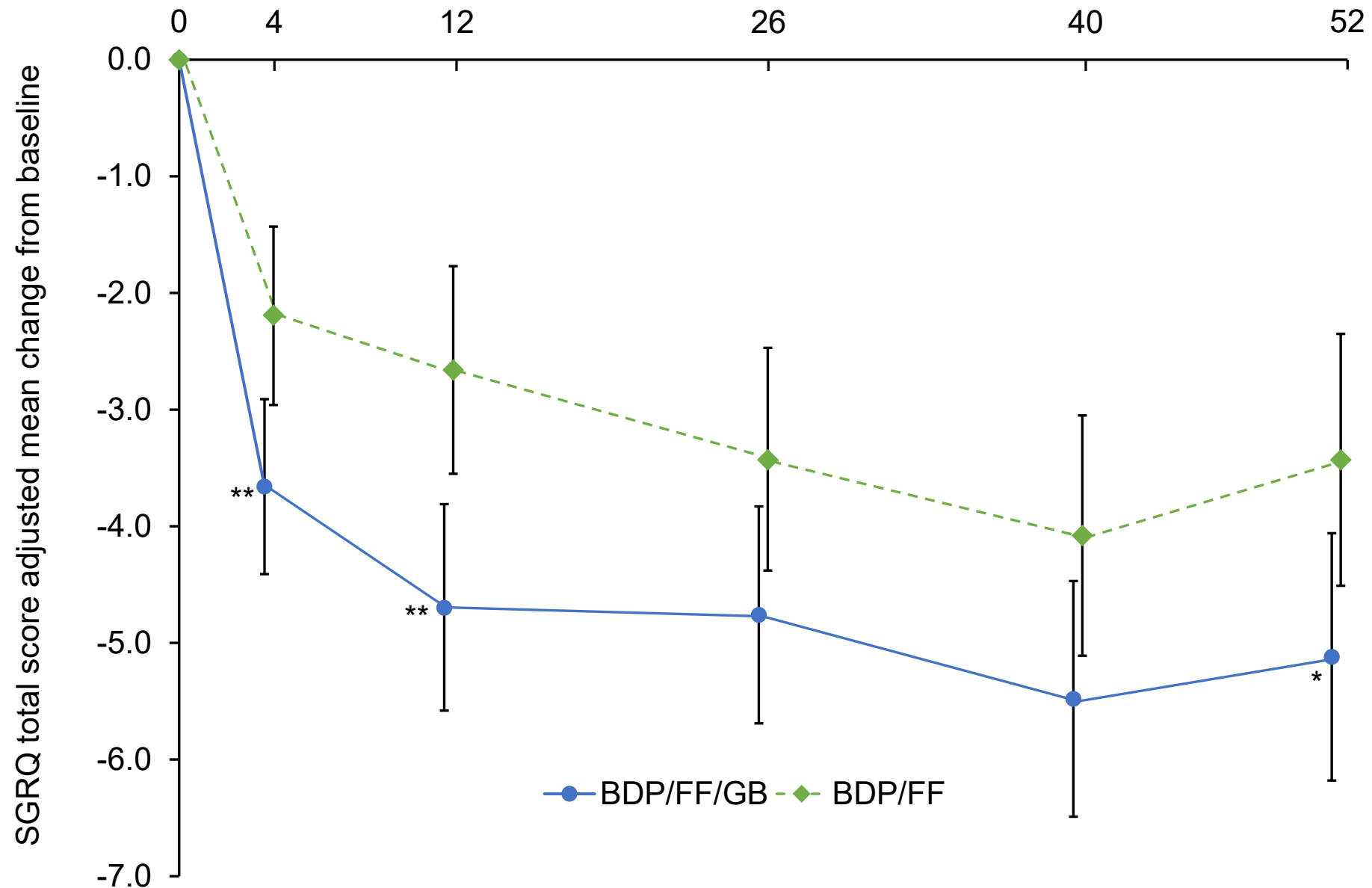


Figure 3b

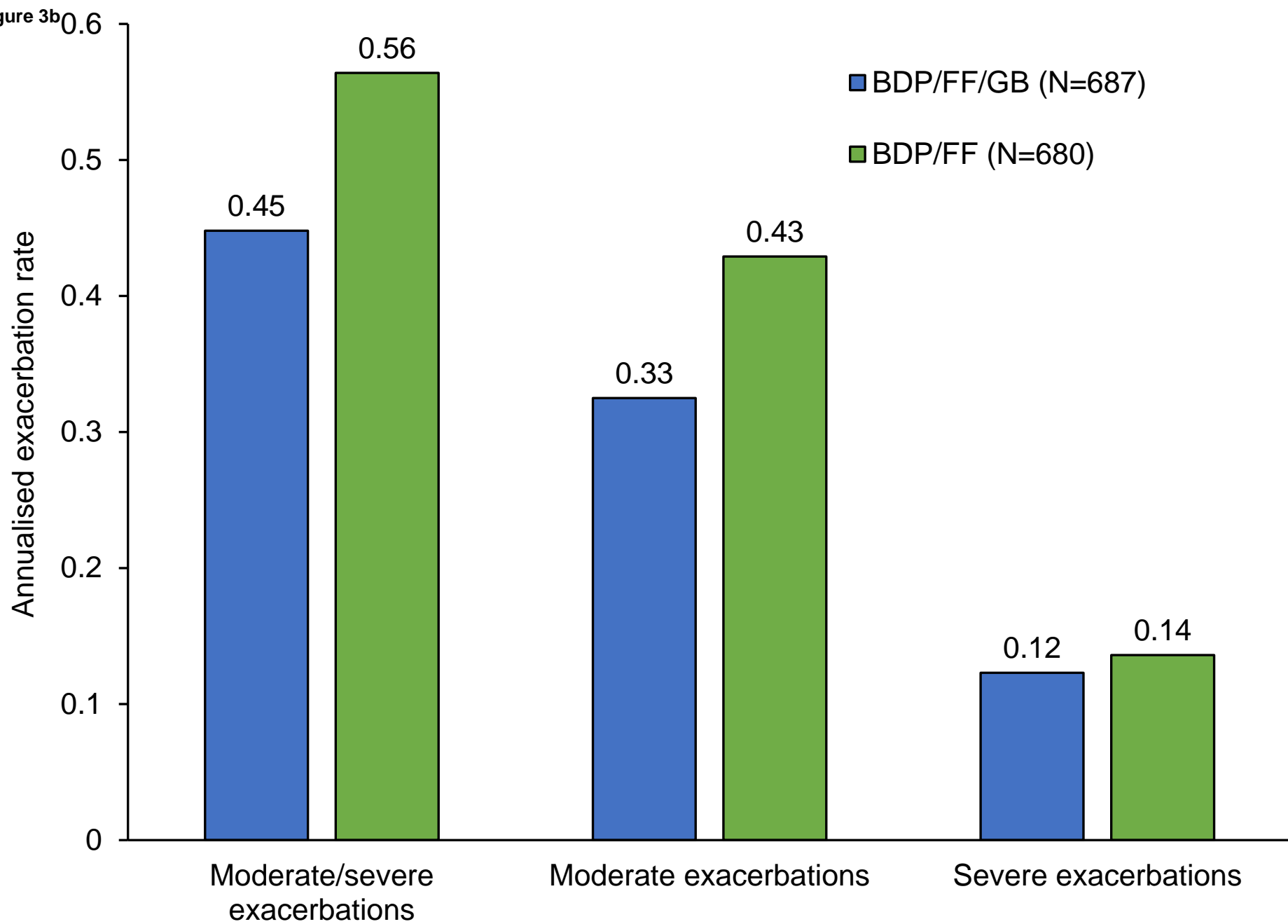
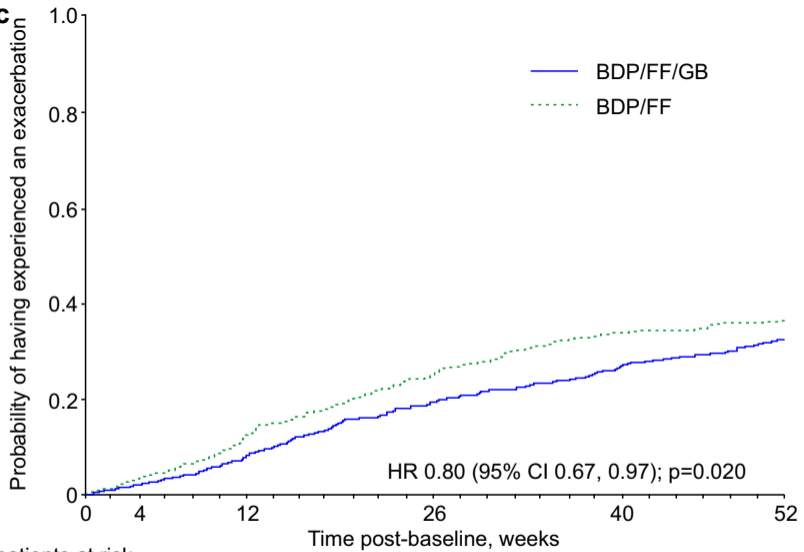


Figure 3c



Number of patients at risk

BDP/FF/GB	n=687	669	620	528	465	292
BDP/FF	n=680	649	588	483	414	265

Supplementary Material

[Click here to download Supplementary Material: TRILOGY supplement \(25 July 2016\).pdf](#)

CCD-1207-PR-0091
CLINICAL STUDY PROTOCOL

EUDRACT No. : 2013-001057-27

A 52-WEEK, DOUBLE-BLIND, RANDOMIZED, MULTINATIONAL, MULTICENTRE, 2-ARM PARALLEL-GROUP, ACTIVE-CONTROLLED CLINICAL TRIAL OF FIXED COMBINATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRROLATE BROMIDE ADMINISTERED VIA pMDI (CHF 5993) VERSUS FIXED COMBINATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE ADMINISTERED VIA pMDI IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Version No.: 1.0
Date: 01/10/2013

The information contained in this document is confidential and will not be disclosed to others without written authorization from Chiesi Farmaceutici S.p.A., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered or for discussions with local regulatory authorities, Ethics Committee/Investigational Review Boards, or people participating in the conduct of the study.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AC	Adjudication Committee
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ALT (GPT)	Alanine aminotransferase
ANCOVA	ANalysis of COVariance
AST (GOT)	Aspartate aminotransferase
BDP	Beclometasone dipropionate
BDI/TDI	Baseline Dyspnea Index / Transition Dyspnea Index
BID	Bis in die, twice a day
BMI	Body Mass Index
BP	Blood Pressure
β-HCG	β-Human Chorionic Gonadotrophin
BUN	Blood Urea Nitrogen
Ca	Calcium
CAT	COPD Assessment Test
CI	Confidence Interval
Cl	Chlore
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
(e)-CRF	(Electronic) - Case Report Form
CRO	Clinical Research Organization
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EMA	European Medicine Agency
EXACT(-PRO)	EXAcerbations of Chronic pulmonary disease Tool
FEV₁	Forced expiratory volume in 1 second (L)
FF	Formoterol Fumarate
FPFV	First Patient First Visit
FVC	Forced vital capacity (L)
γ-GT	Gamma-glutamyltransferase
GB	Glycopyrrolate Bromide
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	Haemoglobin
HCRU	Health Care Resources Utilisation
HcT	Haematocrit
HR	Heart Rate
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology (Voice and Web-based)
ITT	Intention to Treat
IV	Intravenous
K	Potassium
LABA	Long-acting β ₂ agonist
LAMA	Long-acting muscarinic antagonist

LPLV	Last Patient Last Visit
MACE	Major adverse cardiovascular events
M3	Muscarinic M3 receptors
MedDRA	Medical Dictionary for Regulatory Activities
Na	Sodium
NYHA	New York Heart Association
PDE	Phosphodiesterase
PLT	Platelets
pMDI	pressurised Metered Dose Inhaler
PP	Per-Protocol
PR	Time Interval Between the P and R wave in the ECG
PRO	Patient-Reported Outcome (PRO)
QRS	Time Interval Between the Q and R and S wave in the ECG
QTc	Time interval between the Q and T waves in the ECG (corrected for HR)
RBC	Red Blood Cell
SABA	Short-acting β_2 agonist
SAE	Serious Adverse Event
SAMA	Short Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGRQ	Saint George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
WBC	White Blood Cell
WHO	World Health Organisation

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APPENDICES

Appendix I	Minimum list of Source Data Required
Appendix II	Patient leaflet (Instructions for use) and administration scheme
Appendix III	Instructions for use of Aerochamber Plus TM Flow-Vu antistatic VHC spacer
Appendix IV	Sample of Patient Card

1. BACKGROUND INFORMATION AND STUDY RATIONALE

Chronic obstructive pulmonary disease (COPD) is a major public health problem in the world [1]. COPD is a serious and disabling disease, which imposes a large burden on patients, health care systems and society, with increasing prevalence and mortality predicted in the coming decades. It is a disease characterised by airflow limitation not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to prolonged exposure to noxious particles or gases. Tobacco smoking is the primary cause leading to inflammation and direct damaging of lungs, but it is likely that other COPD risk factors (i.e. heavy exposure to occupational dusts and chemicals, or to indoor/outdoor air pollution) can trigger a similar inflammatory process, and it is believed that such inflammation can lead to COPD.

Cholinergic tone is the major reversible component of airway obstruction in COPD and cholinergic mechanisms are also important in regulation of submucosal gland secretion which is increased in chronic bronchitis.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD 2011) guidelines recommend that the main therapeutic goals, besides the prevention of disease progression, is to relieve symptoms, improve health status and prevent/treat exacerbations. Bronchodilators are the mainstay of pharmacologic therapy for chronic obstructive pulmonary disease (COPD), and are recommended by international guidelines as first-line therapy in symptomatic patients and those who demonstrate airflow limitation.

The main classes of bronchodilators include β_2 -agonists and anti-cholinergic agents. They are recommended in all current guidelines as appropriate treatment for first-line maintenance therapy of COPD. Anticholinergic drugs, long-acting muscarinic antagonists (LAMAs), mostly used in COPD are ammonium quaternary salts such as tiotropium bromide. Alike LAMAs, long-acting β_2 -agonists (LABAs) such as formoterol fumarate exhibit sustained and prolonged effects and both have been shown to lessen symptoms and reduce exacerbations.

Glycopyrrolate is a quaternary ammonium, antimuscarinic agent used orally to control gastric acidity, parenterally as an antisialogogue and to reverse neuromuscular blockade, and studied inhaled in asthma and COPD. Inhaled Glycopyrrolate has been shown to induce prolonged bronchodilation in patients with asthma [2, 3, 4] and has been found to be an effective bronchodilator in COPD [5, 6, 7].

GOLD guidelines highlight that, for patients uncontrolled with bronchodilator monotherapy, combination therapy is recommended. In patients with more severe disease, adding a long acting muscarinic antagonist (LAMA) to a LABA/ ICS combination is an attractive alternative considering the different molecular mechanisms of action of these drugs. Triple therapy with LABA, LAMA and ICS is widely used in clinical practice. Several clinical studies have investigated this treatment approach and showed that 'triple therapy' is more effective in terms of pulmonary function improvement and symptoms control as compared to bronchodilator monotherapy or ICS/LABA [8, 9, 10, 11].

Chiesi developed a fixed combination of Beclometasone Dipropionate (BDP) and Formoterol Fumarate (FF) pMDI which has been marketed under the trade name Foster®.

Foster® is also named CHF 1535 or BDP/FF or Beclometasone dipropionate/Formoterol fumarate within this document.

The efficacy and safety of Foster® 100/6 μg per actuation were demonstrated in adult patients with moderate or severe persistent asthma at the dose of 1 or 2 inhalations twice daily. Foster® is currently being evaluated in COPD patients.

Chiesi has also developed a pMDI formulation of Glycopyrrolate bromide (GB) using the extrafine Modulite® technology to be combined with Beclometasone dipropionate and Formoterol fumarate for the treatment of patients with severe COPD.

Chiesi is now developing a triple fixed dose combination by combining Foster® with Glycopyrrolate bromide, for COPD patients that would benefit from ICS/LABA and LAMA combined therapy. This triple fixed dose combination is named CHF 5993, or Beclometasone dipropionate/Formoterol fumarate/Glycopyrrolate bromide, or BDP/FF/GB within this document.

The trial design will be optimised to measure exacerbation rates by using the Exacerbations of Chronic Pulmonary Disease Tool (EXACT), developed means of collecting patient-reported outcome (PRO) data, which helps to capture the frequency of exacerbations.

This PRO is being collected using a digital platform technology to enhance the efficiency of data capture; the physician will be able to monitor EXACT scores real time on a daily basis.

The daily EXACT score transmission enhances the contact between patients and physicians. The automatic alert to the physician 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.

Indeed, this study has been designed to compare the efficacy and safety of the CHF 5993 pMDI combination to the equivalent dose of Foster® in COPD patients after 52 weeks of treatment.

This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments) current Good Clinical Practices and all other applicable laws and regulations.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To demonstrate the superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of lung function (change from baseline in pre-dose and 2-hour post-dose morning FEV₁ at Week 26).
- To demonstrate the superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of dyspnea (Transition Dyspnea Index focal score at Week 26).

2.2 Secondary and Exploratory Objectives

- To evaluate the effect of CHF 5993 pMDI on other lung function parameters, patient's health status, clinical outcome measures and COPD exacerbations.
- To collect data in order to assess the impact of study treatments on health economic outcomes.
- To assess the safety and the tolerability of the study treatments.

3. STUDY DESIGN

This is a phase III, double-blind, randomized, multinational, multicentre, 2-arm parallel-group, active-controlled study in approximately 1304 randomised patients (652 patients per group). Approximately 145 sites will be involved.

