Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY)

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Title: Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial

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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 compared extrafine beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB; 'fixed triple') with tiotropium and BDP/FF+tiotropium ('open triple').
Methods
Eligible patients had COPD, post-bronchodilator forced expiratory volume in 1s (FEV1) <50%, ≥1 moderate-to-severe COPD exacerbation in the previous 12 months, and COPD Assessment Test total score ≥10. After a 2-week run-in period receiving open-label tiotropium 18µg, one inhalation once daily (OD) via single-dose dry-powder inhaler (SDDPI; HandiHaler), patients were randomised (2:2:1) to 52 weeks with: tiotropium, one inhalation OD via SDDPI; BDP/FF/GB 100/6/12·5µg, two actuations twice daily (BID) via pressurised metered-dose inhaler (pMDI); or BDP/FF 100/6µg, two actuations BID via pMDI + tiotropium 18µg, one inhalation OD via SDDPI. Primary endpoint: moderate-to-severe COPD exacerbation rate. Key secondary: change from baseline in pre-dose FEV1 at Week 52. ClinicalTrials.gov: NCT01911364.
Findings
The study ran between January 21, 2014, and March 18, 2016. A total of 2691 patients were randomised to fixed triple (n=1078), tiotropium (n=1075) or open triple (n=538). Moderate-to-severe exacerbation rates (95%CI) were 0·46 (0·41, 0·51), 0·57 (0·52, 0·63) and 0·45 (0·39, 0·52) for fixed triple, tiotropium and open triple; fixed triple was superior to tiotropium (rate ratio 0·80 [95%CI 0·69, 0·92]; p=0·003). For Week 52 pre-dose FEV1, fixed triple was superior to tiotropium (mean difference 0·061L [0·037, 0·086]; p<0·0001) and non-inferior to open triple (-0·003L [-0·033, 0·027]; p=0·852). Adverse events were reported by 594 (55%) patients with fixed triple, 622 (58%) with tiotropium and 309 (58%) with open triple.
Interpretation

In TRINITY, treatment with extrafine fixed triple had clinical benefits compared to tiotropium in patients with symptomatic COPD, FEV1 <50% and an exacerbation history.

Funding
Chiesi Farmaceutici SpA.

Title

Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial

Authors

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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 compared extrafine beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB; 'fixed triple') with tiotropium and BDP/FF+tiotropium ('open triple').

Methods

Eligible patients had COPD, post-bronchodilator forced expiratory volume in 1s (FEV_1) <50%, ≥1 moderate-to-severe COPD exacerbation in the previous 12 months, and COPD Assessment Test total score ≥10. After a 2-week run-in period receiving open-label tiotropium 18µg, one inhalation once daily (OD) via single-dose dry-powder inhaler (SDDPI; HandiHaler), patients were randomised (2:2:1) to 52 weeks with: tiotropium, one inhalation OD via SDDPI; BDP/FF/GB 100/6/12·5µg, two actuations twice daily (BID) via pressurised metered-dose inhaler (pMDI); or BDP/FF 100/6µg, two actuations BID via pMDI + tiotropium 18µg, one inhalation OD via SDDPI. Primary endpoint: moderate-to-severe COPD exacerbation rate. Key secondary: change from baseline in pre-dose FEV_1 at Week 52. ClinicalTrials.gov: NCT01911364.

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open triple (–0·003L [–0·033, 0·027]; p=0·852). Adverse events were reported by 594 (55%) patients with fixed triple, 622 (58%) with tiotropium and 309 (58%) with open triple.

Interpretation

In TRINITY, treatment with extrafine fixed triple had clinical benefits compared to tiotropium in patients with symptomatic COPD, FEV_1 <50% and an exacerbation history.

Funding

Chiesi Farmaceutici SpA.

Introduction

COPD is a progressive disease, characterised by the presence of symptoms and exacerbations.[1] Much of the burden of COPD is due to exacerbations, which are associated with increased disease progression, reduced quality of life, and increased costs (especially hospitalisation).[2–5] In patients at risk of exacerbations, most current guidelines recommend starting with either a long-acting muscarinic antagonist or a combination of an inhaled corticosteroid and a long-acting β_2-agonist.[1,6] 'Triple therapy' with an inhaled corticosteroid, a long-acting β_2-agonist and a long-acting muscarinic antagonist is recommended in patients with exacerbations despite initial treatment,[1,6] and is frequently used for the management of COPD. However, few studies have addressed the added value of triple therapy for preventing exacerbations. Although two 12-week studies have suggested that triple therapy can provide a greater reduction in exacerbations compared with a long-acting muscarinic antagonist,[7,8] longer trials are needed to assess moderate and severe exacerbations, not least because of their marked seasonality.[9] Only one long term study has compared triple therapy to a long-acting muscarinic antagonist; there was no reduction in exacerbation rate over 12 months.[10] However, this study did not evaluate the clinical efficacy of a triple therapy delivered in a single inhaler.

Currently, patients with COPD receiving triple therapy must use at least two inhalers, typically a combined inhaled corticosteroid plus long-acting β_2-agonist in one inhaler and a long-acting muscarinic antagonist in a second. Often these inhalers are of different types and designs, which may in turn negatively impact correct inhaler use and treatment adherence. A single inhaler combining extrafine formulations of the inhaled corticosteroid beclometasone dipropionate (BDP), the long-acting β_2-agonist formoterol fumarate (FF) and the long-acting muscarinic antagonist glycopyrronium bromide (GB) has been developed to simplify this regime, with extrafine formulations able to reach and treat not only the large but also the small airways.[11] In the TRINITY study that we describe in this manuscript, we evaluated the benefits of extrafine BDP/FF/GB ('fixed triple') over a monotherapy long-acting

muscarinic antagonist, tiotropium, with a free combination of BDP/FF in one inhaler and tiotropium in a second inhaler (‘open triple’) as control. The primary hypothesis was that fixed triple would be superior to tiotropium in terms of the moderate and severe COPD exacerbation rate over 52 weeks of treatment.

Methods

Study design

TRINITY was a randomised, parallel group, double-blind, double-dummy, active-controlled study, conducted in 224 sites across 15 countries. The sites were a mixture of primary (n=17), secondary (n=121) and tertiary care (n=48), and specialist investigation units (38).