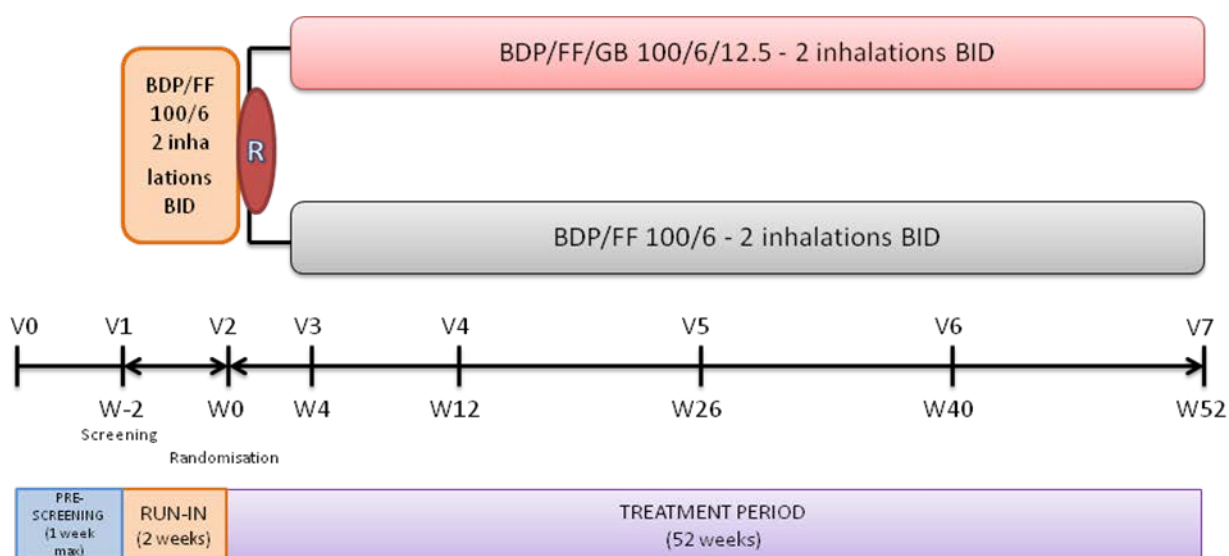
A total of 8 clinic visits (V0 to V7) will be performed during the study, as follows:

- A pre-screening visit (V0) will be carried out in order to fully explain the study to potential patients and to obtain the written informed consent from the patient and instruct the patient on screening visit procedures (such as medication restrictions and fasting).
- A screening visit (V1, no more than 7 days after V0) will help establishing the eligibility of patients for inclusion in the study (including routine haematology and blood chemistry, medical history, physical examination, a 12-lead ECG, spirometric parameters after salbutamol, vital signs and training for the use of inhalers). This visit will be followed by a 2-week open-label run-in period where patients will be on CHF 1535 pMDI (Foster®) 400/24µg per day.
- After the randomisation visit (V2), patients will be assessed after 4, 12, 26, 40 and 52 weeks of treatment (from V3 to V7) at clinic/hospital.

During the run-in and the randomised treatment periods, patients will complete the EXACT-PRO questionnaire and will record rescue medication use and treatment compliance daily in the digital platform configured for the study.

AEs, SAEs and COPD exacerbations will be monitored throughout the study.

Assessments and tests will be performed according to the study flow diagram included in [section 7.1](#).



The end of the trial is defined as the last visit of the last patient in the trial.

4. PATIENT SELECTION CRITERIA

4.1 Patient Recruitment

Outpatients attending the hospital clinics/study centres will be recruited.

A total of 1304 patients (652 patients per group) will be randomised in order to reach a total of 1088 evaluable patients at Week 26 (544 per group), considering a non-evaluable rate of approximately 16.5% at this time point.

Note: At least 20% of patients with very severe airflow limitation (post-bronchodilator FEV₁ at screening < 30% of predicted normal value) will be randomised in the study.

Financial compensation fees may be given to the patients according to local law and regulations to compensate patients' time, travel expenses and for any inconvenience caused by the study.

4.2 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Male or female adults aged ≥ 40 years with written informed consent obtained prior to any study-related procedure.
2. Patients with a diagnosis of COPD (according to GOLD guidelines, revised 2013) at least 12 months before the screening visit.
3. Current smokers or ex-smokers who quit smoking at least 6 months prior to screening visit, with a smoking history of at least 10 pack years [pack-years = (number of cigarettes per day x number of years)/20].
4. A post-bronchodilator $FEV_1 < 50\%$ of the predicted normal value **and** a post-bronchodilator $FEV_1/FVC < 0.7$, within 30 min after 4 puffs (4 x 100 μ g) of salbutamol pMDI. If this criterion is not met at screening, the test can be repeated once before randomisation visit.
5. A documented history of at least one exacerbation in the 12 months preceding the screening visit.

COPD exacerbation will be defined according to the following: *“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 necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalization”*

Also documented visits to an emergency department due to COPD exacerbation are considered acceptable to fulfil this criterion.

6. Patients under double therapy for at least 2 months prior to screening with either:
 - Inhaled corticosteroids/long-acting β -agonist or
 - Inhaled corticosteroids/long-acting muscarinic antagonist or
 - Inhaled long-acting β -agonist and inhaled long-acting muscarinic antagonist or

Patients under monotherapy with long-acting muscarinic antagonist for at least 2 months prior to screening.

7. Symptomatic patients at screening with a CAT score ≥ 10 .
8. Symptomatic patient at screening with a BDI focal score ≤ 10 . This criterion must be confirmed at randomisation (Visit 2).
9. A cooperative attitude and ability to be trained to use correctly the pMDI inhalers.
10. A cooperative attitude and ability to be trained to use correctly the spacer Aerochamber Plus™. The criterion on spacer applies only to patients who are using a spacer for the administration of their COPD medications at screening.
11. A cooperative attitude and ability to be trained to use correctly electronic devices with COPD questionnaire.

4.3 Exclusion Criteria

The presence of any of the following will exclude a patient from study enrolment:

1. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are willing to use one or more of the following reliable methods of contraception:
 - a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
 - b. Hormonal contraception (implantable, patch, oral)
 - c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical vaults/caps) with spermicidal foam/gel/film/cream/suppository.
 - d. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

Reliable contraception should be maintained throughout the study until the last study visit. "True abstinence" is acceptable only if it is in line with the preferred and usual lifestyle of the patient.

Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at screening and end of treatment, urine pregnancy test will be performed at all clinic visits except Visit 7.

Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea") or women permanently sterilized (e.g. tubal occlusion, hysterectomy or bilateral salpingectomy) can be enrolled in the study.

2. Diagnosis of asthma or history of allergic rhinitis or atopy (atopy which may raise contraindications or impact the efficacy of the study drug according to investigator's judgement).
3. Patients requiring use of the following medications:
 - a. Systemic steroids for COPD exacerbation in the 4 weeks prior to screening
 - b. A course of antibiotics for COPD exacerbation longer than 7 days in the 4 weeks prior to screening
 - c. PDE 4 inhibitors in the 4 weeks prior to screening
 - d. Use of antibiotics for a lower respiratory tract infection (e.g pneumonia) in the 4 weeks prior to screening.
4. COPD exacerbation requiring prescriptions of systemic corticosteroids and/or antibiotics or hospitalization during the run-in period.
5. Patients treated with non-cardioselective β -blockers in the month preceding the screening visit or during the run-in period.
6. Patients treated with long-acting antihistamines unless taken at stable regimen at least 2 months prior to screening and to be maintained constant during the study or if taken as PRN.
7. Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia.
8. Known respiratory disorders other than COPD which may impact the efficacy of the study drug according to investigator's judgement. This can include but is not limited to α -1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease.
9. Patients who have clinically significant cardiovascular condition (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV, left ventricular failure, acute myocardial infarction).
10. Patients with atrial fibrillation (AF):
 - a. **Persistent:** AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC) within 6 months from screening.

- b. **Long standing Persistent** as defined by continuous atrial fibrillation diagnosed for less than 6 months and or without a rhythm control strategy.
 - c. **Permanent:** for at least 6 months with a resting ventricular rate ≥ 100 /min controlled with a rate control strategy (i.e., selective β -blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy).
11. An abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to investigator's judgement.
Patients whose electrocardiogram (ECG) (12 lead) shows QTcF >450 ms for males or QTcF >470 ms for females at screening or at randomisation visits are not eligible.
12. Medical diagnosis of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that in the opinion of the investigator would prevent use of anticholinergic agents.
13. History of hypersensitivity to M3 Antagonists, β_2 -agonist, corticosteroids or any of the excipients contained in any of the formulations used in the trial which may raise contraindications or impact the efficacy of the study drug according to the investigator's judgement.
14. Clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease which may impact the efficacy or the safety of the study drug according to investigator's judgement.
15. Patients with serum potassium levels < 3.5 mEq/L (or 3.5 mmol/L).
16. Unstable concurrent disease: e.g. uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; significant hepatic impairment; significant renal impairment; uncontrolled gastrointestinal disease (e.g. active peptic ulcer); uncontrolled neurological disease; uncontrolled haematological disease; uncontrolled autoimmune disorders, or other which may impact the efficacy or the safety of the study drug according to investigator's judgement.
17. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening visit.
18. Participation in another clinical trial where investigational drug was received less than 8 weeks prior to screening visit.

4.4 Patient Withdrawals

Patients may be discontinued from the study for any of the following reasons:

- An adverse event occurs that, in the opinion of the investigator, makes it unsafe for the patient to continue in the study. In this case, the appropriate measures will be taken.
- The patient is lost to follow-up.
- The patient withdraws consent.
- The patient's safety is affected by violation of inclusion or exclusion criteria or use of non-permitted concomitant medication.
- The patient is unwilling or unable to adhere to the study requirements, i.e. non-compliance.
- The sponsor or the regulatory authorities or the Ethics Committee(s), for any reason, terminates the entire study, or terminates the study for this trial site or this particular patient.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawals of patients should be avoided. Violations detected during the course of the study do not necessarily constitute reasons for discontinuation. Based on a common agreement between the Investigator and the Sponsor, the patient may continue his/her study participation if the detected violations do not affect either the protocol population targeted not the safety of the patient.

Furthermore, a **COPD exacerbation is not a reason to withdraw the patient from the study**, unless the Investigator deems it necessary.

However, should a patient discontinue the study, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation, including questionnaires, at the time of the withdrawal will be performed with an explanation of the exact reason why the patient is withdrawing from the study.

The Investigator is responsible for the optimal individual treatment for the patient.

In case of withdrawal, the Investigator must fill in the “Study Termination Visit” in the eCRF, reporting the main reason for withdrawal.

If a patient is withdrawn/dropped-out of the study after receiving the test treatment, the patient study number and corresponding test treatments should not be reassigned to another patient.

In order to collect as complete as possible information in the clinical study database, all ADRs and SAEs ongoing at the time the subject’s study participation ends should be evaluated up to 14 days after last study drug intake. After this period, all unresolved ADRs and SAEs will be reported as “ongoing” in the eCRF.

For pharmacovigilance purposes, it must be emphasised that after a patient withdraws from a trial, the Investigator is still responsible for reporting Serious Adverse Events he/she considers causally-related to the study drug.

5. CONCOMITANT MEDICATIONS

5.1 Permitted concomitant Medications

1. Inhaled salbutamol administered as rescue medication. A minimum period of 6 hours should elapse between the use of rescue salbutamol and the spirometric measurements.
2. Long-acting antihistamines if taken at stable regimen at least 2 months prior to screening or if taken PRN. For patients not under stable long-acting antihistamines, short courses are allowed during the study period (≤ 7 days). Other antihistamines are allowed during the study period for short course (≤ 10 days) or if taken PRN.
3. **In case of COPD exacerbation**, short courses of the following therapies are allowed during the treatment period:
 - a) Systemic corticosteroid (oral/IV/IM).
 - b) Inhaled short acting β_2 -agonists and/or short acting muscarinic antagonists or combination of both.
 - c) Nebulised β_2 -agonists, anticholinergics and/or steroids.
 - d) Antibiotics.
 - e) Oxygen.
 - f) Mechanical ventilation at the investigator’s discretion.
4. Short courses (≤ 10 days) of nasal corticosteroids (maximum 4 courses) are allowed during the treatment period.

5. In case of a concomitant disease any appropriate treatment not interfering with the study evaluation parameters will be allowed.

5.2 Non-permitted concomitant Medications

1. Depot corticosteroids.
2. Oral/IV/IM corticosteroids (short courses allowed in case of COPD exacerbation during the treatment period).
3. Nebulised β_2 -agonists, anticholinergics and/or steroids (short courses allowed in case of COPD exacerbation during the treatment period).
4. Inhaled corticosteroids (pMDI and DPI).
5. Inhaled long-acting β_2 -agonists or fixed combination of corticosteroids and long-acting β_2 -agonists other than study treatments (e.g. salmeterol plus fluticasone or formoterol plus budesonide).
6. Inhaled long-acting muscarinic antagonists.
7. Inhaled short acting β_2 -agonists (other than salbutamol) (Short course are allowed in case of COPD exacerbation during the treatment period).
8. Inhaled fixed combinations of a short-acting β_2 -agonist and a short-acting muscarinic antagonist (short course allowed in case of COPD exacerbation during the treatment period).
9. Inhaled short-acting muscarinic antagonists (ipratropium and oxytropium) (Short course allowed in case of COPD exacerbation during the treatment period).
10. Non-cardioselective β -blockers.
11. Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), Selective Serotonin Re-uptake Inhibitors (SSRIs) and other drugs known to prolong the QTc interval unless already taken at the time of the screening visit.
12. PDE 4 inhibitors (eg roflumilast).
13. Oral xanthine derivatives (e.g. theophylline) 7 days prior to screening visit or during the study period.
14. Leukotriene modifiers.
15. Non- potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug).

Prior to screening spirometry the following wash out periods for concomitant medications must be respected:

▪ Inhaled and/or nebulised short-acting β_2 -agonists:	6 hours
▪ Inhaled and/or nebulised short acting muscarinic antagonists:	12 hours
▪ Inhaled SABA/SAMA fixed combinations:	12 hours
▪ Inhaled long acting muscarinic antagonist:	72 hours
▪ Inhaled long-acting β_2 -agonists:	12 hours
▪ Inhaled “ultra” long-acting β_2 -agonists (indacaterol):	72 hours
▪ Inhaled and/or nebulised corticosteroids:	12 hours
▪ Inhaled ICS/LABA fixed combinations:	12 hours
▪ Leukotriene modifiers:	72 hours
▪ Oral xanthine derivatives	7 days

Prior to each other spirometry the following wash out periods for concomitant medications must be respected:

- Inhaled and/or nebulised short-acting β_2 -agonists: 6 hours
- Inhaled and/or nebulised short acting muscarinic antagonists: 12 hours
- Inhaled SABA/SAMA fixed combinations: 12 hours
- Nebulised corticosteroids: 12 hours

6. TREATMENT(S)

The study medication will be supplied to the clinical site under the responsibility of the Sponsor, who will also provide the Pharmacist/Investigator with appropriate certificates of analytical conformity.

6.1 Appearance and Content

- **CHF 5993 pMDI 100/6/12.5 μg - Test product**

Active ingredient: Beclometasone dipropionate/Formoterol fumarate/Glycopyrrolate bromide
100/6/12.5 μg per metered dose

Excipient: HFA-134a propellant, ethanol anhydrous, hydrochloric acid

Presentation: Each canister contains 120 doses

- **CHF 1535 pMDI 100/6 μg - Reference product**

Active ingredient: Beclometasone dipropionate/Formoterol fumarate
100/6 μg per metered dose

Excipient: HFA-134a propellant, ethanol anhydrous, hydrochloric acid

Presentation: Each canister contains 120 doses

- **Placebo CHF 5993 pMDI Placebo - used only for training**

Excipient: HFA-134a propellant, ethanol anhydrous

Presentation: Each canister contains 120 puffs

Salbutamol, to be used as rescue medication, will be purchased locally and provided by Investigator site to patients. Patients will take the usual rescue (salbutamol) on an as-needed basis.

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

The selection of the dose for CHF 5993 HFA pMDI (100/6/12.5 μg per inhalation) is based on the results of previous studies performed in Chiesi with Glycopyrrolate pMDI (dose ranging study) with or without CHF 1535 100/6 μg in patients with COPD.

6.2.2 Dosage

6.2.2.1 Run-in period:

- **CHF 1535 pMDI (Foster[®]) 100/6 μg**

- 2 inhalations b.i.d. (Total daily dose : BDP 400 μg /FF 24 μg)

6.2.2.2 Randomised Treatment period:

- **Treatment A: CHF 5993 pMDI 100/6/12.5 μg**

- 2 inhalations b.i.d. (Total daily dose: BDP 400 μg /FF 24 μg /GB 50 μg)

- **Treatment B: CHF 1535 pMDI 100/6 µg**
 - 2 inhalations b.i.d. (Total daily dose: BDP 400µg/FF 24µg)

6.2.3 Administration

6.2.3.1 Run-in period (from Visit 1 to 2):

At Visit 1 (screening), each eligible patient will receive 1 box with 1 canister of CHF 1535 pMDI (to be used in the morning and in the evening) as run-in medication, in replacement of their current therapy.

CHF 1535 pMDI (Foster®) will be administered twice a day: 2 puffs in the morning (before 10:00 am) and 2 puffs in the evening (before 10:00 pm).