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 tiotropium 18 µg, one inhalation once daily (in the morning) via single-dose dry-powder inhaler (SDDPI; HandiHaler [Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany]). At the end of the 2-week run-in (Visit 2), patients were randomised with a 2:2:1 ratio to one of three treatment groups: 1) to continue to receive tiotropium 18 µg, one inhalation once daily via SDDPI, or 2) to receive extrafine BDP/FF/GB 100/6/12·5 µg, two actuations twice daily via pressurised metered-dose inhaler (pMDI), or 3) extrafine BDP/FF 100/6 µg, two actuations twice daily via pMDI + tiotropium 18 µg, one inhalation once daily via SDDPI. 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 as needed (100 µg per actuation, via pMDI), but 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); long-acting β_2-agonists (12 h; 72 h for ultra-long-acting β_2-agonists); long-acting muscarinic antagonists (72 h); inhaled corticosteroids (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). There were no protocol amendments.

Patients

The main inclusion criteria were: ≥40 years of age; current or ex-smokers; diagnosis of COPD, with post-bronchodilator (salbutamol 400 µg) forced expiratory volume in 1 second (FEV_1) <50% and a ratio of FEV_1 to forced vital capacity <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 for at least 2 months prior to screening of inhaled corticosteroid plus long-acting β_2-agonist (as an open or fixed combination), or inhaled corticosteroid plus long-acting muscarinic antagonist, or inhaled long-acting β_2-agonist plus long-acting muscarinic antagonist (as an open or fixed combination), or long-acting muscarinic antagonist monotherapy (patients receiving triple therapy of inhaled corticosteroid, long-acting β_2-agonist and long-acting muscarinic antagonist were not eligible). In addition, all patients were to be symptomatic, with a COPD Assessment Test total score ≥10. 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; COPD exacerbation in the 4 weeks prior to screening or during the run-in period; clinically significant cardiovascular conditions or laboratory abnormalities (including persistent, long-standing or permanent atrial fibrillation); or unstable concurrent disease that may have impacted efficacy or safety (as judged by the investigator). The full inclusion and exclusion criteria are in the appendix.

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 in the ratio 2:2:1 to fixed triple, tiotropium or open triple. Randomisation was stratified by country and severity of airflow limitation (post-bronchodilator FEV_1 categories <30% predicted, or 30% to <50% predicted, with a minimum of 20% of recruited patients to be <30% predicted). Patients, investigators, site staff and sponsor personnel were blinded to treatment assignment for the duration of the study. To achieve this blinding,

a double-dummy approach was used, with all patients using a pMDI twice daily (containing BDP/FF/GB, BDP/FF or placebo) and an SDDPI once daily (containing tiotropium or placebo).

Procedures

At Visit 2, baseline (pre-dose) data were collected for spirometry and St George's Respiratory Questionnaire (SGRQ, a measure of health-related quality of life). FEV_1 was determined from forced spirometry manoeuvres, with inspiratory capacity [IC] determined from slow spirometry (IC is a measure of hyperinflation). At each subsequent visit, pre-dose (morning) spirometry was conducted (with centralised spirometry used to improve the quality), and data were collected from the SGRQ. 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

The primary objective was to demonstrate superiority of fixed triple over tiotropium in terms of moderate-to-severe COPD exacerbation rate over 52 weeks of treatment. The two key secondary objectives were both based on change from baseline in pre-dose FEV_1 at Week 52 – to demonstrate superiority of fixed triple over tiotropium, and to demonstrate non-inferiority of fixed triple relative to open triple. The secondary efficacy variables were: time to first moderate-to-severe, and to first severe COPD exacerbation; rate of severe and of moderate COPD exacerbations over 52 weeks of treatment; pre-dose FEV_1 at all the other clinic visits and averaged over the treatment period; FEV_1 response (change from baseline in pre-dose FEV_1 ≥100 mL) at Weeks 26 and 52; pre-dose IC at all clinic visits; SGRQ response (decrease from baseline in total score ≥4, which is the minimal clinically important difference [12]) at Weeks 26 and 52; SGRQ total score at all clinic visits; and percentage of days without rescue medication use and average number of puffs per day. For all variables,

the following comparisons were prespecified: fixed triple vs tiotropium; fixed triple vs open triple; open triple vs tiotropium.

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, antibiotics, or hospital admission, or a combination of these.[13] Events were classified as moderate or severe according to European Medicines Agency/Committee for Medicinal Products for Human Use guidelines,[13] with severe exacerbations being those requiring hospital admission 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.

Treatment-emergent adverse events 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 adverse events. Blood pressure was recorded pre-dose and at 10 min post-dose at each visit, with electrocardiogram (ECG) data captured at the same time points at Weeks 26 and 52. Major adverse cardiovascular events were adjudicated by an independent adjudication committee, comprising four cardiologists.

Statistical analysis

We estimated that 2580 randomly assigned patients (1032 patients in each of the fixed triple and tiotropium groups, and 516 in the open triple group) would be required, considering non-assessable rates of approximately 13%, 16·5% and 20% at Weeks 12, 26 and 52, respectively. With the use of a two-sided significance level of 0·05, this sample size provided an overall study power of 80%, and in particular: (1) 93·3% power to detect a rate ratio of 0·8 for moderate-to-severe COPD exacerbations between the fixed triple and tiotropium groups, using a negative binomial model and assuming a rate of 0·9 exacerbations per patient per year in the tiotropium group and an over-dispersion parameter of the negative binomial

193 distribution of 0·56; (2) 99·7% power to detect a mean difference of 60 mL between fixed
194 triple and tiotropium in pre-dose FEV_1 at Week 52, assuming a standard deviation (SD) of
195 260 mL; (3) assuming 9% of completed patients with major protocol deviations, 86·0%
196 power to demonstrate the non-inferiority of fixed triple relative to open triple in pre-dose
197 FEV_1 at Week 52 in the per protocol population, with a non-inferiority margin of –50 mL and
198 assuming no difference between treatments and a SD of 260 mL (one-sided significance
199 level of 0·025).

200 The number of moderate-to-severe COPD exacerbations (primary endpoint) was analysed
201 using a negative binomial model including treatment, country, number of COPD
202 exacerbations in the previous year, severity of airflow limitation and smoking status at
203 screening as fixed effects, and log-time on study as an offset. Two COPD exacerbations
204 were considered as a single episode in the statistical analysis if the second exacerbation
205 started less than 10 days after the end of the systemic corticosteroids and/or antibiotics
206 intake for the previous exacerbation. The change from baseline in pre-dose FEV_1 (key
207 secondary endpoint) was analysed using a linear mixed model for repeated measures
208 (MMRM), with data up to discontinuation included in the analysis for withdrawn patients. This
209 model included treatment, visit, treatment by visit interaction, country, number of COPD
210 exacerbations in the previous year, severity of airflow limitation and smoking status at
211 screening as fixed effects, and baseline value and baseline by visit interaction as covariates.

212 To deal with multiplicity, the primary and the key secondary comparisons were performed in
213 the following prespecified hierarchical order: (1) superiority of fixed triple over tiotropium in
214 terms of moderate-to-severe COPD exacerbation rate; (2) superiority of fixed triple over
215 tiotropium in terms of pre-dose FEV_1; (3) non-inferiority of fixed triple relative to open triple in
216 terms of pre-dose FEV_1. At each step of the procedure, no confirmatory claims were to be
217 made unless the objectives were met in all the preceding steps. No multiplicity adjustments
218 were applied in the analysis of secondary endpoints, and for these variables p-values were
219 interpreted descriptively. Subgroup analyses of the primary and key secondary endpoints

were prespecified, with patients grouped according to severity of airflow limitation, smoking status, sex, reversibility to salbutamol, COPD phenotype (chronic bronchitis, emphysema, or mixed), blood eosinophil concentration at screening, and age, with the primary endpoint also analysed according to presence of cardiovascular comorbidities and number of exacerbations in the previous 12 months. Sensitivity analyses were performed on the primary and key secondary endpoints to assess the potential impact of missing data, as described in the appendix.

The severe and moderate exacerbation rates were analysed using the same model as the primary endpoint. The times to first exacerbation were analysed using a Cox proportional hazards model, and the responder analyses for FEV_1 and SGRQ were conducted using a logistic model. In these models, the same fixed effects as in the analysis of the primary endpoint were included, with the baseline value also considered in the responder analyses. The changes from baseline in pre-dose IC, SGRQ total score and rescue medication use endpoints were analysed using a similar MMRM model as for the key secondary endpoint.

Primary, key secondary, and other secondary endpoints were analysed in the intention-to-treat population classified as all randomly assigned patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment. Non-inferiority of the key secondary endpoint was also tested in the per-protocol population, classified as all patients in the intention-to-treat population with no major protocol deviations. Safety outcomes were analysed in the safety population, which was classified as all randomly assigned patients who received at least one dose of study drug. An independent Data Safety Monitoring Board, composed of three independent clinicians and one independent biostatistician, provided a quarterly independent scrutiny of the study. All analyses presented in this manuscript were done with SAS software, version 9·2. The study is registered with ClinicalTrials.gov, number NCT01911364.

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 (JV) responsible for the decision to submit for publication.

Results

The study ran between January 21, 2014, and March 18, 2016. We recruited 3433 patients to the study, of whom 2691 were randomly assigned to one of the treatment groups (1078 to fixed triple, 1075 to tiotropium and 538 to open triple), with 986 (91·5%) completing the study in the fixed triple group, 914 (85·0%) in the tiotropium group, and 496 (92·2%) in the open triple group, see Figure 1. Patients in the tiotropium group were significantly more likely to prematurely withdraw from the study than either of the other two groups (p<0·0001). Compliance to treatment was high, with a median of 94·6%, 94·3% and 94·9% of doses taken in the fixed triple, tiotropium and open triple groups, respectively. Median exposure in all three groups was 365·0 days, with ranges of 3–402, 1–403 and 4–399 for fixed triple, tiotropium and open triple, respectively. Baseline characteristics of the recruited patients are shown in Table 1. More than 83% of patients had at least one concomitant disease. Cardiac disorders were reported in 41% of the patients in the fixed triple group, 43% of the patients in the tiotropium group and 40% of the patients in the open triple group.

Table 1. Baseline characteristics (Safety population)

	Fixed triple (N=1077)	**Tiotropium (N=1076)**	**Open triple (N=537)**
Sex, n (%)			
Male	829 (77·0)	830 (77·1)	397 (73·9)
Female	248 (23·0)	246 (22·9)	140 (26·1)
Race, n (%)			
White	1067 (99·1)	1071 (99·5)	532 (99·1)
Black/African American	1 (0·1)	0 (0·0)	0 (0·0)
Other	9 (0·8)	5 (0·5)	5 (0·9)
Age (years), mean (SD)	63·4 (8·7)	63·3 (8·4)	62·6 (8·9)
Body-mass index (kg/m²), mean (SD)	26·4 (5·1)	26·2 (4·7)	26·3 (5·3)
Blood leukocyte concentration (10^9/L), mean (SD)	7·68 (2·19)	7·71 (2·09)	7·83 (2·32)
Blood eosinophil concentration (10^9/L), mean (SD)	0·20 (0·17)	0·20 (0·17)	0·20 (0·17)
Blood eosinophil proportion (%)	2·63 (2·19)	2·67 (2·24)	2·66 (2·17)
Smoking status, n (%)			
Ex-smoker	560 (52·0)	573 (53·3)	271 (50·5)

	Fixed triple (N=1077)	Tiotropium (N=1076)	Open triple (N=537)
Current smoker	517 (48·0)	503 (46·7)	266 (49·5)
Time since first COPD diagnosis (years), mean (SD)	7·9 (5·6)	8·2 (6·1)	7·8 (5·4)
FEV_1 (L), mean (SD)*	1·117 (0·330)	1·119 (0·312)	1·127 (0·331)
FEV_1 % of predicted normal value, mean (SD)*	36·6 (8·3)	36·6 (8·1)	36·7 (8·3)
<30%, n (%)	228 (21·2)	229 (21·3)	113 (21·0)
≥30% and <50%, n (%)	849 (78·8)	847 (78·7)	424 (79·0)
FVC (L), mean (SD)*	2·713 (0·774)	2·716 (0·763)	2·743 (0·790)
FEV_1/FVC ratio*, mean (SD)	0·42 (0·10)	0·43 (0·11)	0·42 (0·10)
Reversibility (%), mean (SD)	7·8 (14·0)	7·3 (13·6)	8·6 (14·7)
Inspiratory capacity (L), mean (SD)	1·975 (0·585)	1·962 (0·588)	1·948 (0·589)
Chronic bronchitis†, n (%)	772 (71·7)	781 (72·6)	383 (71·3)
Exacerbation rate in the previous year (range)	1·3 (1, 11)	1·3 (1, 5)	1·2 (1, 7)
CAT total score, mean (SD)	21·5 (5·8)	21·6 (5·8)	21·7 (6·0)
COPD medication at study entry, n (%)			
ICS/LABA	802 (74·5)	804 (74·7)	378 (70·4)
ICS/LAMA	37 (3·4)	30 (2·8)	18 (3·4)
LABA/LAMA	125 (11·6)	124 (11·5)	74 (13·8)
LAMA	113 (10·5)	118 (11·0)	67 (12·5)
Spacer use during the study, n (%)	207 (19·2)	211 (19·6)	112 (20·9)
Patients with at least one concomitant disease, n (%)‡	904 (83·9)	900 (83·6)	446 (83·1)
Hypertension	616 (57·2)	608 (56·5)	293 (54·6)
Ischaemic heart disease	331 (30·7)	351 (32·6)	157 (29·2)
Myocardial ischaemia	187 (17·4)	194 (18·0)	86 (16·0)
Coronary artery disease	119 (11·0)	134 (12·5)	65 (12·1)
Angina pectoris	47 (4·4)	48 (4·5)	22 (4·1)
Ischaemic cardiomyopathy	5 (0·5)	9 (0·8)	0 (0·0)
Myocardial infarction	2 (0·2)	1 (0·1)	4 (0·7)
Cardiac failure	201 (18·7)	197 (18·3)	92 (17·1)
Diabetes mellitus	109 (10·1)	102 (9·5)	61 (11·4)
Arteriosclerosis coronary artery	86 (8·0)	83 (7·7)	43 (8·0)
Osteochondrosis	53 (4·9)	59 (5·5)	28 (5·2)
Cholecystitis chronic	49 (4·5)	49 (4·6)	27 (5·0)
Obesity	53 (4·9)	40 (3·7)	30 (5·6)