6.2.3.2 Randomised Treatment period (from Visit 2 to 7):

During the randomised treatment period, each patient will receive 4 treatments kits in total, each one covering maximum a 14-week period:

- The first kit will be dispensed at Week 0 (Visit 2): the confirmed eligible patients will be randomised and will receive treatment A (CHF 5993 pMDI) or treatment B (CHF 1535 pMDI).
- The others 3 kits (treatment A or B, according to the randomisation) will be dispensed respectively at Week 12 (Visit 4), Week 26 (Visit 5) and Week 40 (Visit 6).

Each treatments kit will consist of 1 box containing 4 inhalers (4 CHF 5993 pMDI or 4 CHF 1535 pMDI): 2 inhalers (numbered 1 and 2 and with sun pictograms) to be used in the morning and 2 inhalers (numbered 1 and 2 and with moon pictograms) to be used in the evening.

The study drug will be administered twice a day in the morning (before 10.00 am) and in the evening (before 10.00 pm):

- **Morning administration:**
 - ➔ One inhalation from the morning inhaler SUN 1
 - ➔ One inhalation from the morning inhaler SUN 2
- **Evening administration:**
 - ➔ One inhalation from the evening inhaler MOON 1
 - ➔ One inhalation from the evening inhaler MOON 2

To the extent possible, the time of dosing must remain constant for each patient for the whole duration of the study.

Per day, 4 inhalations will be performed (2 in the morning from the 2 morning inhalers and 2 in the evening from the 2 evening inhalers). After each inhalation, the patient must hold his/her breath for as long as possible.

For more details regarding the instructions for use of Study Treatments, please refer to [Appendix II](#). Of note, the **first administration of study treatments will take place at the clinics/hospital at every visit.**

Administration via a spacer (AeroChamber Plus™ Flow-Vu antistatic) in a subset of patients

In case patients are used to inhale their pMDI COPD medications using a spacer device, they shall continue using a spacer for both run-in and treatment medications' inhalations. The spacer device to be used in the study, the **AeroChamber Plus™ Flow-Vu antistatic Valved Holding Chamber**

(referred as AeroChamber Plus™ in the rest of the document), will be assigned to the patient by the Investigator (1 spacer will be distributed with the study medication at visit V1, V4, V5 and V6).

For these patients, **each inhalation** (for the run-in and randomisation periods) **must be performed via AeroChamber Plus™ Flow-Vu antistatic VHC. For each puff, the patient must inhale slowly and deeply and** hold his breath as long as possible. For more details concerning the use of the pMDI with spacer, please refer to the [Appendix III](#).

6.2.3.3 Use of pressurized Metered Dose Inhaler

- **Priming of the inhalers**

All the inhalers must be primed before first use or if they have not been used for 14 days or more. The priming must be carried out according to the instructions ([Appendix II](#)).

- **Cleaning of the inhalers**

All the inhalers (CHF 5993 pMDI or CHF 1535 pMDI) must be cleaned regularly (once a week) by the patient, wiping the outside and inside of the mouthpiece with a dry cloth, according to the instructions provided ([Appendix II](#)).

6.2.3.4 Use of a spacer (for patients who need it)

The inhalation of study drugs via the spacer must be done according to the AeroChamber Plus™ commercial leaflet (see [Appendix III](#)).

The spacer **device** can be used right out-of package and then **it must be washed weekly (at home)**, according to cleaning instructions of [Appendix III](#).

6.2.4 Patient Training

During the screening visit, each patient will receive a training kit containing placebo pMDI and will be instructed by the Investigator on how to use the pressurised Meter Dose Inhalers (pMDIs), on the method of inhalation and duration of breath holding after inhalation, according to the instructions for use ([Appendix II](#)). The proper use of the inhalers will be checked again at randomization visit.

One training kit will be used per patient. This training kit will be kept at the site by the Investigator (it will not be dispensed to the patients).

If the patient is used to take COPD pMDI medications via a spacer, he/she will be trained to use Aerochamber Plus™.

6.3 Packaging

All investigational products will be prepared in accordance with Good Manufacturing Practices (GMP) as required by the current Good Clinical Practices (GCP).

Chiesi will supply the study drugs for the run-in period and the randomised treatment period.

6.3.1 Training kit

- Primary packaging: Canister of CHF 5993 Placebo plus actuator
- Secondary packaging: One box containing 1 canister plus actuator

6.3.2 Run-in kit

- Primary packaging: Canister of CHF 1535 100/6 µg plus actuator
- Secondary packaging: One box containing 1 canister plus actuator

6.3.3 Study treatment kits

The study treatment will be packed in kits which cover maximum a 14-week period. Each kit will consist in one box containing 4 canisters.

Two of the four inhalers will be numbered 1 and 2 and labelled with a “sun” pictogram identifying therefore the ones to be used for the morning administration (one puff from each canister).

The remaining two inhalers will be numbered 1 and 2 and labelled with a “moon” pictogram identifying the ones to be used for the evening administration (one puff from each canister).

- Primary packaging: Canister of CHF 5993 100/6/12.5 µg plus actuator
or
Canister of CHF 1535 pMDI 100/6 µg plus actuator
- Secondary packaging: One box containing 4 canisters plus actuators

6.3.4 AeroChamber Plus™ Spacer

- Primary packaging: Spacer AeroChamber Plus™ Flow-Vu antistatic VHC
- Secondary packaging: One box containing 1 spacer AeroChamber Plus™ Flow-Vu antistatic VHC

6.4 Labeling

All the supplies will be labelled according to Annex 13 of EU GMP and according to local law and regulatory requirements.

Labels on canisters will be in English only, as canisters are too small to put the information in multilingual booklet labels which could not allow the right movement of the canister inside the actuator during administration. Labels on the other containers (actuator and box) will be booklet labels with all local languages. Labels on training kits will be in English only, as they will not be dispensed to the patients.

The labels applied on boxes of training, run-in and study treatment kits, as well as on spacer boxes, will have a tear-off part which will be removed and attached to the specific tracking form at the time the box is assigned to the patient.

The labels will contain at least the information below for the study treatments, the run-in medication and the training kits:

Primary packaging (canister plus actuator):

- Study code
- Kit number (*not for training kits*)
- Pharmaceutical dosage form, quantity of dosage units
- Route of administration
- Batch or code number
- Expiry date
- Instructions for use
- Storage conditions
- For clinical trial use only
- Keep out of reach of children
- Sponsor

Secondary packaging (box):

- Study code

- Kit number (*not for training kits*)
- Patient number (*to be filled by the Investigator upon dispensation to the patient*)
- Pharmaceutical dosage form, quantity of dosage units
- Route of administration
- Batch or code number
- Expiry date
- Instructions for use
- Storage conditions
- For clinical trial use only
- Keep out of reach of children
- Sponsor

6.5 Treatment allocation

A balanced block randomisation scheme stratified by Country and severity of airflow limitation (post-bronchodilator FEV₁ at screening < or ≥ 30% of predicted normal value) will be prepared via a computerised system. At least 20% of patients with very severe airflow limitation (post-bronchodilator FEV₁ at screening < 30% of predicted normal value) will be randomised in the study.

Patients will be centrally assigned, in each centre, to one of the two treatment arms at the end of the run-in period through an IRT system (Interactive Response Technology, combination of voice and web response system and also referred as IVRS/IWRS).

The IRT will allocate the patient to a certain treatment group using a list-based randomisation algorithm and assign the study medication kit number corresponding to the treatment group assigned to the patient. The IRT will also generate a confirmation after every IRT transaction is performed.

The Investigator will call the IRT at each visit (from pre-screening to end of treatment) to record the patient number at pre-screening, to enrol and randomise the patient, to obtain the medication kit numbers and to register the patient status in the system. Detailed instructions for use of IRT will be provided to the site.

Note: The patient will be identified by a patient number of nine digits: the 6 first digits correspond to centre number (first 3 for country and 3 last progressive for the site) and the 3 last digits to the screening number (chronological in each site).

6.6 Treatment Code

The medication list will be provided to the labeling facility but will not be available to patients, Investigators, monitors or employees of the centre involved in the management of the trial before unblinding of the data, unless in case of emergency.

The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomization list nor to the medication list.

In case of emergency, unblinding of the treatment code will be done through IRT. The treatment group will be disclosed and confirmation will follow (by fax and/or notification email). The IRT will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the Investigators. The Investigator will be provided with usernames and passwords for randomization purposes and to unblind the study treatment in case of emergency situation, where he/she considers essential to know what treatment the patient was taking. The IRT will promptly notify the Sponsor and the Clinical Monitor whenever a treatment code is unblinded.

Users from Chiesi Corporate Pharmacovigilance will have their own passwords to unblind patients in case of SUSARs to be reported to the competent Regulatory Authorities and Ethic Committees/IRB.

The patient will be provided with a card with the phone numbers of Hospital site and Investigator to be called in case of emergency ([Appendix IV](#)).

6.7 Treatment compliance

Compliance will be evaluated on the basis of the information recorded daily by the patient on the digital platform as well as the information recorded in the eCRF during the treatment visits.

The evaluation of compliance will be done using the following formula:

$$\frac{\text{TOTAL NUMBER OF ADMINISTERED DOSES}}{\text{TOTAL NUMBER OF SCHEDULED DOSES}} \times 100 = \% \text{ OF ADMINISTERED DRUG}$$

The total number of scheduled doses will be calculated on the basis of the extent (days) of exposure of each patient. A range 65-135 % will be taken into account for a satisfactory level of compliance.

6.8 Drug Storage

The Pharmacist/Investigator will be responsible for the safe storage of all medications assigned to this study, in a secure place with restricted access, and maintained within the appropriate ranges of temperature.

The run-in and the study treatment kits must be stored between 2°C and 8°C by the Investigator/Pharmacist at site, protected from heat, frost and direct sunlight.

At the clinic visit, the kit to be dispensed must be removed from the refrigerator and the canister(s) should be taken out of the mouthpiece(s) (actuators) and warmed with the hands for a few minutes before administration to the patient. The canister(s) should never be warmed by artificial means.

The patient should never inhale cold medication.

Once delivered to patients:

Run-In kits and Treatment kits must be stored at temperature below 25°C by the patient at home, not in the refrigerator but protected from heat, frost and direct sunlight.

At this temperature condition the actual use-by-date of the Treatment kits and the run-in kits will be four months (**120 days**) from the date of removal from refrigerator.

Therefore, the Pharmacist/Investigator at the Hospital must write the **use-by-date on the kit labels** once the kits are removed from the refrigerator, before assigning to the patients. The **use-by-date corresponds to the dispensed date plus 4 months (120 days)**.

Also **the training kits** must be stored between 2°C and 8°C by the Investigator/Pharmacist at site. Once removed from the refrigerator, the kits must be stored below 25°C and **kept at the clinic**. They will be used at screening visit and once again at randomisation visit. At this temperature condition the actual use-by-date of the training kits will be 4 months (120 days) from the date of removal from refrigerator.

A temperature recording must be performed on site once daily for storage of kits. The site must check the Min/Max temperatures once daily for adequate storage of refrigerated and ambient kits. The Min/Max temperatures must be recorded in a dedicated temperature tracking form. Any deviation to the requirement for storage will be promptly reported and Sponsor shall assess if the affected study medications can still be used.

6.9 Drug Accountability

The Investigator, or the designated/authorized representative, is responsible for the management of all the study medications to be used for the study. Study medications that should be stored in a locked, secure storage facility with access limited to those individuals authorized to dispense the study medications.

An inventory will be maintained by the Investigator or pharmacist (or other designated individual), to include a signed account of all the study medication(s) received, dispensed and returned by each patient during the trial.

At the conclusion or termination of the study, the Investigator or the pharmacist shall conduct and document a final drug supply (used and unused) inventory. An explanation will be given for any discrepancies.

All the study medications supplied, used or unused, will be returned to the designated distribution centre under Sponsor's responsibility. Return and destruction will not occur until authorized by Chiesi.

6.10 Provision of additional care

At completion of patient's study participation, it is under the Investigator's responsibility to prescribe the most appropriate treatment for the patient or to restore the initial therapy or to refer to the General Practitioner.

7. STUDY PLAN

7.1 Study Schedule

The study plan includes a total of 8 clinic visits (Visit 0 to Visit 7), and will be conducted as follows:

- A **pre-screening visit (Visit 0)** to explain the aim of the study to the patients, to obtain their written informed consent and to prepare patients for the screening visit (V1);
- A **screening visit (Visit 1, no more than 7 days after V0, week -2)**, to verify the patients' eligibility for inclusion in the study (including routine haematology and blood chemistry, medical history, physical examination, a 12-lead ECG, spirometric parameters after salbutamol, vital signs and training for the use of inhalers). This visit will be followed by a 2-week open-label run-in period, where the patients will receive CHF 1535 pMDI (Foster®) at the daily dose of 400/24 µg;
- A **randomisation visit (Visit 2, Week 0)** when patients will be randomised to one of the two treatment arms. This visit will be followed by a 52-week treatment period with the assigned drugs.
- Five **subsequent visits** scheduled during the treatment period after 4 (**Visit 3**), 12 (**Visit 4**), 26 (**Visit 5**), 40 (**Visit 6**) and 52 (**Visit 7**) weeks of treatment.
- Pre-dose and post-dose spirometry (pre-bronchodilator and post-bronchodilator at Visit 1), 12-lead ECG, vital signs, dyspnea assessments will be performed at all visits.
- Rescue medication use, compliance with the treatment and EXACT-PRO questionnaire will be recorded daily (via an electronic diary) during the run-in and randomised treatment periods, using a digital platform.

A subset of patients (10% of the randomised patients) will undergo a **24h Holter recording** evaluation.

The study plan and scheduled tests are summarised in the following flow-chart:

3. Triplicate pre-dose ECG
4. 24h Holter recordings performed in a subset of 10 % of the randomised patients.
5. Within 30 min after 4x100 µg salbutamol. It can be repeated once before Visit 2 if the inclusion criterion no. 4 is not met at V1.
6. Including FEV₁, FVC. Please to verify that wash-out of rescue medication (at least 6h) or run-in/study medication have been respected in the morning of the visit for the pre-dose measurements.
7. Training to the use of Aerochamber Plus™ spacer performed only for patients used to take COPD pMDI medications via a spacer.
8. BDI (Baseline Dyspnea Index) only.
9. TDI (Transition Dyspnea Index) only.
10. For females of childbearing potential only.
11. Aerochamber Plus™ dispensed only to patients used to take COPD pMDI medications via a spacer.

7.1.1 Visit 0 (Pre-screening visit)

A pre-screening visit will be carried out in order to fully explain the study to potential eligible patient. The following procedures will take place:

- The written informed consent signed by the patient will be collected after the study has been fully explained by the investigator. The investigator or his/her designee should provide them ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial.
- Demographic data will be collected.
- Instructions will be given to the patient for the next screening visit (V1) such as **concomitant medications to be withdrawn** prior to the visit.
- As soon as the informed consent is signed, the investigator (or his/her designee) will connect to IRT to allocate a 9 digits unique patient's number (3 digits identifying the country, 3 digits identifying the site, last 3 digits identifying the screening number sequentially assigned in each site).

Before discharge,

- A **patient card** with the Investigator's contact details will be handed out to the patient.
- An **appointment** for the screening visit (V1) will be taken in the morning before 9:00 am, **within 1 week**. The appointment day may vary depending on the wash-out patient shall respect for the screening visit. Patients will be instructed:
 - ➔ To fast overnight (at least 10 hours) for the next visit in order to perform blood sampling (only water is allowed);
 - ➔ Not to take salbutamol or other SABA used as rescue in the 6 hours preceding the next visit, unless absolutely necessary.
 - ➔ Not to take his/her usual medication for COPD (LABA, ICS, LAMA, SAMA ...) in accordance with [section 5.2](#).

7.1.2 Visit 1 (Screening visit /Week -2)

A screening visit will be carried out in the morning (before 9:00 am) in order to identify eligible consenting patients for the study.

If any of the wash-outs for COPD medications have not been respected, the visit needs to be re-scheduled within 3 days. This is allowed only once. If any of the relevant wash-outs is not respected again before the rescheduled visit, the patient will be discontinued and recorded in the IRT and eCRF as screen failure.

The following procedures will take place:

- **For the subset of patients performing 24h-Holter evaluation:** The Holter electrodes will be placed. Electrodes will be twin electrodes in order to be used to record the further

planned procedure of 12-lead ECG (pre salbutamol). Patients will have an ambulatory 24-hour digital ECG Holter device and the recording start should remain the same for all the study visits (for V1, 60 minutes prior to salbutamol administration, the total registration will be at least 25 hours) (See [section 7.2.6](#)).

These patients will also be requested to visit the site the **next morning** in order to stop the 24-hour digital ECG Holter device.

- A medical history and smoking status will be recorded. Previous medications in the past 3 months must be collected.
- Concomitant medications being taken by the patient will be recorded. Intake of non-permitted medication constitutes a non-eligibility criterion for enrolment in the study.
- A full physical examination will be performed.
- A urine pregnancy test in women with childbearing potential will be performed.
- Weight and height will be recorded.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before salbutamol administration, after 10 minutes of rest, in resting position (see [section 7.2.4](#)).
- A 12-lead ECG will be performed before salbutamol administration, after 10 minutes of rest (see [section 7.2.5](#)). A patient will not be eligible in case of QTcF >450 ms for males or QTcF >470 ms for females, or in case of abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to investigator's judgement.
- A blood sample will be collected before salbutamol administration, after an overnight fasting (at least 10h), for the assessments of (see [section 7.2.3](#)):
 - standard haematology and blood chemistry;
 - a serum β -HCG test will be performed in women of childbearing potential.

The blood samples must be collected **after vital signs and 12-lead ECG recording**.

In case of non-interpretable data, another determination must be performed as soon as possible and prior to Visit 2 (randomisation visit).