FEV_1 = 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. *Measured after salbutamol was administered. †Includes patients with a mixed chronic bronchitis and emphysema phenotype. ‡Only diseases where 5% of patients or more were affected in any group are included here.

The rates of moderate-to-severe COPD exacerbations were 0·46, 0·57 and 0·45 per patient per year for fixed triple, tiotropium and open triple, respectively (Figure 2a). Extrafine fixed triple was superior to tiotropium, with an adjusted rate ratio of 0·80 (95% CI 0·69, 0·92; p=0·003), indicating a significant 20% reduction in the rate with fixed triple (Figure 2a). The rates of moderate-to-severe exacerbations were similar with fixed triple and open triple, with an adjusted rate ratio of 1·01 (95% CI 0·85, 1·21; p=0·887) (Figure 2a). The results of the subgroup analyses are shown in the appendix. Of note, compared with tiotropium monotherapy, the effect of the two triple therapies on exacerbation rate was greater in the subgroups with higher eosinophil concentrations. In the subgroup with eosinophil count ≥2%, the triple therapies significantly reduced exacerbation rates vs tiotropium by 30% (rate ratio: 0·70 [95% CI: 0·58, 0·85]) and 31% (0·69 [0·55, 0·87]) for fixed and open triple, respectively; corresponding reductions in the <2% subgroup were 7% (0·93 [0·75, 1·17]) and 9% (0·91 [0·69, 1·20]). In the subgroup with eosinophil count ≥$0{\cdot}2x10^9$ cells/L, the reductions were 36% (0·64 [0·51, 0·81]) and 38% (0·62 [0·47, 0·83]) for fixed and open triple, respectively; in the <$0{\cdot}2x10^9$ cells/L subgroup, reductions were 8% (0·92 [0·77, 1·10]) and 9% (0·91 [0·72, 1·14]). In addition, compared with open triple, fixed triple significantly reduced the rate of moderate-to-severe exacerbations in the subgroup of patients with more than one exacerbation in the previous 12 months (0·71 [0·51, 0·995]).

The time to first moderate-to-severe exacerbation was significantly extended with fixed triple vs tiotropium, with a hazard ratio (HR) of 0·84 (95% CI 0·72, 0·97; p=0·015; Figure 2b). Fixed triple and open triple showed similar effects on this variable (HR 1·06 [95% CI 0·88, 1·27]; p=0·569). Fixed triple significantly reduced the rate of severe exacerbations compared with tiotropium by 32%, and of moderate exacerbations by 16%, with similar rates to open triple (Figure 2c). The time to first severe exacerbation was significantly prolonged with fixed

triple compared with tiotropium (HR 0·70 [95% CI 0·52, 0·95]; p=0·021), and was similar for fixed triple and open triple (HR 1·05 [95% CI 0·70, 1·57]; p=0·822).

The adjusted mean changes from baseline in pre-dose FEV_1 at Week 52 (the key secondary efficacy variable) were 0·082 L (95% CI 0·065, 0·100), 0·021 L (0·003, 0·039) and 0·085 L (0·061, 0·110) for fixed triple, tiotropium and open triple, respectively. Both of the key secondary objectives were met, with fixed triple superior to tiotropium (adjusted mean difference 0·061 L [95% CI 0·037, 0·086]; p<0·0001) and non-inferior to open triple (–0·003 L [–0·033, 0·027]; p=0·852) in pre-dose FEV_1 at Week 52. Non-inferiority between fixed triple and open triple was confirmed in the per-protocol population. The results of the subgroup analyses were broadly consistent with the overall results (appendix). For this endpoint, eosinophil levels did not consistently influence the results.

For pre-dose FEV_1 at all other visits and averaged over the treatment period, fixed triple was superior to tiotropium and similar to open triple (Figure 3a). Averaged over the treatment period, the adjusted mean changes from baseline in pre-dose FEV_1 were 0·080 L (0·067, 0·093), 0·022 L (0·009, 0·036) and 0·091 L (0·073, 0·110) with fixed triple, tiotropium and open triple, respectively. The adjusted mean difference between fixed triple and tiotropium was statistically significant (0·058 L [0·039, 0·077]; p<0·0001), whereas the values were similar for fixed triple and open triple (difference –0·011 L [–0·034, 0·012]; p=0·337). In terms of FEV_1 change from baseline, patients were more likely to respond (response defined as ≥100 mL increase) to fixed triple than to tiotropium at both Weeks 26 and 52 (Table 2), with a similar percentage of responders in the fixed triple and open triple groups. Fixed triple was also superior to tiotropium for change from baseline in pre-dose IC; and was similar to open triple at all visits except Week 12 (Figure 3b).