- Pre-bronchodilator spirometry will be carried out: the patients will have to perform a FVC manoeuvre to assess parameters (FEV₁, FVC) (see [section 7.2.1](#)).
- A FEV₁ and FVC test within 30 minutes after intake of 4 puffs (4 x 100 μ g) of salbutamol pMDI will be performed. To be eligible, post-salbutamol FEV₁ must be < 50% of the patient's predicted normal value **and** post-salbutamol FEV₁/FVC < 0.7.

If the criteria are not met, this test can be performed **once more before Visit 2** after an appropriate wash-out from bronchodilators.
- The CAT will be completed to evaluate if the patient is symptomatic (see [section 7.2.8](#)). Symptomatic patients at screening with a CAT score ≥ 10 are eligible.
- The BDI questionnaire will be completed and BDI focal score will be assessed. Only symptomatic patient with a BDI focal score ≤ 10 are eligible (see [section 7.2.7](#)).
- The exacerbation assessment will be done. A documented history of at least one exacerbation in the 12 months preceding screening shall be checked (according to Inclusion Criterion 5). Eligible patients shall remain free of exacerbation requiring systemic steroids for 4 weeks prior to screening. If a COPD exacerbation within 4 weeks prior to screening is treated by course of antibiotics no longer than 7 days or with other allowed medications, patient is eligible.
- Any AE occurred since the signature of the informed consent will be checked and recorded. In case of any clinically significant abnormality revealed during the physical examination or screening procedures, it will be recorded in the patient's medical history, unless its start date

is after the informed consent signature date. In this case, it will be recorded as an adverse event.

- If patient is eligible for entry into the run-in, inclusion criteria 9, 10 and 11 can then be checked. He/she will be trained, with training kits containing placebo, to the proper use of pMDI (see [section 6.2.4](#) and [appendix II](#)). The corresponding tear-off label will be stuck in the patient specific dispensation tracking form. For the patient using a spacer, patient will be trained to the proper use of pMDI device via the AeroChamber Plus™ as per instructions for use ([Appendix III](#)). The corresponding tear-off label will be stuck in the patient specific dispensation tracking form.
- Patient will be instructed on how to daily record the medications intake (run-in and rescue) as well as the COPD symptoms (EXACT-PRO questionnaire) in the electronic Diary and on how to transmit the data daily on the digital platform (see [section 7.2.9](#)).
- The investigator will access IRT also in order to obtain the run-in medication (CHF 1535 pMDI) to be dispensed to the patient together with instructions for use. Patient will be instructed to inhale 2 puffs of run-in medication in the morning (before 10:00 am) and 2 puffs in the evening (before 10:00 pm). **The first administration of run-in medication will take place at the clinic visit (before 10:00 am) under medical supervision.** If the patient is using a spacer, medication will be taken via the Aerochamber Plus™ used for the training of the patient. In this case, all the medications for all the study will be taken via the spacer.
- If the patient is not eligible, the investigator will access the IRT to record the status of the patient as screen failure.
- Patient will be instructed to stop the non-permitted COPD medications in accordance with [section 5.2](#).
- Rescue salbutamol, for as needed use, will be dispensed by the Investigator. Patients will keep this rescue salbutamol throughout the study period (will be replaced if needed); nevertheless patient will be instructed to bring this medication at each visit in order to check the need for replacement.

Before discharge

- **Medication for the run-in period** will be dispensed and the corresponding tear-off label will be stuck in the patient specific dispensation tracking form and the kit number will be recorded in the corresponding electronic CRF (e-CRF). The use-by-date must be filled-in on the label. The patients will be instructed to inhale 2 puffs in the morning and 2 puffs in the evening of the canister of run-in kit **with the exception of the next visit's morning**. Patient will be also instructed to take salbutamol as rescue if necessary.
If the patient should use a spacer, an Aerochamber Plus™ will be given to the patient with the medication and the patient will be instructed to use it for each inhalation.
- **An electronic diary will be dispensed.** Patient must complete and transmit the daily electronic Diary until visit 2. It is important to ensure a good compliance of the patient to the use of the electronic diary during the run-in period in order to set up the EXACT-PRO baseline score.
- **An appointment for Visit 2** will be made in 2 week (± 2 days) time from Visit 1, in the morning (at approximately the same time of the day) before 9:00 am. Patients will be instructed:
 - ➔ **Not to take salbutamol in the 6 hours preceding the next visit**, unless absolutely necessary.
 - ➔ **Not to take run-in medication in the morning of the next visit.**

- To **bring back the run-in and rescue medications** (in their boxes), the **electronic Diary** and the spacer if the patient take drugs via the Aerochamber Plus™, at the next visit.
- **For the subset of patients performing 24h-Holter evaluation:** The Holter must be recorded before any randomisation treatment intake. Therefore, Holter patients will be **invited to the clinic the day before planned visit 2 between 7:00 and 8:00** in order to place the electrodes and start the Holter recorder at least 1 hour before the run-in drug intake. Electrodes will be twin electrodes in order to be used to record the further planned procedure of 12-lead ECG. Patients will have an ambulatory 24-hour digital ECG Holter device and the recording start should remain the same for all the study visits. (See [section 7.2.6](#)) The total registration will be **at least 25 hours**.

7.1.3 Visit 2 (Randomisation/ Start of Treatment Period /Week 0)

The visit 2 will start in the morning (before 9:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected, or run-in medication (CHF 1535 pMDI) has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. Only one re-schedule is allowed. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or run-in medication intake occurs again in the morning of the re-scheduled visit, the patient will be discontinued and recorded as screen failure in the IRT and eCRF.

The following procedures will be performed:

- **For the subset of patients performing 24h-Holter evaluation:** the Holter recorder will be stopped: the total registration will be at least **25 hours**.
- Medication for the run-in period will be collected, as well as the AeroChamber Plus™ spacer if previously provided;
- The investigator will check in the electronic diary portal whether patient has been transmitting the EXACT-PRO and run-in medication/rescue intake daily since screening. **In case of lack of compliance, instructions on how to use the electronic diary will be given again to the patient** (see [section 7.2.9](#)).
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the patient will be withdrawn from the study and recorded as screen failure in the IRT. (see [section 5.2](#)).
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The occurrence of COPD exacerbations will be evaluated (see [section 7.2.10](#)) and data recorded in the eCRF. In case of exacerbation during the run-in, the patient will not be randomised (see also [sections 5](#)) and recorded as screen failure in the IRT.
- The occurrence of other adverse events will be checked and recorded if any.
- A urine pregnancy test in women with childbearing potential will be performed.
- A full physical examination will be performed.
- Weight will be recorded.
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.4](#)).

- The BDI questionnaire will be filled in by the patient and BDI focal score will be assessed. Only symptomatic patient with a BDI focal score ≤ 10 will be randomised (see [section 7.2.7](#)).
- Three pre-dose 12-lead ECG (baseline ECG to be done in triplicate at randomisation visit) will be performed after 10 minutes of rest (see [section 7.2.5](#)). A patient will not be randomised in case of average QTcF >450 ms for males or average QTcF >470 ms for females, or in case of abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to investigator's judgement.
- The proper use of pressurized metered dose inhaler will be checked and patient will be retrained to the usage of the pMDI using the Training kit previously assigned at V1 (see [section 6.2.4](#)).
- If the patient is used to take COPD pMDI medications via a spacer, he/she will be re-trained using the Aerochamber PlusTM provided at Visit 1 and used for the run-in.
- Eligibility criteria will be reviewed.

For eligible patients:

- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.12](#)).
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see [section 7.2.11](#)).
- Investigator will collect Health economic information as per [section 7.2.13](#).
- A FVC pre-dose spirometry measurement will be then performed to assess FEV₁ and FVC prior to patient randomisation. This measurement will constitute the baseline value (see [section 7.2.1](#)).
- The patient will be randomised and the treatment will be allocated according to the central randomisation system. Investigator will access IRT in order to obtain the appropriate kit number for the first 12-week treatment period.
- **The first administration of the study drug will take place at the clinic visit (before 10:00 am) under supervision of the Investigator.** The corresponding tear-off labels will be stuck in the dispensation tracking form and the kit number will be recorded in the corresponding electronic CRF (e-CRF). The use-by-date must be filled-in on the labels. Drug administration will be done according to [section 6.2.3](#). For the patient who needs using a spacer, medication will be taken via the Aerochamber PlusTM given to the patient at Visit 1.
- Vital signs (SBP and DBP) will be measured 10 minutes post-dose, after 10 minutes of rest (see [section 7.2.4](#)).
- A 10 minutes post-dose 12-lead ECG (including the evaluation of HR and QTcF) will be performed after 10 minutes of rest (see [section 7.2.5](#)).
- Spirometry will be performed 2h post-dose: the patients will have to perform a FVC manoeuvre in order to measure FEV₁ and FVC. For each time point, spirometry consists in three acceptable manoeuvres (see [sections 7.2.1](#)).

Before discharge

- **Study medication** will be dispensed to the patient together with instructions for use. Drug administration will be done according to [section 6.2.3](#). Patient will be instructed to take salbutamol as rescue if necessary. For patient who is using a spacer, he/she will be reminded

to use the Aerochamber Plus™ for each inhalation. Investigator will dispense also salbutamol if needed.

- **The electronic diary (the same given at V1) will be given back to the patient.** Patient must continue to daily fill in the EXACT-PRO questionnaire, the medication and the rescue taken and to transmit daily the data in the digital platform until visit 3.
- **An appointment for Visit 3** will be made at 4 weeks (± 3 days) from Visit 2 (at approximately the same time as Visit 2, before 9:00 am). The patient will be instructed:
 - ➔ **To bring back the study medication** (in the box), the electronic Diary and the spacer if the patient take drugs via the Aerochamber Plus™ at the next visit.
 - ➔ To avoid taking salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
 - ➔ **Not to take the morning dose of the study medication before coming to the clinic visit** (it will be administered at the clinic visit).

7.1.4 Visit 3 (Week 4 of Treatment Period)

The visit 3 will start in the morning (before 9:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected or the study drug has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or study drug intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with wash-out not respected will be recorded in the CRF.

The following procedures will be performed:

- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the need for the patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest. If the patient is withdrawn, he/she will be recorded as discontinued in the IRT.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The investigator will check in the electronic diary portal whether patient has been transmitting the EXACT-PRO and study medication/rescue intake daily since randomisation. **In case of lack of compliance, instructions on how to use the electronic diary will be given again to the patient** (see [section 7.2.9](#)).
- The occurrence of COPD exacerbations and other adverse events will be evaluated and recorded in the eCRF (see [section 7.2.10](#)) (if any).
- A urine pregnancy test in women with childbearing potential will be performed.
- A full physical examination will be performed.
- Weight will be recorded.
- The TDI questionnaire will be filled in by the patient and TDI score will be assessed before the study treatment dose intake (see [section 7.2.7](#)).
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.12](#)).

- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see [section 7.2.11](#)).
- Investigator will collect Health economic information as per [section 7.2.13](#).
- Pre-dose (prior to study medication administration) and 10 minutes post-dose vital signs (SBP and DBP) will be measured after 10 minutes of rest (see [section 7.2.4](#)).
- Pre-dose (prior to study medication administration) and 10 minutes post-dose 12-lead ECG (including the evaluation of HR and QTcF) will be performed after 10 minutes of rest (see [section 7.2.5](#)).
- A pre-dose (prior to study medication administration) and 2 hours post-dose spirometry measurements will be carried out: the patients will have to perform a pre-dose FVC manoeuvre to measure FEV₁ and FVC parameters. 2h post-dose FVC manoeuvre will be also performed. For each time point, spirometry consists in three acceptable manoeuvres (see [sections 7.2.1](#)).
- **The morning dose of study medication will be administered at the clinic (before 10:00 am) under supervision of the Investigator from the kit dispensed at Visit 2.** For the patient who needs using a spacer, medication will be taken via the Aerochamber Plus™.
- The Investigator will access IRT just to register the status of the patient.

Before discharge

- **Study medication** (dispensed at V2) will be returned to the patient together with instructions for use. Patient will be instructed to take salbutamol as rescue if necessary. For administration of study medications, patient will be given with the same instructions as the ones given at V2. For patient who is using a spacer, he/she will be reminded to use the Aerochamber Plus™ for each inhalation. Salbutamol will be given to the patient if needed.
- **The electronic Diary (the same given at V1) will be dispensed.** Patient must continue to daily fill in the EXACT-PRO questionnaire, the medication and the rescue taken and to transmit daily the data until visit 4.
- **An appointment for Visit 4** will be made within 8 weeks from Visit 3 (at approximately the same time as other visits, before 9:00 am). **The time window should not exceed 12 weeks (±5 days) from Visit 2.**

The patient will be instructed:

- ➔ To **bring back** the **study medication** (in the box), the electronic Diary and the spacer if the patient take drugs via the Aerochamber Plus™, at the next visit.
- ➔ To avoid taking salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
- ➔ **Not to take the morning dose of the study medication before coming to the clinic visit** (it will be administered at the clinic visit).

7.1.5 Visit 4 (Week 12 of Treatment Period)

The visit 4 will start in the morning (before 9:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected or the study drug has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed

only once. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or study drug intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with wash-out not respected will be recorded in the CRF.

The following procedures will be performed:

- The study medication (in the box) provided at Visit 2 will be collected, as well as the AeroChamber Plus™ spacer previously provided. The Investigator will also check whether new rescue shall be provided to the patient.
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the need for the patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest. If the patient is withdrawn, he/she will be recorded as discontinued in the IRT.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The investigator will check in the electronic diary portal whether patient has been transmitting the EXACT-PRO and study medication/rescue intake daily since previous visit. **In case of lack of compliance, instructions on how to use the electronic Diary will be given again to the patient** (see [section 7.2.9](#)).
- The occurrence of COPD exacerbations and other adverse events will be evaluated and recorded in the eCRF (if any) (see [section 7.2.10](#)).
- A urine pregnancy test in women with childbearing potential will be performed.
- A full physical examination will be performed.
- Weight will be recorded.
- The TDI questionnaire will be filled in by the patient and TDI score will be assessed before the study treatment dose intake (see [section 7.2.7](#)).
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.12](#)).
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see [section 7.2.11](#)).
- Investigator will collect Health economic information as per [section 7.2.13](#).
- Pre-dose and 10 minutes post-dose vital signs (SBP and DBP) will be measured after 10 minutes of rest (see [section 7.2.4](#)).
- Pre-dose and 10 minutes post-dose 12-lead ECG (including the evaluation of HR and QTcF) will be performed after 10 minutes of rest (see [section 7.2.5](#)).
- A pre-dose (prior to study medication administration) and 2 hours post-dose spirometry measurements will be carried out: the patients will have to perform a pre-dose FVC manoeuvre to measure FEV₁ and FVC parameters. 2h post-dose FVC manoeuvre will be also performed. For each time point, spirometry consists in three acceptable manoeuvres (see [sections 7.2.1](#)).
- Investigator will access IRT in order to obtain the appropriate kit number for the next treatment period. **The morning dose of the study drug will be administered at the clinic (before 10:00 am) under supervision of the Investigator.** (see precaution for administration in [section 6.2.3](#)). The corresponding tear-off label will be stuck in the dispensation tracking form and the kit number will be recorded in the corresponding electronic CRF (e-CRF). The use-by-date must be filled-in on the labels. For the patient who

needs using a spacer, a new Aerochamber Plus™ spacer will be assigned and medication will be taken via this spacer.

Before discharge

- **Study medication** will be dispensed to the patient together with instructions for use. Drug administration will be done according to [section 6.2.3](#). For patient who is using a spacer, he/she will be reminded to use the Aerochamber Plus™ for each inhalation. Salbutamol will be given to the patient if needed.
- **The electronic Diary (the same given at V1) will be back to the patient.** Patient must continue to daily fill in the EXACT-PRO questionnaire, the medication and the rescue taken and to transmit daily the data until visit 5.
- **An appointment for Visit 5** will be made within 14 weeks from Visit 4 (at approximately the same time as other visits, before 9:00 am). **The time window should not exceed 26 weeks (±5 days) from Visit 2.**

The patient will be instructed for **Visit 5**:

- ➔ To fast overnight (at least 10 hours) for the next visit in order to perform blood sampling (only water is allowed);
- ➔ To **bring back** the **study medication** (in the box), the electronic Diary and the spacer if the patient take drugs via the Aerochamber Plus™ at the next visit.
- ➔ To avoid taking salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
- ➔ **Not to take the morning dose of the study medication before coming to the clinic visit (Visit 5)** (it will be administered at the clinic visit).

7.1.6 Visit 5 (Week 26 of Treatment Period)

The visit 5 will start in the morning (before 9:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected or the study drug has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or study drug intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with wash-out not respected will be recorded in the CRF.

The following procedures will be performed:

- **For the subset of patients performing 24h-Holter evaluation**: The Holter electrodes will be placed. Electrodes will be twin electrodes in order to be used to record the further planned procedure of 12-lead ECG (pre and post study medication dose). Patients will have an ambulatory 24-hour digital ECG Holter device and the recording start should remain the same for all the study visits (60 minutes before study medication intake) (see [section 7.2.6](#))
These patients will also be requested to visit the site the **next morning** in order to stop the 24-hour digital ECG Holter device. The total registration will be at least 25 hours.

- The study medication (in the box) provided at Visit 4 will be collected, as well as the AeroChamber Plus™ spacer previously provided. The Investigator will also check whether new rescue shall be provided to the patient.
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the need for the patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest. If the patient is withdrawn, he/she will be recorded as discontinued in the IRT.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The investigator will check in the electronic diary portal whether patient has been transmitting the EXACT-PRO and study medication/rescue intake daily since previous visit. **In case of lack of compliance, instructions on how to use the electronic Diary will be given again to the patient** (see [section 7.2.9](#)).
- The occurrence of COPD exacerbations and other adverse events will be evaluated and recorded in the eCRF (if any) (see [section 7.2.10](#)).
- A urine pregnancy test in women with childbearing potential will be performed.
- A full physical examination will be performed.
- Weight will be recorded.
- The TDI questionnaire will be filled in by the patient and TDI score will be assessed before the study treatment dose intake (see [section 7.2.7](#)).
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.12](#)).
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see [section 7.2.11](#)).
- Investigator will collect Health economic information as per [section 7.2.13](#).
- Pre-dose and 10 minutes post-dose vital signs (SBP and DBP) will be measured after 10 minutes of rest (see [section 7.2.4](#)).
- Pre-dose and 10 minutes post-dose 12-lead ECG (including the evaluation of HR and QTcF) will be performed after 10 minutes of rest (see [section 7.2.5](#)).
- A blood sample will be collected prior to study drug administration, after an overnight fasting (at least 10h), for the assessments of standard haematology and blood chemistry (see [section 7.2.3](#)).

The blood samples must be collected **after pre-dose vital signs and pre-dose 12-lead ECG recording**.

In case of non-interpretable data, another determination must be performed as soon as possible.

- A pre-dose (prior to study medication administration) and 2 hours post-dose spirometry measurements will be carried out: the patients will have to perform a pre-dose FVC manoeuvre to measure FEV₁ and FVC parameters. 2h post-dose FVC manoeuvre will be also performed. For each time point, spirometry consists in three acceptable manoeuvres (see [sections 7.2.1](#)).
- Investigator will access IRT in order to obtain the appropriate kit number for the next treatment period. **The morning dose of the study drug will be administered at the clinic (before 10:00 am) under supervision of the Investigator.** (see precaution for administration in [section 6.2.3](#)). The corresponding tear-off label will be stuck in the dispensation tracking form and the kit number will be recorded in the corresponding electronic CRF (e-CRF). The use-by-date must be filled-in on the labels. For the patient who

needs using a spacer, a new Aerochamber Plus™ spacer will be assigned and medication will be taken via this spacer.

Before discharge

- **Study medication** will be dispensed to the patient together with instructions for use. Drug administration will be done according to [section 6.2.3](#). For patient who is using a spacer, he/she will be reminded to use the Aerochamber Plus™ for each inhalation. Salbutamol will be given to the patient if needed.
- **The electronic Diary (the same given at V1) will be back to the patient.** Patient must continue to daily fill in the EXACT-PRO questionnaire, the medication and the rescue taken and to transmit daily the data until visit 6.
- An **appointment for Visit 6** will be made within 14 weeks from Visit 5 (at approximately the same time as other visits, before 9:00 am). **The time window should not exceed 40 weeks (±5 days) from Visit 2.**

The patient will be instructed for **Visit 6**:

- ➔ To **bring back** the **study medication** (in the box), the electronic Diary and the spacer if the patient take drugs via the Aerochamber Plus™ at the next visit.
- ➔ To avoid taking salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
- ➔ **Not to take the morning dose of the study medication before coming to the clinic visit** (it will be administered at the clinic visit).

7.1.7 Visit 6 (Week 40 of Treatment Period)

The visit 6 will start in the morning (before 9:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected or the study drug has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or study drug intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with wash-out not respected will be recorded in the CRF.

The following procedures will be performed:

- The study medication (in the box) provided at Visit 5 will be collected, as well as the AeroChamber Plus™ spacer previously provided. The Investigator will also check whether new rescue shall be provided to the patient.
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the need for the patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest. If the patient is withdrawn, he/she will be recorded as discontinued in the IRT.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.

- The investigator will check in the electronic diary portal whether patient has been transmitting the EXACT-PRO and study medication/rescue intake daily since previous visit. **In case of lack of compliance, instructions on how to use the electronic Diary will be given again to the patient** (see [section 7.2.9](#)).
- The occurrence of COPD exacerbations and other adverse events will be evaluated and recorded in the eCRF (if any) (see [section 7.2.10](#)).
- A urine pregnancy test in women with childbearing potential will be performed.
- A full physical examination will be performed.
- Weight will be recorded.
- The TDI questionnaire will be filled in by the patient and TDI score will be assessed before the study treatment dose intake (see [section 7.2.7](#)).
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.12](#)).
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see [section 7.2.11](#)).
- Investigator will collect Health economic information as per [section 7.2.13](#).
- Pre-dose and 10 minutes post-dose vital signs (SBP and DBP) will be measured after 10 minutes of rest (see [section 7.2.4](#)).
- Pre-dose and 10 minutes post-dose 12-lead ECG (including the evaluation of HR and QTcF) will be performed after 10 minutes of rest (see [section 7.2.5](#)).
- A pre-dose (prior to study medication administration) and 2 hours post-dose spirometry measurements will be carried out: the patients will have to perform a pre-dose FVC manoeuvre to measure FEV₁ and FVC parameters. 2h post-dose FVC manoeuvre will be also performed. For each time point, spirometry consists in three acceptable manoeuvres (see [sections 7.2.1](#)).
- Investigator will access IRT in order to obtain the appropriate kit number for the next treatment period. **The morning dose of the study drug will be administered at the clinic (before 10:00 am) under supervision of the Investigator.** (see precaution for administration in [section 6.2.3](#)). The corresponding tear-off label will be stuck in the dispensation tracking form and the kit number will be recorded in the corresponding electronic CRF (e-CRF). The use-by-date must be filled-in on the labels. For the patient who needs using a spacer, a new Aerochamber PlusTM spacer will be assigned and medication will be taken via this spacer.

Before discharge

- **Study medication** will be dispensed to the patient together with instructions for use. Drug administration will be done according to [section 6.2.3](#). For patient who is using a spacer, he/she will be reminded to use the Aerochamber PlusTM for each inhalation. Salbutamol will be given to the patient if needed.
- **The electronic Diary (the same given at V1) will be back to the patient.** Patient must continue to daily fill in the EXACT-PRO questionnaire, the medication and the rescue taken and to transmit daily the data until visit 7.
- **An appointment for Visit 7** will be made within 12 weeks from Visit 6 (at approximately the same time as other visits, before 9:00 am). **The time window should not exceed 52 weeks (±5 days) from Visit 2.**

The patient will be instructed for **Visit 7**:

- To **fast overnight** (at least 10 hours) for the next visit in order to perform blood sampling (only water is allowed).
- To **bring back** the **study medication** (in the box), the electronic Diary and the spacer if the patient take drugs via the Aerochamber Plus™ at the next visit.
- To avoid taking salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
- **Not to take the morning dose of the study medication before coming to the clinic visit (Visit 7)** (it will be administered at the clinic visit).

7.1.8 Visit 7 (Week 52 / End of Treatment Period)

The visit 7 will start in the morning (before 9:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected or the study drug has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or study drug intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with wash-out not respected will be recorded in the CRF.

The following procedures will be performed:

- **For patients performing 24h-Holter evaluation:** the Holter electrodes will be placed. Electrodes will be twin electrodes in order to be used to record the further planned procedure of 12-lead ECG (pre and post study medication dose). Patients will have an ambulatory 24-hour digital ECG Holter device and the recording start should remain the same for all the study visits (60 minutes before study medication intake) (see [section 7.2.6](#)). These patients will also be requested to visit the site the **next morning** in order to stop the 24-hour digital ECG Holter device. The total registration will be at least 25 hours.
- The study medication (in their boxes) provided at the previous Visit will be collected, as well as the AeroChamber Plus™ spacer previously provided.
- Changes of concomitant medications being taken by the patient will be recorded.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The investigator will check in the electronic diary portal whether patient has been transmitting the EXACT-PRO and study medication/rescue intake daily since previous visit.
- The occurrence of COPD exacerbations and other adverse events will be evaluated and recorded in the eCRF (if any) (see [section 7.2.10](#)). The status of any unresolved AEs recorded during the study must be checked and updated.
- A full physical examination will be performed.
- Weight will be recorded.
- The TDI questionnaire will be filled in by the patient and TDI score will be assessed before the study treatment dose intake (see [section 7.2.7](#)).
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.12](#)).

- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see [section 7.2.11](#)).
- Investigator will collect Health economic information as per [section 7.2.13](#).
- Pre-dose and 10 minutes post-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.4](#)).
- Pre-dose and 10 minutes post-dose 12-lead ECG (including the evaluation of HR and QTcF) will be performed after 10 minutes of rest (see [section 7.2.5](#)).
- A blood sample will be collected prior to study drug administration and **after an overnight fasting** for the assessments of (see [section 7.2.3](#)):
 - standard haematology and blood chemistry;
 - a serum β -HCG test will be performed in women of childbearing potential.The blood sample must be collected **after the vital signs and 12-lead ECG recording**. In case of non-interpretable data, another determination must be performed as soon as possible.
- A pre-dose (prior to study medication administration) and 2 hours post-dose spirometry measurements will be carried out: the patients will have to perform a pre-dose FVC manoeuvre to measure FEV₁ and FVC parameters. 2h post-dose FVC manoeuvre will be also performed. For each time point, spirometry consists in three acceptable manoeuvres (see [sections 7.2.1](#)).
- **The last morning dose of study medication will be administered at the clinic (before 10:00 am) under supervision of the Investigator from the kit dispensed at Visit 6 (40 weeks)**. For the patient who needs using a spacer, medication will be taken via the Aerochamber Plus™.
- The Investigator will access IRT to register the completion of the study for the patient.
- At investigator discretion, the pre-study patient's therapy will be resumed or changed if appropriate.
- At the end of the patient's participation in the trial, she/he will be discharged from the unit, providing that all her/his safety assessments are satisfactory.

7.1.9 Study Termination Visit (for a patient withdrawn before Week 52)

If a patient is withdrawn before the end of treatment period, a final evaluation will be done.

The Investigator must fill in the study termination visit in the eCRF. The explanations regarding the reasons of withdrawal and all the assessments performed will be inserted.

The following procedures will be performed:

- **For the subset of patients performing 24h-Holter evaluation**: The Holter electrodes will be placed. Electrodes will be twin electrodes in order to be used to record the further planned procedure of 12-lead ECG. Patients will have an ambulatory 24-hour digital ECG Holter device and the recording start should remain the same for all the study visits (60 minutes before study medication intake) (see [section 7.2.6](#))
These patients will also be requested to visit the site the **next morning** in order to stop the 24-hour digital ECG Holter device. The total registration will be at least 25 hours.
- The study medication (in their boxes) provided at the previous Visit will be collected, as well as the AeroChamber Plus™ spacer previously provided.

- Changes of concomitant medications being taken by the patient will be recorded.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The investigator will check in the electronic diary portal whether patient has been transmitting the EXACT-PRO and study medication/rescue intake daily since previous visit.
- The occurrence of COPD exacerbations and other adverse events will be evaluated and recorded in the eCRF (if any) (see [section 7.2.10](#)). The status of any unresolved AEs recorded during the study must be checked and updated.
- A full physical examination will be performed.
- Weight will be recorded.
- The TDI questionnaire will be filled in by the patient (see [section 7.2.7](#)).
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.12](#)).
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see [section 7.2.11](#)).
- Investigator will collect Health economic information as per [section 7.2.13](#).
- Vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.4](#)).
- 12-lead ECG (including the evaluation of HR and QTcF) will be performed after 10 minutes of rest (see [section 7.2.5](#)).
- If possible, a blood sample will be collected for the assessments of (see [section 7.2.3](#)):
 - standard haematology and blood chemistry;
 - a serum β -HCG test will be performed in women of childbearing potential.The blood sample must be collected **after the vital signs and 12-lead ECG recording**.
- Spirometry measurements will be carried out: the patients will have to perform a FVC manoeuvre to measure FEV₁ and FVC parameters. Spirometry consists in three acceptable manoeuvres (see [sections 7.2.1](#)).
- The Investigator will access IRT to register the discontinuation of the patient of the study.
- At investigator discretion, the pre-study patient's therapy will be resumed or changed if appropriate.
- At the end of the patient's participation in the trial, she/he will be discharged from the unit, providing that all her/his safety assessments are satisfactory.

7.2 Investigations

7.2.1 Spirometry

Pulmonary function tests (FEV₁, FVC) will be carried out under medical supervision in either a clinic or hospital and will be recorded using a computer-operated spirometer.

Throughout the study, the clinic visits and the lung function measurements will start in the morning between 7:00 and 9:00 a.m., approximately at the same time of the day for each patient.

Lung function measurements and daily calibration of the spirometer will be done according to the recommendation of the Official Statement of the European Respiratory Society and American Thoracic Society[12]. All sites will be provided with equipments and a central spirometry lab will be used. Investigator sites will be trained to the use of the system during the investigator meeting. Lung function measurements will be done with patients either standing or sitting (for each patient,

this should be consistent throughout the study) with the nose clipped after at least 10 minutes rest. Values will be corrected for BTPS conditions.

Calibration of the spirometer must be performed by the same investigator or deputy (to the extent possible) at each visit prior to any spirometry manoeuvres and the reports must be kept with the source study documents.

The specific procedures for centralised spirometry will be provided to the investigator by the centralised spirometry company.

Forced Expiratory Volume in the 1st second (**FEV₁**, L), Forced Vital Capacity (**FVC**, L) will be recorded at each visit under medical supervision. At screening, the post-bronchodilator FEV₁ values (within 30 min after administration of 4X100 µg salbutamol) will be considered for eligibility.

Forced Expiratory Volume in the 1st second (**FEV₁**, L), Forced Vital Capacity (**FVC**, L) will be recorded at each clinic visit from a forced vital capacity manoeuvre. For FEV₁ and FVC, **the highest value from three technically satisfactory attempts** will be recorded (irrespective of the curve they come from). The chosen value should not exceed the next one by more than 150mL. If the difference is larger, up to 8 measurements will be made and the largest value be reported. The ratio **FEV₁/FVC** will be derived from these **highest values** of each parameter [13].

The rescue medication (salbutamol) must be withheld as much as possible for at least 6 hours prior to starting the pre-dose assessment at each visit.

Study medication (run-in and after randomisation) should not be taken in the morning of the visits.

The wash-out for medications permitted for COPD exacerbations should be respected (see sections 5.1 and 5.2).

If the wash-out has not been respected the visit needs to be re-scheduled to take place within 2 days (3 days at V1). If the wash-out for rescue medication or for medications permitted for COPD exacerbations is not respected, or study medication intake occurs again before the re-scheduled visit:

- at V1 and V2, the patient will be discontinued
- from V3 to V7, the visit will be performed anyway and details of the intake (time and quantity) documented.

7.2.2 Use of rescue medication

The daily use of rescue medication will be recorded daily in the electronic diary. Each day, patient will have to record in the device the number of puffs taken during the last 24 hours.

7.2.3 Laboratory tests (including pregnancy test)

- **Standard haematology and blood chemistry**

The blood samples for standard haematology and blood chemistry will be collected in the morning after an overnight (at least 10 hours) fasting at Visit 1, Visit 5 and Visit 7. The collection will always be done after vital signs and ECG measurements, and before intake of study medication.

The following parameters will be assessed **by a central laboratory**:

- **Blood Chemistry**: creatinine, BUN, fasting serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase (γ-GT), total bilirubin,

alkaline phosphatase, sodium, potassium, calcium, and chloride electrolytes (Na, K, Ca, Cl), albumin.

- Haematology: red blood cells count (RBC), white blood cells count (WBC) and differential, total haemoglobin (Hb), hematocrit (Hct), platelets count (PLT).
- Pregnancy test (serum β -HCG): only for females of childbearing potential and only at Visit 1 and Visit 7.

Note: a urine pregnancy test will be performed from visits 1 to 6. According to local regulation, a urine pregnancy test may be performed on a monthly basis.

Blood collection and sample preparation will be performed according to procedures provided by **the central laboratory** which will be in charge to transmit the results to the Investigator.

Clinically significant abnormalities at Visit 1 not due to a pre-existing condition or clinically significant changes at Visit 5 and Visit 7 in the medical opinion of the investigator will be reported as adverse events in the eCRF.

7.2.4 Vital signs: Blood pressure evaluation and body weight

Systolic and Diastolic Blood Pressure (SBP, DBP) will be assessed after 10 min in the resting position.

Pre-dose and 10 minutes post-dose evaluations will be done at all visit (only pre-bronchodilator evaluation at screening visit).

Body weight must be assessed at each visit preferably using the same weighing scale for a same patient.

7.2.5 12-lead ECG

A centralised ECG will be used. Pre-dose and 10 minutes post-dose 12-lead ECG measurements will be done at all visit (only pre-bronchodilator at screening visit).

Before recording, patients should be resting in a quiet supervised setting with minimal stimulation (e.g. no television, loud music, computer games) and lay in a resting position for 10 minutes before each nominal ECG time point.

At baseline (**Visit 2**), the pre-dose ECG will be recorded in **triplicate**. The triplicate ECG will consist of 3 ECG recordings in rapid succession (consecutively) and not more than 2 minutes apart. QTc value will be calculated using the Fridericia formula (Fridericia-corrected $QTc = QT / \sqrt[3]{RR}$). It will be calculated automatically by the ECG recorder. Heart rate (HR), PR and QRS values will be also evaluated from ECG at all visits.

Clinically significant abnormalities at Visit 1 not due to a pre-existing condition or clinically significant changes at the following visits in the medical opinion of the investigator will be reported as adverse events in the eCRF.

ECGs with computerized protocol interpretation are considered normal if

- $40 \leq \text{Heart rate} \leq 110$ bpm,
- $120 \text{ ms} \leq \text{PR} \leq 210$ ms,
- $\text{QRS} \leq 120$ ms.