Table 2. FEV_1 and SGRQ responder analysis (intention-to-treat population)

	Responders, n (%)			Odds ratio (95% CI)		
	Fixed triple (N=1077)	**Tiotropium (N=1074)**	**Open triple (N=538)**	**Fixed triple vs tiotropium**	**Fixed triple vs open triple**	**Open triple vs tiotropium**
FEV_1[a]						
Week 26	421 (39·1)	306 (28·5)	204 (37·9)	1·61 (1·34, 1·93); p<0·0001	1·04 (0·84, 1·30); p=0·694	1·54 (1·23, 1·92); p=0·0001
Week 52	408 (37·9)	295 (27·5)	210 (39·0)	1·62 (1·35, 1·95); p<0·0001	0·95 (0·76, 1·18); p=0·627	1·71 (1·37, 2·13); p<0·0001
SGRQ[b]						
Week 26	508 (47·2)	438 (40·8)	276 (51·3)	1·32 (1·10, 1·57); p=0·002	0·81 (0·65, 1·00); p=0·049	1·63 (1·32, 2·02); p<0·0001
Week 52	494 (45·9)	423 (39·4)	254 (47·2)	1·33 (1·11, 1·59); p=0·002	0·91 (0·73, 1·13); p=0·373	1·47 (1·18, 1·83); p=0·0006

a. Response defined as ≥100 mL increase from baseline; b. Response defined as ≥4 units decease from baseline. SGRQ = St George's Respiratory Questionnaire.

More patients on fixed triple than on tiotropium alone were responders in terms of SGRQ total score (decrease from baseline ≥4 units) at both Weeks 26 and 52, with a similar percentage of responders in the two triple therapy groups at the end of the study (Table 2). Fixed triple was associated with a significantly greater improvement in mean SGRQ total score than tiotropium at all time points except Week 26, and a similar mean change from baseline in SGRQ total score to open triple at most timepoints, with the exception of Weeks 26 and 52 (appendix). Compared with the group of patients receiving fixed triple, those receiving tiotropium required significantly more rescue medication, both when analysed in terms of puffs per day and the percentage of days with no use, with rescue medication use similar in the fixed triple and open triple groups (appendix).

A similar proportion of patients had adverse events in the three groups (Table 3). Most events were mild or moderate in severity. Pneumonia was reported in a small number of patients, with similar incidence in the three treatment groups (2·6%, 1·8% and 2·2% for fixed

triple, tiotropium and open triple, respectively). One serious adverse event occurred in one (0·1%) patient in the tiotropium group. This was an episode of angina pectoris, considered moderate in severity, and although the patient fully recovered it resulted in withdrawal from the study. Fewer patients experienced adverse events leading to discontinuation of study drug in the two triple therapy groups than in the tiotropium group. The most common adverse event leading to study drug discontinuation was COPD exacerbation (8 [0·7%], 14 [1·3%] and 5 [0·9%] patients in the fixed triple, tiotropium and open triple groups, respectively). Adverse events resulted in a total of 57 deaths, with the highest percentage of patients with fatal events in the tiotropium group, and similar percentages in the two triple therapy groups. None of the deaths were considered related to study treatment.

Table 3. Adverse events and serious adverse events (≥2% in any group for adverse events and ≥0·5% in any group for serious adverse events and treatment-related adverse events) (Safety population).

Number (%) of patients	**Fixed triple (N=1077)**	**Tiotropium (N=1076)**	**Open triple (N=537)**
Adverse events	594 (55·2)	622 (57·8)	309 (57·5)
COPD	351 (32·6)	383 (35·6)	167 (31·1)
Nasopharyngitis	57 (5·3)	66 (6·1)	20 (3·7)
Headache	43 (4·0)	41 (3·8)	18 (3·4)
Dyspnoea	23 (2·1)	37 (3·4)	8 (1·5)
Pneumonia	28 (2·6)	19 (1·8)	12 (2·2)
Ischaemic heart disease	22 (2·0)	22 (2·0)	9 (1·7)
Angina pectoris	10 (0·9)	8 (0·7)	5 (0·9)
Myocardial ischaemia	6 (0·6)	3 (0·3)	3 (0·6)
Coronary artery disease	3 (0·3)	5 (0·5)	1 (0·2)
Myocardial infarction	4 (0·4)	3 (0·3)	0 (0·0)
Acute coronary syndrome	0 (0·0)	1 (0·1)	0 (0·0)
Coronary artery insufficiency	0 (0·0)	1 (0·1)	0 (0·0)
Ischaemic cardiomyopathy	0 (0·0)	1 (0·1)	0 (0·0)
Cough	18 (1·7)	23 (2·1)	9 (1·7)
Respiratory tract infection, viral	15 (1·4)	15 (1·4)	13 (2·4)
Serious adverse events	140 (13·0)	164 (15·2)	68 (12·7)

Number (%) of patients	**Fixed triple (N=1077)**	**Tiotropium (N=1076)**	**Open triple (N=537)**
COPD	76 (7·1)	100 (9·3)	35 (6·5)
Pneumonia	21 (1·9)	14 (1·3)	9 (1·7)
Ischaemic heart disease	10 (0·9)	11 (1·0)	4 (0·7)
Myocardial infarction	4 (0·4)	3 (0·3)	0 (0·0)
Myocardial ischaemia	3 (0·3)	1 (0·1)	3 (0·6)
Coronary artery disease	2 (0·2)	4 (0·4)	0 (0·0)
Angina pectoris	1 (0·1)	2 (0·2)	1 (0·2)
Acute coronary syndrome	0 (0·0)	1 (0·1)	0 (0·0)
Cardiac failure	5 (0·5)	11 (1·0)	3 (0·6)
Treatment-related adverse events	25 (2·3)	33 (3·1)	27 (5·0)
Dry mouth	5 (0·5)	10 (0·9)	10 (1·9)
Muscle spasms	6 (0·6)	0 (0·0)	3 (0·6)
Dysphonia	3 (0·3)	2 (0·2)	3 (0·6)
Oral candidiasis	3 (0·3)	2 (0·2)	3 (0·6)
Treatment-related serious adverse events	0 (0·0)	1 (0·1)	0 (0·0)
Severe adverse events	91 (8·4)	100 (9·3)	34 (6·3)
Adverse events leading to study drug discontinuation	33 (3·1)	62 (5·8)	15 (2·8)
Adverse events leading to death	20 (1·9)	29 (2·7)	8 (1·5)
All MACEs	20 (1·9)	23 (2·1)	7 (1·3)

COPD = chronic obstructive pulmonary disease exacerbations. MACE = major adverse cardiovascular events, including acute myocardial infarction, arrhythmias, cardiovascular death, heart failure and stroke.