In case of relevant ECG abnormalities, the inclusion of the patient will be judged by the investigator and in consultation with the Chiesi Corporate Cardiac Leader. The final decision for enrolment would be documented in the Medical File of the patient.

For eligible patients, QTcF values must be $QTcF \leq 450$ (males) and 470 ms (females) (as per Exclusion Criterion 11).

7.2.6 24-hour digital Holter

The sub-group of patients selected for this procedure will have an ambulatory 24-hour digital Holter provided by a vendor selected by Sponsor placed on Visit 1, Visit 2, Visit 5 and Visit 7 approximately 60 minutes prior to any drug administration (i.e. salbutamol at visit 1, run-in medication the day before Visit 2, and blinded drug for the subsequent visits during treatment period).

Monitoring will continue for 24-hour after study drug administration till the following morning (so the actual duration of ECG Holter recording will be of approximately 25 hours).

Clinically significant abnormalities at Visit 1 not due to a pre-existing condition or clinically significant changes at Visit 2, Visit 5 and Visit 7 in the medical opinion of the investigator will be reported as adverse events in the eCRF.

Two sets of analysis will be conducted for this trial: arrhythmia and electrocardiographic.

Details of arrhythmia analysis and how the Holter variables are calculated can be found in the Holter Analysis Plan from Holter vendor provider.

The database will be made from discrete 12-lead ECGs (10-sec recording duration each one) that will be extracted from the Holter recording.

7.2.7 Baseline and Transition Dyspnea Indexes (BDI and TDI)

Clinical instruments were developed in order to provide a more comprehensive assessment of the severity of dyspnea. In this trial, the Baseline (BDI) and Transition (TDI) Dyspnea Indexes [14] will be used.

Dyspnea at baseline will be assessed with the BDI [14]. This instrument has 3 domains (functional impairment, magnitude of task and magnitude of effort) with the values added for a combined focal score. Functional impairment determines the impact on breathlessness on the ability to carry out activities; magnitude of task determines the type of task that causes breathlessness, magnitude of effort establishes the level of effort that results in breathlessness. The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12). The changes from baseline is measured by the TDI score which ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (-9 to +9).

The same investigator or deputy will interview specifically the patients during the study period.

BDI will be assessed at Visit 1 (screening) and Visit 2 (randomisation). Only symptomatic patients with a $BDI \leq 10$ are eligible at screening. Patients can be randomized only if $BDI \leq 10$ is confirmed at Visit 2.

TDI will be evaluated in the morning of each Visit from Visit 3 to Visit 7.

Specific instructions for adequate completion and grading using the questionnaire will be provided to the investigator or deputy.

At each visit, data collected by Investigator on paper will be entered by the Investigator in the eCRF.

7.2.8 COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a quick and easy to use questionnaire. It was specifically designed to measure candidate items regarding daily symptoms, activity limitations and other manifestations of the COPD. The 8 items which are included in the CAT cover cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy. It has been developed to be self-administered by patients, and is simple enough that nearly all patients should be able to understand and complete it easily by themselves.

The CAT will be filled in at Visit 1. **Only symptomatic patients with a CAT score ≥ 10 are eligible at screening.**

At each visit, data collected by Investigator on paper will be entered by the Investigator in the eCRF.

7.2.9 The EXACT-PRO questionnaire

The EXACT-PRO (EXAcacerbations of Chronic pulmonary disease Tool – Patient Reported Outcome) is a validated, patient-reported outcome (PRO) measure to evaluate exacerbation-related outcomes of treatment of chronic obstructive pulmonary disease using electronic real-time based technology.

The questionnaire is composed of 14 items covering various domains as breathlessness, cough and sputum, chest symptoms and overall status (tiredness, weakness and sleep disturbances). Each question weights individually to the total score varying from 0 to 100. The health status of the patient is correlated to the global score meaning higher score corresponds to more severe health status of the patient. This instrument has been translated and validated in the major European languages.

The EXACT-PRO will be loaded on an electronic diary together with questions to record daily rescue medication intake and study medication compliance (run-in and treatment). The EXACT-PRO will be filled in daily by the patient.

The EXACT score will be monitored and will raise alert to the physician in case of relevant increases.

7.2.10 COPD 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 necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalization.”*

The exacerbations will be classified as moderate or severe as per EMA/CMHP guidelines definitions [15]:

- **Moderate:** exacerbations that require treatment with systemic corticosteroids and/or antibiotics;
- **Severe:** exacerbations that require hospitalisation or result in death.

Emergency room attendance includes any unscheduled visit at any healthcare institution, i.e. at the emergency department or at a pneumological division, requiring an urgent medical advice or extra visit to physician:

- ER associated with systemic steroids/antibiotics will be classified as moderate

- ER associated with systemic steroids/antibiotics and at least 24 hours of stay will be considered as hospitalisation and therefore classified as severe.
- ER admission without prescription of systemic steroids/antibiotics will not be considered a moderate/severe exacerbation.

The recognition of potential COPD exacerbations will be primarily (but not exclusively, as the patient may seek medical advice regardless of the EXACT records) optimised by the daily report of worsened symptoms through the EXACT questionnaire. In that intent, the investigator will carefully train the patient to recognise the worsening of signs and symptoms associated with COPD exacerbations. The patient will also be instructed on how to report these signs and symptoms in the EXACT questionnaire.

Patients will be regularly reminded through the digital platform used for the study to call the investigational site if his/her symptoms worsen. The contact details will be indicated on the patient card distributed to the patient at the pre-screening visit.

Investigators and site personnel will also be notified by electronic means (such as emails or through the dedicated web-portal) when the EXACT score increases above the given threshold. Each investigator will be able to review the individual patient's results onto his/her own computer. The signal of the change in symptoms will alert the investigator to check his/her patient's status. This will be triggered by a variation in patient's symptoms beyond the normal day-to-day variability.

Based on consistent worsening symptoms/status, actions from the investigator will be recommended. The physician will be directed to diagnose the cause of the worsening symptoms and decide whether to ask the patient to come to the clinic for an unscheduled visit and whether additional treatment is required.

The physician will record an exacerbation in the eCRF if there is a change in regular medication i.e. prescriptions of systemic corticosteroids and/or antibiotics or hospitalization.

The duration of treatment for the exacerbation and the duration of hospitalization will be collected and recorded in the eCRF. Patient will be instructed to complete their electronic diary, **whenever possible**, in the course of hospitalization/health care utilization.

COPD exacerbations interpreted as due to lack of efficacy (instead of, e.g., to concurrence with acute viral infection), should not be classified drug related.

The assessment of worsening symptoms during any extra unscheduled visit may include but is not restricted to the following:

- Breathlessness
- Wheeze
- Chest tightness
- Cough
- Fever
- Change in sputum production or purulence
- Unusual increase of use of "rescue" salbutamol

Investigators will use additional diagnostic procedures (e.g. lung function tests, blood oxygen levels, chest X-ray, ECG) at their own discretion to obtain diagnosis.

In case of acute exacerbations during the study, the patients will be allowed to receive any medical intervention that is considered necessary for the appropriate control of the symptoms (e.g. oral/iv/im

corticosteroids, antibiotics, nebulised bronchodilators/steroids, short courses of oxygen therapy/mechanical ventilation) (for the complete list of allowed medications, refer to [sections 5.1](#))

For patients who exhibit worsening COPD disease status while on study treatment, the investigator is encouraged to maximise the use of therapies in classes different from the ones of the study treatments (e.g. short-acting anticholinergic, short-acting β 2-agonist).

In case of COPD exacerbation, guidelines are provided to the physicians on how to treat the exacerbation, even though they are not mandatory.

1. For exacerbation therapy, advice is to start with antibiotic - usually amoxicillin or amoxicillin/clavulanic acid at standard doses for 7 days when there is increase in sputum purulence or sputum volume.
2. When patient has symptoms affecting daily living activity, then to start oral prednisolone 30 mg daily for 7 days and then reduce to zero over next 5 days (as many patients ask for reducing dosages).

The intake of study medication shall be maintained in case of exacerbation but may be temporarily withdrawn if necessary upon investigator's discretion, and the Investigators will carefully annotate in the CRF all treatments they deem necessary to administer for the most appropriate treatment of the exacerbation. All necessary extra-visits will be scheduled in order to evaluate the patient's clinical conditions.

In the recovery period after exacerbation episode, if the condition of the patient allows, any possible effort should be made to remove all additional medication used in the treatment of the exacerbation, and to restart the treatment of the patient according to the protocol as early as possible.

If a COPD exacerbation occurs close to a study clinic visit, the Investigator may postpone the visit within 5 days if he/she judges it necessary.

A COPD exacerbation is not a reason to withdraw the patient from the study, unless the Investigator deems it necessary.

7.2.11 St. George's Respiratory Questionnaire (SGRQ)

Health Related Quality of Life will be assessed by the St. George's Respiratory Questionnaire, a 76-item questionnaire developed to measure health in chronic airflow limitation [[16](#), [17](#)]. Three component scores are calculated: symptoms, activity and impacts on daily life. Moreover, a total score will be calculated, with lower scores corresponding to better health.

The questionnaire will be completed by patients at all visits from randomisation (Visit 2) until the end of study participation (Visit 7). The questionnaire will be checked for completeness and collected before the patient leaves the center.

7.2.12 EQ-5D-3L Health Questionnaire

The EQ-5D-3L is primarily designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

The questionnaire will be completed by patients at all visits from randomisation (Visit 2) until the end of study participation (Visit 7). The questionnaire will be checked for completeness and collected before the patient leaves the center.

At each visit, data collected by Investigator on paper will be entered by the Investigator in the eCRF.

7.2.13 Health Economic information

Information on the total use of healthcare resources and absence from work associated with the patients's condition will be collected during the trial.

Whether the patient has a job, it will be recorded in the eCRF as well as patient work information.

Health Economic information will be collected by the Investigator based on patient interviews at each visit from randomisation visit (Visit 2) until end of treatment (Visit 7).

8. EFFICACY ASSESSMENTS

Primary efficacy variables

- Change from baseline in pre-dose morning FEV₁ at Week 26.
- Change from baseline to the 2-hour post-dose value of FEV₁ at Week 26
- TDI focal score at Week 26.

Secondary efficacy variables

- Change from baseline in pre-dose morning FEV₁ at all the other clinic visits.
- Change from baseline to the average over the treatment period in pre-dose morning FEV₁.
- FEV₁ response (change from baseline in pre-dose morning FEV₁ \geq 100 ml) at Week 26 and Week 52.
- Change from baseline to the 2-hour post-dose value of FEV₁ at all the other clinic visits.
- Change from pre-dose to the 2-hour post-dose value of FEV₁ at all clinic visits.
- TDI focal score at all the other clinic visits.
- TDI response (focal score \geq 1) at Week 26 and Week 52.
- Change from baseline in the SGRQ total score and domain scores at all clinic visits.
- SGRQ response (change from baseline in total score \leq -4) at Week 26 and Week 52.
- Change from baseline to each inter-visit period and to the entire treatment period in the percentage of days without intake of rescue medication and in the average use of rescue medication (number of puffs/day).
- Moderate and severe COPD exacerbation rate over 52 weeks of treatment.
- Time to first moderate or severe COPD exacerbation.

Exploratory efficacy variables

- Change from baseline in pre-dose morning FVC at all clinic visits.
- Change from baseline to the 2-hour post-dose value of FVC at all clinic visits.
- Change from pre-dose to the 2-hour post-dose value of FVC at all clinic visits.
- Change from baseline to each inter-visit period and to the entire treatment period in the average EXACT-PRO total score and domain scores.

Health economic variables

- EQ-5D-3L VAS score and EQ-5D-3L index at all clinic visits.
- Number of hospital admissions due to COPD and other causes.

- Number of hospital days due to COPD and other causes.
- Number of emergency room visits due to COPD and other causes.
- Number of ambulance rides to hospital due to COPD and other causes.
- Number of unscheduled contacts due to COPD:
 - family practitioner
 - specialist outpatients setting
 - specialist hospital outpatients setting.
- Number of days with professional home assistance due to COPD.
- Number of days with family caregivers due to COPD.
- Number of days with oxygen therapy use due to COPD.
- Unplanned diagnostic or instrumental tests performed due to COPD.
- Lost productivity due to COPD (sick leave days from work, anticipated retirement).
- Mortality.

9. SAFETY ASSESSMENTS

Safety variables

- Adverse events (AEs) and adverse drug reactions (ADRs).
- Vital signs (systolic and diastolic blood pressure).
- BMI.
- 12-lead ECG parameters: heart rate (HR), QTcF, PR and QRS.
- 24-hour ECG Holter (on a subset of 10% of the randomised patients).
- Standard haematology and blood chemistry.

10. ADVERSE EVENT REPORTING

10.1 Definitions

An **Adverse Event** is “any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment”.

An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An **Adverse Drug Reaction** is an “untoward and unintended responses to an investigational medicinal product related to any dose administered”.

All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression “reasonable causal relationship” means to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

A **Serious Adverse Event (SAE)/Serious Adverse Drug Reaction** is any untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- **Results in death**

Death is not an adverse event but an outcome. It is the cause of death that should be regarded as the adverse event. The only exception to this rule is “sudden death” where no cause has been established; in this latter instance, “sudden death” should be regarded as the adverse event and “fatal” as its reason for being serious.

- **Is life-threatening**

Life-threatening refers to an event in which the patient was at risk of death at the time of the event (e.g., aplastic anaemia, acute renal failure, and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.

- **Requires hospitalisation or prolongation of existing hospitalisation**

Hospitalization refers to a situation whereby an AE is associated with unplanned overnight admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalization for the treatment of a medical condition that occurs on an “elective” or “scheduled” basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as a AE. Complications that occur during the hospitalisation are AEs. If a complication prolongs hospitalisation, the event is a SAE.

- **Results in persistent or significant disability or incapacity.**

The term significant disability should be viewed as any situation whereby an AE has a clinically important effect on the patient’s physical or psychological well-being to the extent that the patient is unable to function normally.

- **Is a congenital anomaly or birth defect**

- **Is a medically significant adverse event**

This criterion allows for any situations in which important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation may jeopardise the patient’s health or may require intervention to prevent one of the above outcomes.

Examples of such events are: intensive treatment in an emergency room or at home for bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether an event is serious because medically significant.

A **Non-Serious Adverse Event/Non-Serious Adverse Drug Reaction** is an adverse event or adverse drug reaction that does not meet the criteria listed above for a serious adverse event/serious adverse drug reaction.

10.2 Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable product information (Investigator’s Brochure for an unauthorised investigational product or Summary of Product Characteristics or approved Package Insert for an authorised product), otherwise it is considered unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events. For example, an event more specific or more severe than described in the Investigator’s Brochure would be considered as “unexpected”. Examples of such events are: (a) acute renal failure as a labelled ADR with a

subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

In the event an exacerbation is interpreted as due to lack of efficacy, it should not be classified as drug related.

10.3 Intensity of Adverse Event

Each Adverse Event must be rated on a 3-point scale of increasing intensity:

- **Mild:** The event causes a minor discomfort, or does not interfere with daily activity of the patient, or does not lead to either modification of test treatment dosage or establishment of a correcting treatment.
- **Moderate:** The event perturbs the usual activity of the patient and is of a sufficient severity to make the patient uncomfortable. The event leads to a diminution of dosage of the test treatment, or a temporary interruption of its administration or to the establishment of a correcting treatment.
- **Severe:** The event prevents any usual routine activity of the patient and causes severe discomfort. It may be of such severity to cause the definitive interruption of test treatment.

10.4 Causality Assessment

The following “binary” decision choice will be used by the Investigator to describe the causality assessment:

- Reasonable possibility of a relatedness
- No reasonable possibility of relatedness

The expression “reasonable possibility of relatedness” is meant to convey, in general, that there are facts (evidence) or arguments meant to suggest a causal relationship.

The Investigator will be asked to consider the following before reaching a decision on causality assessment:

- Time relationship between study drug intake and event’s onset;
- Dechallenge (did the event abate after stopping drug?);
- Rechallenge (did the event reappear after reintroduction?);
- Medical history;
- Study treatment(s);
- Mechanism of action of the study drug;
- Class effects;
- Other treatments-concomitant or previous;
- Withdrawal of study treatment(s);
- Lack of efficacy/worsening of existing condition;
- Erroneous treatment with study medication (or concomitant);
- Protocol related process.

10.5 Action taken with the study drug

- None
- Study drug permanently discontinued
- Study drug temporarily discontinued
- Study drug dose reduced
- Study drug dose increased
- Unknown/Not applicable.

10.6 Other actions taken

- Specific therapy/medication
- (Prolonged) Hospitalisation

10.7 Outcome

Each Adverse Event must be rated by choosing among:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal
- Unknown.

10.8 Recording Adverse Events

All Adverse Events occurring during the course of the study must be documented in the Adverse Event page of the Electronic Case Report Form (eCRF). Moreover, if the Adverse Event is serious, the Serious Adverse Event Form must also be completed.

It is responsibility of the Investigator to collect all adverse events (both serious and non-serious) derived by spontaneous, unsolicited reports of patients, by observation and by routine open questionings.

The recording period for Adverse Events is the period starting from the Informed Consent signature until the patient's study participation ends.

If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE eCRF page must be completed, as appropriate. A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the clinically significant abnormal laboratory finding, should be reported on AE eCRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded.

In order to collect as complete as possible information in the clinical study database, all ADRs and SAEs ongoing at the time the patient's study participation ends should be evaluated up to 14 days after last study drug intake. After this period, all unresolved ADRs and SAEs will be reported as "ongoing" in the eCRF.

For pharmacovigilance purposes, all SAEs should be followed-up in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or the patient is lost to follow-up. Follow-up may therefore continue until after the patient has left the study up to 30 days after his/her discontinuation from the study for unrelated SAEs, and without timelines for related SAEs.

10.9 Reporting Serious Adverse Events to Chiesi

The Investigator must report all Serious Adverse Events to the Chiltern Safety Contact within 24 hours of awareness. The information must be sent by providing the completed Serious Adverse Event form. At a later date, the Chiltern Safety Contact will report all information to Chiesi Corporate Pharmacovigilance, the Clinical Study Manager and the Clinical Research Physician.

- Reporting of SAEs from the investigator site is from the time of patient's signature of informed consent and until the patient's study participation ends. All new Serious Adverse Events occurring beyond this time frame and coming to the attention of the investigator must be recorded only if they are considered [in the opinion of the investigator] causally-related to the study drug.

- Up to the closure of the site, SAE reports should be reported to the Chiltern Safety Contact. All new related SAEs occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

10.10 Reporting Serious Adverse Events to Regulatory Authorities/Ethics Committees/IRB

All SUSARs, which occur with the investigational medicinal products within or outside the concerned clinical trial, if required, will be reported in compliance with the timelines and standards for reporting SUSARs set out in the EU Directive 2001/20/EC [Directive 2001/20/EC of the European parliament and of the council of 4/April/2001] and linked guidance [European Commission, Enterprise and Industry Directorate General: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use, latest version]. The EMA and the concerned national health authorities (if applicable) will be informed through Eudravigilance, while the Ethics Committees and the investigators by CIOMS I form or by periodic line- listings produced by Chiesi Corporate Pharmacovigilance.

With regard to regulations in force for Pharmacovigilance, the Investigator must fulfill his/her obligation according to the law in force in his country.

10.11 General Notes

- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the Chiltern Safety Contact by fax together with the Serious Adverse Event form, retaining a copy on site with the case report form;
- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the Chiltern Safety Contact as soon as available, retaining a copy on site with the case report form;
- In case of pregnancy, the patient will be immediately withdrawn from the study and she will be followed with due diligence until the outcome of the pregnancy is known. The pregnancy must be reported by the investigator within 24 hours by fax/e-mail/via Monitor to the Chiltern Safety Contact using the paper Pregnancy Report Form. The Chiltern Safety Contact will inform Chiesi of the pregnancy within one working day of being notified.

The first two pages of the Pregnancy Report Form should be completed by the investigator with all the available information and sent to the Chiltern Safety Contact. The third page will be completed as soon as the investigator has knowledge of the pregnancy outcome. If it meets the criteria for immediate classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator should follow the procedure for reporting SAEs.

- If it is the partner, rather than the patient, who is found to be pregnant, the same procedure regarding pregnancy report is to be followed and the Pregnancy Report Form should be completed.
- If the pregnancy is discovered before taking any dose either of study drug or of the run-in medication, the pregnancy does not need to be reported; it is only required that the patient is immediately withdrawn from the study.

10.12 Independent Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) is being established, in order to have an independent scrutiny of the study and a better safety insurance of those subjects who will be recruited in the trial.

Through the involvement of external expert advisors, an unbiased evaluation of the overall safety will be provided, with particular regard to:

- ❖ the incidence of major adverse health outcomes (i.e. Serious Adverse Events) during the run-in period
- ❖ any occurring differential risk for major adverse health outcomes (as previously defined) in the different treatment arms during the study
- ❖ any other relevant study data/assessments.

The DSMB will be composed by independent Clinicians and one independent Biostatistician.

A document with the DSMB procedures will be established by the members during the first meeting. The DSMB will have periodical face-to-face and telephone meetings, as appropriate, and a Safety Assessment Report will be issued after each meeting.

The Monitoring of Safety will be accomplished through the evaluation of the rate of Adverse Events (AEs), Serious Adverse Events (SAEs) and COPD exacerbations in the overall study population and in each treatment arm, with a specific attention to the occurrence of SAEs of particular concern for the study patient population, if any.

All relevant listings will be transmitted for evaluation to the DSMB according to the agreed timelines.

The DSMB will have access to the relevant modules of the study IRT with the authorization to:

- unblind the study treatment (if necessary)
- evaluate the trial status (e.g. number of screened patient, screening failures, randomized patients, drop-outs, completers) on an ongoing basis.

Any additional information will be promptly made available by the Sponsor upon request of the DSMB members, as well as any request for additional clinical/instrumental/ laboratory evaluations deemed appropriate by the DSMB will be transmitted to the Investigator and followed-up by the Sponsor.

The Sponsor (and other study personnel) may be involved in some parts of the DSMB meetings, however, they will never have access to unblinded data and/or unblinded/coded comparisons.

All DSMB members will keep as confidential all information and data deriving from the DSMB activity, without disclosing them to others.

10.13 Adjudication Committee for MACE

An Adjudication Committee (AC) will be established, in order to have a particular scrutiny of some potentially relevant adverse events to perform a MACE evaluation.

Through the involvement of external expert advisors, an unbiased evaluation of the following adverse events will be provided:

- ❖ **Acute MI** (acute coronary syndrome, non-fatal myocardial infarction);
- ❖ **Stroke** (non-fatal stroke);
- ❖ **Cardiovascular death**(cardiac arrest, sudden death);
- ❖ **Arrhythmias: New-Sustained Supraventricular and Sustained Ventricular**;
- ❖ **Heart Failure** (change in the status)

The AC will be composed by three cardiologists and will meet at the end of the study to adjudicate the data in blinded condition.

Any additional available information will be promptly made available by the Sponsor upon request of the AC members, as well as any request for additional clinical/instrumental/ laboratory evaluations deemed appropriate by the AC will be transmitted to the Investigator and followed-up by the Sponsor. If the data available will be insufficient by the Committee to permit a definitive diagnosis, then the original reporter's diagnosis will be accepted

The Sponsor Corporate Cardiac Leader and other study personnel will be involved in this AC. However, they will never have access to unblinded data and/or unblinded/coded comparisons as the other AC members.

All AC members will keep as confidential all information and data deriving from the AC activity, without disclosing them to others.

11. DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her designee.

All patients who will sign the informed consent will be databased. For patients who are screened but not randomized a minimum set of information is required: date of informed consent signed, demography, assessment of inclusion/exclusion criteria when applicable, primary reason for not continuing, adverse events and concomitant medications if any.

Questionnaires answers will be databased.

Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Medical history and Adverse Events will be coded using the MedDRA dictionary; medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical classification (ATC).

External data (Spirometry, 12-lead ECG, 24h Holter, laboratory tests, data from electronic diary) will be processed centrally and reconciled against data recorded in the eCRF as part of cleaning activities.

After cleaning of data, a review meeting will be held to determine the occurrence of any protocol violation and to define the patient populations for the analysis. Once the database has been declared to be complete and accurate, it will be locked, the randomization codes will be opened and the planned statistical analysis will be performed. Only authorised and well-documented updates to the study data are possible after database lock. A CD-ROM of the patient data will be sent after database lock at the investigational site for archiving.

12. STATISTICAL METHODS

12.1 Sample size

The sample size has been calculated to demonstrate the superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of change from baseline in pre-dose morning FEV₁, change from baseline to the 2-hour post-dose value of FEV₁ and TDI focal score at Week 26.

A total of 1304 patients (652 patients per group) will be randomised in order to reach a total of 1088 evaluable patients at Week 26 (544 per group), considering a non-evaluable rate of approximately 16.5% at this time point. This sample size will provide:

- approximately 97.7% power to detect a mean difference of 60 ml in favour of CHF 5993 pMDI in change from baseline in pre-dose morning FEV₁ at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 250 ml;
- approximately 99.6% power to detect a mean difference of 70 ml in favour of CHF 5993 pMDI in change from baseline to the 2-hour post-dose value of FEV₁ at a two-sided significance level of 0.05, assuming a SD of 250 ml. Taking into account the power close to 100% and the strong correlation expected with the change from baseline in pre-dose morning FEV₁, it is reasonable to assume an overall power of 97.7% for the two FEV₁-based primary variables;
- approximately 87.1% power to detect a mean difference of 0.6 units in favour of CHF 5993 pMDI in TDI focal score at a two-sided significance level of 0.05, assuming a SD of 3.2

units. Two recent studies in moderate-severe COPD population [18, 19] showed significant differences between glycopyrronium bromide (NVA237) and placebo in terms of TDI focal score 26 weeks after randomisation, with the MCID of 1 unit reached only in one trial. However, in the present study, the effect of glycopyrrolate bromide on TDI will be evaluated on top of a double combination ICS/LABA, therefore the possibility of smaller differences but still clinically significant considering the severe-very severe COPD population, should be taken into account. For this reason the sample size calculation is based on a mean difference in TDI focal score between treatments of 0.6 units. Of note, the mean difference between combinations LABA/LAMA and LAMA alone observed in three studies where the concomitant use of ICS was allowed ranged from 0.26 to 0.6 units [20, 21, 22, 23]. Therefore, our assumption corresponds to the maximum effect size observed in these trials.

An overall study power for the primary efficacy analysis of approximately 85% will therefore be ensured.

At least 20 % of patients with very severe airflow limitation (post-bronchodilator FEV₁ at screening < 30% of predicted normal value) will be randomised in the study.

12.2 Populations for analysis

- **Safety population:** all randomized patients who receive at least one dose of the study treatment.
- **Intention-to-treat (ITT) population:** all randomized patients who receive at least one dose of the study treatment and with at least one available evaluation of efficacy after the baseline.
- **Per protocol (PP) population:** all patients from the ITT population without any major protocol deviation (e.g., wrong inclusions, poor compliance, non-permitted medications). Exact definition of major protocol deviations will be discussed by the study team during the blind review of the data and described in the Data Review Report.

Since the superiority of CHF 5993 pMDI over CHF 1535 pMDI will be tested, the primary efficacy analyses will be based on the ITT population. These analyses will be also performed on the PP population for sensitivity purposes.

The secondary efficacy variables and the health economic variables will be analysed in the ITT population (and on the PP population if relevant) and the safety variables will be analysed in the Safety population.

In case of deviation between randomised treatment and treatment actually received, the treatment actually received will be used in the safety analyses (i.e. an as-treated analysis will be performed).

Analyses stratified by relevant factors may be performed for selected efficacy and/or safety variables. These stratified analyses will be defined a priori in the Statistical Analysis Plan.

12.3 Statistical analysis

A detailed Statistical Analysis Plan (SAP) will be described in a separate document. The plan might be reviewed and updated as a result of the blind review of the data and will be finalized before breaking the blind.

12.3.1 Descriptive Statistics

- Descriptive statistics for quantitative variables will include n (the number of non-missing values), mean, SD, median, minimum and maximum values. The 1st and the 3rd quartiles will be also presented for the EQ-5D-3L VAS score and the EQ-5D-3L index. The rate (number of events per year or number of days per year) may also be presented for health economic

variables. Categorical variables will be summarized by using frequency count and percent distribution.

12.3.2 Missing data

- For the primary efficacy analysis, linear mixed models for repeated measures will be used to handle missing data. Under the Missing At Random (MAR) assumption, these models provide an unbiased estimate of the treatment effect that would have been observed if all patients had continued on treatment for the full study duration [24]. Sensitivity analyses tailored to the missing data pattern observed will be defined a priori in the SAP to investigate the robustness of the conclusions of the study.
- The BDI and the TDI focal scores will be considered as missing if at least one response will be included among the following: “W”, “X”, “Y”, “Z”.
- Only COPD exacerbations with onset during the randomised treatment period (i.e., before study completion or discontinuation) will be included in the analysis.
- The domain scores of the SGRQ will be considered non-missing if the following conditions will be satisfied:
 - Symptoms score: missing items ≤ 2 ;
 - Activity score: missing items ≤ 4 ;
 - Impacts score: missing items ≤ 6 .

If at least one domain score will be missing, the total score will be considered as missing.

- A minimum of 7 days with available measurements will be required in each inter-visit period (including run-in period) and in the entire treatment period to consider the following variables as non-missing: percentage of days without intake of rescue medication, average use of rescue medication, EXACT-PRO total score and domain scores.
- Further details on dealing with missing data, along with the handling of possible outliers, will be described in the SAP. Other critical missing data, if any, will be discussed during the blind review of the data. Decisions will be fully documented in the Data Review Report.

12.3.3 Patient demographics and baseline characteristics

The following variables will be summarised by treatment group on the ITT population (and on the Safety or PP populations, if relevant): demographic characteristics, medical history and concomitant diseases, previous and concomitant medications, efficacy and safety parameters at screening and/or at baseline.

12.3.4 Primary efficacy variables

- The comparisons between CHF 5993 pMDI and CHF 1535 pMDI will be conducted according to a hierarchical testing procedure. The primary efficacy variables will be considered in the following order:
 1. change from baseline in pre-dose morning FEV₁ at Week 26;
 2. change from baseline to the 2-hour post-dose value of FEV₁ at Week 26;
 3. TDI focal score at Week 26;

At each step of the procedure, no confirmatory claims will be made unless the superiority of CHF 5993 pMDI over CHF 1535 pMDI will be demonstrated in all the preceding steps.

- Change from baseline (Visit 2) in pre-dose morning FEV₁ will be analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, Country, number of COPD exacerbations in the previous year (1 or >1), severity of airflow limitation (post-bronchodilator FEV₁ at screening < or $\geq 30\%$ of predicted normal value) and smoking status as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each

treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) at Week 26 will be estimated by the model. Superiority of CHF 5993 pMDI over CHF 1535 pMDI will be demonstrated by a statistically significant difference between treatments (defined as $p < 0.05$) favouring CHF 5993 pMDI.

- Change from baseline (Visit 2 pre-dose) to the 2-hour post-dose value of FEV₁ will be analysed using a similar model as for change from baseline in pre-dose morning FEV₁. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs at Week 26 will be estimated by the model. Superiority of CHF 5993 pMDI over CHF 1535 pMDI will be demonstrated by a statistically significant difference between treatments at Week 26 favouring CHF 5993 pMDI.
- TDI focal score will be analysed using a similar model as for change from baseline in pre-dose morning FEV₁. The BDI (Baseline Dyspnea Index) focal score assessed at Visit 2 will be considered in the model as the baseline value. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs at Week 26 will be estimated by the model. Superiority of CHF 5993 pMDI over CHF 1535 pMDI will be demonstrated by a statistically significant difference between treatments favouring CHF 5993 pMDI.

12.3.5 Secondary efficacy variables

- For change from baseline in pre-dose morning FEV₁, the adjusted means in each treatment group and the adjusted mean differences between treatments at all the other clinic visits and averaged over the treatment period will be estimated with their 95% CIs by the same model used for the primary efficacy analysis. In the estimation of the averages over the treatment period equal weights will be assigned to the clinic visits.
- FEV₁ response at Week 26 and Week 52 will be compared between treatment groups using a logistic model including treatment, Country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as factors and the baseline value as a covariate.
- For change from baseline to the 2-hour post-dose value of FEV₁, the adjusted means in each treatment group and the adjusted mean differences between treatments at all the other clinic visits will be estimated with their 95% CIs by the same model used for the primary efficacy analysis.
- At each clinic visit (from Visit 3 onwards), the change from pre-dose to the 2-hour post-dose value of FEV₁ will be analysed using an ANCOVA model including treatment, Country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as fixed effects, and the pre-dose value at the visit as a covariate.
- For TDI, the adjusted means in each treatment group and the adjusted mean differences between treatments at all the other clinic visits will be estimated with their 95% CIs by the same model used for the primary efficacy analysis.
- TDI response at Week 26 and Week 52 will be compared between treatment groups using a similar model as for FEV₁ response.
- Change from baseline (Visit 2) in the SGRQ total score and domain scores at all clinic visits will be compared between treatment groups using a similar model as for the primary efficacy variables.
- SGRQ response at Week 26 and Week 52 will be compared between treatment groups using a similar model as for FEV₁ response.
- Change from baseline (run-in period) to each inter-visit period in the percentage of days without intake of rescue medication and in the average use of rescue medication will be

analysed using a similar model as for the primary efficacy variables. The inter-visit period will be considered instead of visit in the model. For these variables, the change from baseline to the entire treatment period will be analysed using an ANCOVA model including treatment, Country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as fixed effects and the baseline value as a covariate.

- The number of moderate and severe COPD exacerbations during the treatment period will be analysed using a negative binomial model including treatment, Country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as fixed effects, and log-time on study as an offset. The adjusted exacerbation rates in each treatment group and the adjusted rate ratio with its 95% CI will be estimated by the model.
- The time to first moderate or severe COPD exacerbation will be analysed using a Cox proportional hazards model including treatment, Country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as factors. A Kaplan-Meier plot will also be presented.

Exploratory efficacy variables

- Change from baseline in pre-dose morning FVC and in 2-hour post-dose FVC at all clinic visits will be analysed using a similar model as for the primary efficacy variables.
- At each clinic visit (from Visit 3 onwards), the change from pre-dose to the 2-hour post-dose value of FVC will be analysed using a similar model as for FEV₁.
- Change from baseline (run-in period) to each inter-visit period and to the entire treatment period in the average EXACT-PRO total score and domain scores will be analysed using similar models as for rescue medication use.

Health economic variables

- Health economic variables will be summarised by treatment group using descriptive statistics.
- The details on other analyses of health economic data will be provided in a separate analysis plan. This health economic analysis will not be part of the Clinical Study Report. A dedicated report will be generated.

12.3.6 Safety variables

- The number and the percentage of patients experiencing adverse events (AEs), adverse drug reactions (ADRs), serious AEs (SAEs), severe AEs, AEs leading to discontinuation and AEs leading to death will be summarised by treatment group. AEs will also be summarised by System Organ Class and Preferred Term using the MedDRA dictionary.
- A similar analysis as the one above defined for all AEs will be performed on major adverse cardiovascular events (MACEs).
- Mean change in vital signs (systolic and diastolic blood pressure) from baseline (Visit 2 pre-dose) to each time point after the first study drug intake and from pre-dose to post-dose at each clinic visit will be calculated with its 95% CI by treatment group.
- Mean change in BMI from baseline (Visit 2) to each clinic visit will be calculated with its 95% CI by treatment group.