Mean changes in blood pressure, heart rate and Fridericia's corrected QT (QTcF) interval were small, with no clinically relevant differences between the three groups (treatment differences in change from screening to pre-dose and post-dose at Weeks 26 and 52 are shown in the appendix [Tables 2 and 4], together with the comparisons between pre-dose and post-dose values [Tables 3 and 5] and the largest changes in blood pressure). The percentages of abnormal QTcF interval absolute values and changes were similar in all groups (appendix).

Discussion

The study met the primary and both key secondary endpoints. Extrafine fixed triple resulted in a 20% reduction in the rate of moderate-to-severe COPD exacerbations compared with tiotropium, together with a 0·061 L mean improvement in pre-dose FEV_1. Furthermore, the non-inferiority of fixed triple relative to open triple was demonstrated for pre-dose FEV_1. Fixed triple reduced both moderate and severe exacerbation rates, hyperinflation (as measured by IC) and rescue medication use, with a greater percentage of SGRQ responders compared to tiotropium, and effects generally similar to open triple.

The 20% improvement in exacerbation rates with fixed triple over tiotropium (a first-line treatment in this population[1]) is consistent with the suggested minimum clinically important difference.[12] This is especially notable given the relatively low rate of moderate-to-severe exacerbations in all three groups (0·45 to 0·57 exacerbations per patient per year). We recruited a population that was both symptomatic and at high risk of exacerbations, with a history of approximately 1·3 exacerbations per patient in the year prior to entry. We would therefore anticipate that a high proportion of patients would experience an exacerbation during the study. However, lower than anticipated exacerbation rates have also been seen in other recent trials,[14–18] perhaps because patients often receive improved care in interventional trials with regular, detailed clinic visits. In addition, the treatment adherence in clinical trials is far higher than usually seen in clinical practice.

As mentioned earlier, limited evidence is available for an effect of triple therapy on exacerbations – and indeed, this is the first long-term study to compare a fixed triple with a long-acting muscarinic antagonist. Studies have generally been of short duration, and have generally 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.[10] The study suffered with a small sample size and a high drop-out rate, and low statistical power is likely the explanation why the lower exacerbation rate with triple therapy compared to LAMA monotherapy was not

384 statistically significant. In contrast, 12-week studies have shown a significant 62% reduction
385 in the rate of severe exacerbations (p<0·001) and a 41% reduction in the rate of moderate-
386 to-severe exacerbations (p=0·0032) with triple therapy compared with LAMA monotherapy.[7,8]

387 The results of the current study add to those from the 12-month TRILOGY study, in which
388 this fixed triple combination resulted in a 23% reduction in the rate of moderate-to-severe
389 exacerbations compared with BDP/FF.[23] In addition, we believe that the significant reduction
390 of 32% in the rate of severe exacerbations (those leading to hospitalization or death) with the
391 fixed triple vs tiotropium in TRINITY is particularly important. It is notable that the clinical
392 response to triple therapy (in terms of exacerbation reduction) is consistent and clinically
393 relevant irrespective of whether the use of triple follows an escalation of therapy from inhaled
394 corticosteroid plus long-acting β_2-agonist or from long-acting muscarinic antagonist. More
395 specifically, the two studies together show that triple therapy reduces exacerbation rates and
396 improves lung function compared with either ICS/LABA or LAMA monotherapy.

397 A recent advance in the management of COPD is the availability of combination inhalers
398 containing a long-acting β_2-agonist and a long-acting muscarinic antagonist. Such
399 bronchodilator combination inhalers have a role in the management of COPD – especially
400 since the recent FLAME study suggested that compared with an inhaled corticosteroid/long-
401 acting β_2-agonist combination, a long-acting muscarinic antagonist/ long-acting β_2-agonist
402 combination reduced the rate of COPD exacerbations and improved both lung function and
403 health-related quality of life.[24] Neither TRINITY nor TRILOGY [23] can directly answer the
404 question of the value of adding an inhaled corticosteroid to a long-acting β_2-agonist plus
405 long-acting muscarinic antagonist combination. Furthermore, currently the addition of inhaled
406 corticosteroids to maintenance therapy with the combination of two long-acting
407 bronchodilators is not the most common route to triple therapy.[25]

408 Previous *post-hoc* analyses have shown that eosinophil levels can predict response to
409 inhaled corticosteroids in COPD,[19–21] although the exact cut-points to be used are
410 uncertain.[22] Using a 2% cut-point we found better efficacy in the high eosinophil group

411 regarding the primary outcome, with a 30% reduction in the moderate-to-severe
412 exacerbation rate for fixed triple vs tiotropium, and similar results for the $0{\cdot}2x10^9$ cells/L cut-
413 point. It is worth noting that in the low eosinophil groups we also found 7–8% rate reductions,
414 although these were not statistically significant.

415 This triple therapy approach did not result in any safety findings, with no relevant differences
416 between the three groups. Of particular note, few patients experienced pneumonia, an event
417 that has been associated with ICS use in COPD.[28] In particular, the incidence of pneumonia
418 in this study was lower than that observed in FLAME,[24] where the incidence of pneumonia
419 was 3·2% in the group that received only dual bronchodilator treatment and 4·8% in those
420 who received ICS/LABA.

421 The main limitations of TRINITY are the lower than expected rate of exacerbations, as
422 discussed earlier, together with the potential narrowing of the recruited population due to the
423 inclusion and exclusion criteria that we applied. The recruitment criteria are typical of this
424 type of efficacy study, and it is important to recognise that despite them, a population was
425 recruited with a high prevalence of comorbidities, including more than 40% of patients with
426 cardiac disorders.

427 In conclusion, in TRINITY treatment with extrafine fixed triple therapy had clinically beneficial
428 effects compared to LAMA monotherapy on different components of COPD, namely
429 exacerbations, FEV_1, hyperinflation and health-related quality of life. This consistent
430 improvement in different disease domains increases the chance that stepping up a patient
431 from LAMA to triple therapy will have a clinically meaningful impact.

432

433

Research in context

Evidence before this study

We searched PubMed for articles published before 13 September 2016, using the search term *"Drug Therapy, Combination"[MeSH Terms] OR triple AND COPD AND trial*, with no limits applied. Of the 524 hits, 18 presented data from clinical trials evaluating the efficacy of triple therapy with an inhaled corticosteroid plus a long-acting β_2-agonist plus a long-acting muscarinic antagonist, with one further manuscript presenting data from a retrospective cohort analysis. Of these, six studies compared triple therapy with a long-acting muscarinic antagonist therapy; five compared triple therapy with both long-acting muscarinic antagonist and inhaled corticosteroid plus a long-acting β_2-agonist. Although most studies were of short duration (mostly 12 to 24 weeks), a number showed a reduction in the rate of exacerbations for triple therapy vs long-acting muscarinic antagonist, together with a consistent improvement in bronchodilation. However, results were more variable for the other endpoints, including health-related quality of life, and none of these studies used a single inhaler triple combination.

Added value of this study

This is the first long-term study specifically designed to evaluate the effect of a single inhaler triple therapy versus long-acting muscarinic antagonist therapy on the rate of exacerbations in a population at high exacerbation risk.

Implications of all the available evidence

In comparison to long-acting muscarinic antagonist alone, triple therapy with an inhaled corticosteroid, a long-acting β_2-agonist and a long-acting muscarinic antagonist in a single inhaler reduces the rate of COPD exacerbations in this high risk population, together with improvements in lung function, and in a range of other clinically relevant measures.

Contributors

Jørgen Vestbo contributed to the conception and design of the study, and 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.

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 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.

Viktor Blazhko substantially contributed to the acquisition and interpretation of data for the work, 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, 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.

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.

Declaration of interests

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.

Alberto Papi has nothing to disclose related to the work under consideration for publication. Outside the submitted work, Dr Papi reports grants, personal fees, non-financial support and other from Chiesi, Astrazeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Takeda, Mundipharma and TEVA, personal fees and non-financial support from Menarini, Novartis and Zambon, and grants from Sanofi.

Massimo Corradi received honoraria for consultancy from Chiesi Farmaceutici SpA, the sponsor of the study.

Viktor Blazhko has nothing to disclose.

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.

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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Figure legends

Figure 1. Patient disposition

*One patient randomised to tiotropium received the first dose of study medication, but then withdrew consent before providing any post-baseline data, and so is included in the safety population but not the intention-to-treat population. †One patient randomised to the open triple arm received only tiotropium until discontinuation, and so was included in the tiotropium group for the safety analyses, but the open triple group for the efficacy analyses.

Figure 2a. Adjusted annual rate of moderate-to-severe COPD exacerbations (intention-to-treat population).

Error bars and values in brackets are 95% confidence intervals.

Figure 2b. Time to first moderate-to-severe COPD exacerbation (intention-to-treat population)

Figure 2c. Adjusted annual rate of severe and moderate COPD exacerbations (intention-to-treat population)

Error bars and values in brackets are 95% confidence intervals.

*Figure 3a. Adjusted mean change from baseline in pre-dose FEV_1 (intention-to-treat population). ***p<0·001 vs tiotropium*

FEV_1 = forced expiratory volume in 1 second. Error bars are 95% confidence intervals.

*Figure 3b. Adjusted mean change from baseline in pre-dose IC (intention-to-treat population). *p<0·05, **p<0·01, ***p<0·001 vs tiotropium; ††p<0·01 vs open triple.*

IC = inspiratory capacity. Error bars are 95% confidence intervals.

Title

Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial

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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 compared ~~an~~ extrafine ~~fixed triple combination of~~ beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB; 'fixed triple') with tiotropium and BDP/FF+tiotropium ('open triple') ~~in COPD~~.

Methods

Eligible patients had COPD, post-bronchodilator forced expiratory volume in 1s (FEV_1) <50%, ≥1 moderate-to-severe COPD exacerbation in the previous 12 months, and COPD Assessment Test total score ≥10. After a 2-week run-in period receiving open-label tiotropium 18µg, one inhalation once daily (OD) via single-dose dry-powder inhaler (SDDPI; HandiHaler), patients were randomised (2:2:1) to 52 weeks with: ~~1)~~ tiotropium, one inhalation OD via SDDPI~~,~~ ; ~~2)~~ BDP/FF/GB 100/6/12·5µg, two actuations twice daily (BID) via pressurised metered-dose inhaler (pMDI~~),~~); or ~~3)~~ BDP/FF 100/6µg, two actuations BID via pMDI + tiotropium 18µg, one inhalation OD via SDDPI. Primary endpoint: moderate-to-severe COPD exacerbation rate. Key secondary: change from baseline in pre-dose FEV_1 at Week 52. ClinicalTrials.gov: NCT01911364.

Findings

The study ran between January 21, 2014, and March 18, 2016. A total of 2691 patients were randomised to fixed triple (n=1078), tiotropium (n=1075) or open triple (n=538). Moderate-to-severe exacerbation rates (95%CI) were 0·46 (0·41, 0·51), 0·57 (0·52, 0·63) and 0·45 (0·39, 0·52) for fixed triple, tiotropium and open triple; ~~Fixed~~ fixed triple was superior to tiotropium ~~for moderate-to-severe exacerbation rate~~ (rate ratio 0·80 [95%CI 0·69, 0·92]; p=0·003). For Week 52 pre-dose FEV_1, ~~Fixed~~ fixed triple was superior to tiotropium (mean difference 0·061L [0·037, 0·086]; p<0·0001) and non-inferior to open triple (–0·003L [–0·033,

0·027]; p=0·852) ~~in Week 52 pre-dose FEV_1~~. Adverse events were reported by 594 (55%) patients with fixed triple, 622 (58%) with tiotropium and 309 (58%) with open triple.

Interpretation

In TRINITY, treatment with ~~an~~ extrafine fixed triple ~~combination~~ had clinical benefits ~~when~~ compared to tiotropium in patients with symptomatic COPD, ~~an~~ FEV_1 <50% and an exacerbation history.

Funding

Chiesi Farmaceutici SpA.

Introduction

COPD is a progressive disease, characterised by the presence of symptoms and exacerbations.[1] Much of the burden of COPD is due to exacerbations, which are associated with increased disease progression, reduced quality of life, and increased costs (especially hospitalisation).[2–5] In patients at risk of exacerbations, most current guidelines recommend starting with either a long-acting muscarinic antagonist or a combination of an inhaled corticosteroid and a long-acting β_2-agonist.[1,6] 'Triple therapy' with an inhaled corticosteroid, a long-acting β_2-agonist and a long-acting muscarinic antagonist is recommended in patients with exacerbations despite initial treatment,[1,6] and is frequently used for the management of COPD. However, few studies have addressed the added value of triple therapy for preventing exacerbations. Although two 12-week studies have suggested that triple therapy can provide a greater reduction in exacerbations compared with a long-acting muscarinic antagonist,[7,8] longer trials are needed to assess moderate and severe exacerbations, not least because of their marked seasonality.[9] Only one long term study has compared triple therapy to a long-acting muscarinic antagonist; there was no reduction in exacerbation rate over 12 months.[10] However, this study did not evaluate the clinical efficacy of a triple therapy delivered in a single inhaler.