- At each time point after the first study drug intake, the mean absolute values of the 12-lead ECG parameters (HR, QTcF, PR and QRS) will be calculated with their 95% CIs by treatment group.
- Change from baseline (Visit 2 pre-dose) in pre-dose 12-lead ECG parameters (HR, QTcF, PR and QRS) will be analysed using a similar model as for the primary efficacy variables. The adjusted means in each treatment group and the adjusted mean differences between treatments will be estimated by the model with their 90% CIs. The same analysis will be performed for change from baseline (Visit 2 pre-dose) in post-dose 12-lead ECG parameters (HR, QTcF, PR and QRS).
- At each visit (from Visit 3 onwards), the change from pre-dose to post-dose in the 12-lead ECG parameters (HR, QTcF, PR and QRS) will be analysed using an ANCOVA model including treatment, Country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as fixed effects, and the pre-dose value at the visit as a covariate. The adjusted means in each treatment group and the adjusted mean differences between treatments will be estimated by the model with their 90% CIs.
- The number and the percentage of patients with a
 - QTcF >450 ms, >480 ms and >500 ms
 - change from baseline (Visit 2 pre-dose) in QTcF >30 ms and >60 ms
 - only for post-dose time points: change from pre-dose at the same visit in QTcF >30 ms and >60 ms

at each time point after the first study drug intake and at any time point after the first study drug intake will be presented by treatment group.

- Change from baseline in 24-hour average HR will be analysed using a similar model as for the primary efficacy variables. The adjusted means in each treatment group and the adjusted mean differences between treatments will be estimated by the model with their 95% CIs.
- The number and the percentage of patients with abnormal findings (including supraventricular arrhythmias, ventricular arrhythmias and non-sustained ventricular tachycardia) in the 24-hour ECG Holter will be summarised by treatment group.
- Mean changes from screening in the laboratory parameters will be calculated with their 95% CIs by treatment group.
- Shift tables from screening to Week 26 and Week 52, with regard to normal range, will be presented by treatment group for the laboratory parameters.

12.3.7 Interim analysis

Interim analysis not planned.

13. ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

The study proposal will be submitted to the Ethics Committee/Institutional Review Board in accordance with the requirements of each country.

The EC/IRB shall give its opinion in writing -clearly identifying the study number, study title and informed consent form approved-, before the clinical trial commences.

A copy of all communications with the EC/IRB will be provided to the Sponsor.

The Investigator should provide written reports to the EC/IRB annually or more frequently if requested on any changes significantly affecting the conduct of the trial and/or increasing risk to the patients (according to the requirements of each country).

14. REGULATORY REQUIREMENTS

The study will be notified to the Health Authorities (or authorized by) according to the legal requirements in each participating country.

Selection of the patients will not start before the approval of the Ethics Committee/Institutional Review Board has been obtained and the study notified to Health Authorities (or authorized by).

The study will be conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practices guidelines and following all other requirements of local laws.

15. INFORMED CONSENT

It is the responsibility of the Investigator to obtain written consent from each patient or from the patient's legal representative prior to any study related procedures taking place.

If the patient and his/her legal representative are unable to read, the informed consent will be obtained in the presence of an impartial witness, eg., a person independent of the study who will read the informed consent form and the written information for the patient.

Consent must be documented by the patient's dated signature. The signature confirms that the consent is based on information that has been understood. Moreover, the Investigator must sign and date the informed consent form.

Each patient's signed informed consent must be kept on file by the Investigator. One copy must be given to the patient.

16. DIRECT ACCESS TO SOURCE DOCUMENTS/DATA

The Investigators or designated must permit trial-related monitoring, audits, Ethics Committee/Institutional Review Board review or regulatory inspection, providing direct access to source data/documents.

17. STUDY MONITORING

Monitoring will be performed by Chiltern who has been designated by Chiesi.

It is understood that the monitor(s) will contact and visit the Investigator/centre before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: case reports form, Investigator study file and source data (source data is any data that is recorded elsewhere to the case report forms), provided that patient confidentiality is respected.

The purposes of these visits are:

- to assess the progress of the study;
- to review the compliance with the study protocol;
- to discuss any emergent problem;
- to check the eCRFs for accuracy and completeness;
- to validate the contents of the CRFs against the source documents;
- to assess the status of drug storage, dispensing and retrieval.
- Prior to each monitoring visit, the Investigator or staff will record all data generated since the last visit on the case report forms. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.
- It is possible that the Investigator site may be audited by Sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

18. QUALITY ASSURANCE

The R&D Quality Assurance Department of Chiesi may perform an audit at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with Good Clinical Practices.

19. INSURANCE AND INDEMNITY

Chiesi holds and will maintain an adequate insurance policy covering damages arising out of Chiesi's sponsored clinical research studies.

Chiesi will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the drug was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and with the study protocol.

The Investigator must notify Chiesi immediately upon notice of any claims or lawsuits.

20. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi.

The Investigator must assure the patient's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the patient's study numbers, names, and (optional) addresses and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi.

21. PREMATURE TERMINATION OF THE STUDY

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.

The Sponsor should submit a written notification to the Regulatory Authority concerned and Ethics Committee/Institutional Review Board providing the justification of premature ending or of the temporary halt.

22. CLINICAL STUDY REPORT

The clinical study report, including the statistical and clinical evaluations, shall be prepared and sent to Co-ordinating Investigator's for agreement and signature.

At the end of the trial a summary of the clinical study report will be provided to all Ethics Committees/Institutional Review Boards, to the Competent Authority of the EU Member State or US concerned and to Investigators.

23. RECORD RETENTION

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file.

Regulations require that essential documents must be retained for at least two years after the final marketing approval in an ICH region or until two years have elapsed since the formal interruption of the clinical development of the product under study.

It is the responsibility of the Sponsor to inform the Investigator of when these documents can be destroyed. The Investigator must contact Chiesi before destroying any trial-related documentation. In addition, all patients' medical records and other source documentation will be kept for the maximum time permitted by the institution.

24. PUBLICATION OF RESULTS

Chiesi is entitled to publish and/or present any results of this study at scientific meetings, and to submit the clinical trial data to national and international Regulatory Authorities. Chiesi furthermore reserves the right to use such data for industrial purposes.

In the absence of a Study Steering Committee, Investigators will inform Chiesi before using the results of the study for publication or presentation, and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual study sites must not be published separately. Negative as well as positive results should be published or otherwise made publicly available.

25. REFERENCES

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APPENDIX I

MINIMUM LIST OF SOURCE DATA REQUIRED

Patients demography file
Patients medical file (diseases, treatments ...)
Study number
Patient identity/number
Randomization number
Medical and surgery history
Previous and concomitant medications
Weight, height
Date of informed consent signature
Date of study visits
Spirometry reports (for test and calibration)
Post-bronchodilator test (when applicable)
Laboratory reports
ECG reports
Questionnaires
Date and time of medication intake
Date and time of investigations
Kits number for run-in period, treatment period and training kits: attribution comparing to the IRT; labels; kit numbers reported in eCRF ...
Labels of study drugs: Use-by-date completed on the labels, ...
Training with pMDI
Examination or assessments carried out during the study
COPD exacerbations
Adverse events / Serious adverse events
If patient is withdrawn, reason
Study end date
Medications on site

APPENDIX II

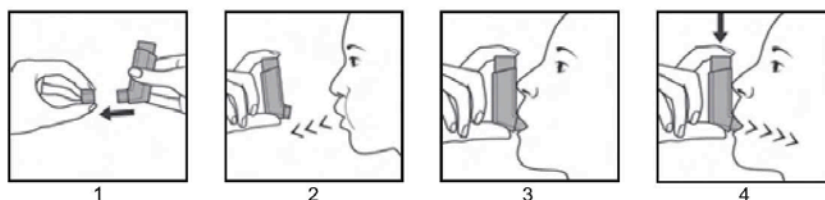
PATIENT LEAFLET (INSTRUCTIONS FOR USE) AND ADMINISTRATION SCHEME

INSTRUCTIONS FOR USE

Before using the inhaler for the first time, or if you have not used the inhaler for 14 days or more, release one puff into the air to make sure the inhaler is working properly.

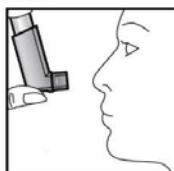
Whenever possible, stand or sit in an upright position when inhaling.

1. Remove the protective cap from the mouthpiece and check that the mouthpiece is clean and free from dust and dirt or any other foreign objects.
2. Breathe out as slowly and deeply as possible.
3. Hold the canister vertically with its body upwards and put your lips around the mouthpiece. Do not bite the mouthpiece.
4. Breathe in slowly and deeply through your mouth and, just after starting to breathe in press down on the top of the inhaler to release one puff.



5. Hold your breath for as long as possible and, finally, remove the inhaler from your mouth and breathe out slowly. Do not breathe into the inhaler. After use, close with the protective cap.

If you need to take another puff, keep the inhaler in the vertical position (see picture below) for about half a minute, then repeat steps 2 to 5.



Important: Do not perform steps 2 to 5 too quickly.

If you see 'mist' coming from the top of the inhaler or the sides of your mouth, this means that the drug will not be getting into your lungs as it should. Take another puff, carefully following the instructions from Step 2 onwards.

If you have weak hands, it may be easier to hold the inhaler with both hands: hold the upper part of the inhaler with both index fingers and its lower part with both thumbs.

To lower the risk of a fungal infection in the mouth and throat, rinse your mouth or gargle with water or brush your teeth each time you use the inhaler.

If the inhaler has been exposed to severe cold, take the canister out of the mouthpiece and warm it with your hands for a few minutes before using. Never warm it by artificial means.

Cleaning:



Remove the cap from the mouthpiece and regularly (once a week) wipe the outside and inside of the mouthpiece with a dry cloth. Do not use water or other liquids to clean the mouthpiece.

ADMINISTRATION SCHEME FOR RUN-IN PERIOD:

ADMINISTRATION SCHEME

RUN-IN Period

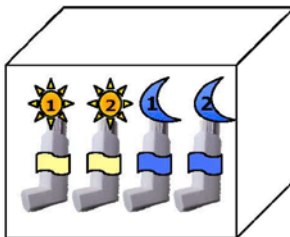




<p>MORNING ADMINISTRATION</p>  <ul style="list-style-type: none">• 2 puffs	<p>EVENING ADMINISTRATION</p>  <ul style="list-style-type: none">• 2 puffs
--	--

ADMINISTRATION SCHEME FOR TREATMENT PERIOD:

ADMINISTRATION SCHEME

TREATMENT Periods



<p>MORNING ADMINISTRATION</p>  <ul style="list-style-type: none">• 1 puff from SUN 1• 1 puff from SUN 2	<p>EVENING ADMINISTRATION</p>  <ul style="list-style-type: none">• 1 puff from MOON 1• 1 puff from MOON 2
--	--

APPENDIX III

INSTRUCTIONS FOR USE OF AEROCHAMBER PLUS™ FLOW-VU ANTISTATIC VHC SPACER



ENGLISH

INTENDED USE

This chamber is intended to be used along with a metered dose inhaler to deliver aerosol medication to your lungs as prescribed by your healthcare provider.



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HOW TO USE YOUR NEW CHAMBER

This chamber can be used directly out-of-package. Before use, ensure these instructions and the instructions supplied with the inhaler have been read.

 1	 2	 3	 4	 5 MOUTHPIECE LARGE MASK
Before use carefully examine the chamber. Replace immediately if any defect is noticed.	Remove caps from inhaler and chamber.	Shake the inhaler immediately before use as per the instructions supplied with it.	Insert the inhaler into the Backpiece of the chamber.	Put mouthpiece into mouth and close lips around it to ensure an effective seal. The Flow-Vu Indicator only moves if you have a good seal.
				Apply mask to face and ensure an effective seal. The Flow-Vu Indicator only moves if you have a good seal.

 6 MOUTHPIECE	 LARGE MASK	 7
Breathe out gently and press the inhaler at the beginning of a slow inhalation. Use the Flow-Vu Indicator to assist in the coordination of this step. Breathe in slowly and deeply through the mouth until a full breath has been taken. Hold breath for 5 – 10 seconds, if possible. Otherwise, keep lips tight on the mouthpiece breathing normally 2 – 3 times through the chamber after inhaler is pressed. SLOW DOWN if you hear the FlowSignal Whistle sound. It means you are inhaling too quickly. Administer one (1) puff at a time.	Breathe out gently and press the inhaler at the beginning of a slow inhalation. Use the Flow-Vu Indicator to count breaths. Maintain seal for 5 – 6 breaths after inhaler is pressed. SLOW DOWN if you hear the FlowSignal Whistle sound. It means you are inhaling too quickly. Administer one (1) puff at a time.	Follow instructions supplied with the inhaler on how long to wait before repeating steps 3 – 6.

CLEANING INSTRUCTIONS


This chamber can be used right out-of-package and then cleaned weekly.

<p>Backpiece</p> <p>1</p> <p>Frontpiece</p>	<p>2</p>	
<p>Remove the Backpiece. To detach the Frontpiece, twist chamber as shown above. Remove mouthpiece cap. (if applicable)</p>	<p>Soak the parts for 15 minutes in a mild solution of liquid dish detergent and lukewarm clean water. Agitate gently. Rinse parts in clean water.</p>	<p>Place parts in top rack of dishwasher. Ensure product is securely placed face up as pictured. OR Run the dishwasher on a normal or light cycle and avoid heated dry. Do not boil or sterilize.</p>
<p>Backpiece</p> <p>1</p> <p>Frontpiece</p>	<p>2</p>	

<p>3</p>	<p>4</p>	<p>5</p> <p>Alignment Feature</p> <p>Flow-Vu[®] Indicator</p>	<p>Notes:</p> <ul style="list-style-type: none"> • Product should be replaced after 12 months of use. • This product contains no latex. • Do not share this medical device. • If you notice medication build-up in your chamber, wash the inside of the chamber gently with a soft cloth. • Dishwashing with overly dirty dishes is not recommended. • If cleaning in a dishwasher use a rinse aid. <p>⚠ Cautions:</p> <ul style="list-style-type: none"> • Do not leave the chamber unattended with children. This is not a toy. • Product may be permanently damaged if boiled, sterilized or cleaned in a dishwasher at a temperature above 70°C.
<p>Shake out excess water and allow to air dry in a vertical position. Ensure parts are dry before reassembly.</p>	<p>To reassemble, fit the Frontpiece on the end of the chamber and twist firmly until securely locked into position. For mouthpiece models, the protective cap should always be placed on the mouthpiece when the chamber is not in use.</p>	<p>Center the Alignment Feature on the Backpiece with the Flow-Vu[®] Indicator, as shown. Press firmly to attach the Backpiece.</p>	
		<p>Alignment Feature</p> <p>Flow-Vu[®] Indicator</p>	

APPENDIX IV

SAMPLE OF PATIENT CARD

<p>In case of emergency please contact:</p> <p>Study Doctor :</p> <p>Name of the Hospital (if applicable):</p> <p>Phone number : .</p> <p>If your study Doctor is not available please contact your family Doctor</p> <p>Mr/Mrs is actually involved in the clinical trial CCD-1207-PR-0091 (EudraCT N° 2013-001057-27) concerning COPD treatment:</p> <p>Patient N° : </p> <p><u>Investigational substances</u> (start at Visit 2 for 52 weeks):</p> <p>- CHF 1535 pMDI 100/6 µg HFA (Foster®) fixed combination of corticosteroid and bronchodilating drug (beclometasone dipropionate/formoterol fumarate 100/6 µg per metered dose) (total daily dose 400/24 µg)</p> <p>or</p> <p>- CHF 5993 pMDI 100/6/12.5 µg HFA, fixed combination of corticosteroid and two bronchodilating drugs (beclometasone dipropionate/ formoterol fumarate/ glycopyrrolate bromide 100/6/12.5 µg per metered dose) (total daily dose 400/24/50 µg)</p> <p>English version</p>	<p></p> <p>Please keep always this Card with You</p> <p>Study start date : </p> <p>Planned visits :</p> <p>Visit 1 : at : </p> <p>Visit 2 : at : </p> <p>Visit 3 : at : </p> <p>Visit 4 : at : </p> <p>Visit 5 : at : </p> <p>Visit 6 : at : </p> <p>Visit 7 : at : </p> <p><u>Run-in medication</u> (start at Visit 1 for 2 weeks): CHF 1535 pMDI (Foster®) combination of corticosteroid and bronchodilating drug (beclometasone dipropionate/ formoterol fumarate 100/6 µg per metered dose) (total daily dose 400/24 µg)</p> <p>Please remember:</p> <ul style="list-style-type: none">➤ No inhalation of the run-in medication or study treatments in the morning of the visit.➤ No rescue medication inhalation 6 hours before the visit (except in the case of emergency). <p>Local CRO information (only if requested by the local law)</p> <p>English version</p>
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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4 and 7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5 (none)
Participants	4a	Eligibility criteria for participants	5-6 and supplement
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	5 (none)
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11 and Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	11
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Throughout results
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Throughout results
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	16 (exacerbation data)
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	All results are from prespecified analyses. Co-primary and exploratory endpoints are distinguished
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Table 4
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	22-3
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	24
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	24

Other information

Registration	23	Registration number and name of trial registry	8
Protocol	24	Where the full trial protocol can be accessed, if available	5 (provided as supplementary material)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10 and 28

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.