Currently, patients with COPD receiving triple therapy must use at least two inhalers, typically a combined inhaled corticosteroid plus long-acting β_2-agonist in one inhaler and a long-acting muscarinic antagonist in a second. Often these inhalers are of different types and designs, which may in turn negatively impact correct inhaler use and treatment adherence. A single inhaler combining extrafine formulations of the inhaled corticosteroid beclometasone dipropionate (BDP), the long-acting β_2-agonist formoterol fumarate (FF) and the long-acting muscarinic antagonist glycopyrronium bromide (GB) has been developed to simplify this regime, with extrafine formulations able to reach and treat not only the large but also the small airways.[11] In the TRINITY study that we describe in this manuscript, we evaluated the benefits of extrafine BDP/FF/GB ('fixed triple') over a monotherapy long-acting

muscarinic antagonist, tiotropium, with a free combination of BDP/FF in one inhaler and tiotropium in a second inhaler (‘open triple’) as control. The primary hypothesis was that fixed triple would be superior to tiotropium in terms of the moderate and severe COPD exacerbation rate over 52 weeks of treatment.

Methods

Study design

TRINITY was a randomised, parallel group, double-blind, double-dummy, active-controlled study, conducted in 224 sites across 15 countries. The sites were a mixture of primary (n=17), secondary (n=121) and tertiary care (n=48), and specialist investigation units (38).

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 tiotropium 18 µg, one inhalation once daily (in the morning) via single-dose dry-powder inhaler (SDDPI; HandiHaler [Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany]). At the end of the 2-week run-in (Visit 2), patients were randomised with a 2:2:1 ratio to one of three treatment groups: 1) to continue to receive tiotropium 18 µg, one inhalation once daily via SDDPI, or 2) to receive extrafine BDP/FF/GB 100/6/12·5 µg, two actuations twice daily via pressurised metered-dose inhaler (pMDI), or 3) extrafine BDP/FF 100/6 µg, two actuations twice daily via pMDI + tiotropium 18 µg, one inhalation once daily via SDDPI. 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 as needed (100 µg per actuation, via pMDI), but 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); long-acting β_2-agonists (12 h; 72 h for ultra-long-acting β_2-agonists); long-acting muscarinic antagonists (72 h); inhaled corticosteroids (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). There were no protocol amendments.

Patients

The main inclusion criteria were: ≥40 years of age; current or ex-smokers; diagnosis of COPD, with post-bronchodilator (salbutamol 400 µg) forced expiratory volume in 1 second (FEV_1) <50% and a ratio of FEV_1 to forced vital capacity <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 for at least 2 months prior to screening of inhaled corticosteroid plus long-acting β_2-agonist (as an open or fixed combination), or inhaled corticosteroid plus long-acting muscarinic antagonist, or inhaled long-acting β_2-agonist plus long-acting muscarinic antagonist (as an open or fixed combination), or long-acting muscarinic antagonist monotherapy (patients receiving triple therapy of inhaled corticosteroid, long-acting β_2-agonist and long-acting muscarinic antagonist were not eligible). In addition, all patients were to be symptomatic, with a COPD Assessment Test total score ≥10. 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; COPD exacerbation in the 4 weeks prior to screening or during the run-in period; clinically significant cardiovascular conditions or laboratory abnormalities (including persistent, long-standing or permanent atrial fibrillation); or unstable concurrent disease that may have impacted efficacy or safety (as judged by the investigator). The full inclusion and exclusion criteria are in the appendix.

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 in the ratio 2:2:1 to fixed triple, tiotropium or open triple. Randomisation was stratified by country and severity of airflow limitation (post-bronchodilator FEV_1 categories <30% predicted, or 30% to <50% predicted, with a minimum of 20% of recruited patients to be <30% predicted). Patients, investigators, site staff and sponsor personnel were blinded to treatment assignment for the duration of the study. To achieve this blinding,

a double-dummy approach was used, with all patients using a pMDI twice daily (containing BDP/FF/GB, BDP/FF or placebo) and an SDDPI once daily (containing tiotropium or placebo).

Procedures

At Visit 2, baseline (pre-dose) data were collected for spirometry and St George's Respiratory Questionnaire (SGRQ, a measure of health-related quality of life). FEV_1 was determined from forced spirometry manoeuvres, with inspiratory capacity [IC] determined from slow spirometry (IC is a measure of hyperinflation). At each subsequent visit, pre-dose (morning) spirometry was conducted (with centralised spirometry used to improve the quality), and data were collected from the SGRQ. 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

The primary objective was to demonstrate superiority of fixed triple over tiotropium in terms of moderate-to-severe COPD exacerbation rate over 52 weeks of treatment. The two key secondary objectives were both based on change from baseline in pre-dose FEV_1 at Week 52 – to demonstrate superiority of fixed triple over tiotropium, and to demonstrate non-inferiority of fixed triple relative to open triple. The secondary efficacy variables were: time to first moderate-to-severe, and to first severe COPD exacerbation; rate of severe and of moderate COPD exacerbations over 52 weeks of treatment; pre-dose FEV_1 at all the other clinic visits and averaged over the treatment period; FEV_1 response (change from baseline in pre-dose FEV_1 ≥100 mL) at Weeks 26 and 52; pre-dose IC at all clinic visits; SGRQ response (decrease from baseline in total score ≥4, which is the minimal clinically important difference [12]) at Weeks 26 and 52; SGRQ total score at all clinic visits; and percentage of days without rescue medication use and average number of puffs per day. For all variables,

the following comparisons were prespecified: fixed triple vs tiotropium; fixed triple vs open triple; open triple vs tiotropium.

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, antibiotics, or hospital admission, or a combination of these.[13] Events were classified as moderate or severe according to European Medicines Agency/Committee for Medicinal Products for Human Use guidelines,[13] with severe exacerbations being those requiring hospital admission 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.

Treatment-emergent adverse events 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 adverse events. Blood pressure was recorded pre-dose and at 10 min post-dose at each visit, with electrocardiogram (ECG) data captured at the same time points at Weeks 26 and 52. Major adverse cardiovascular events were adjudicated by an independent adjudication committee, comprising four cardiologists.

Statistical analysis

We estimated that 2580 randomly assigned patients (1032 patients in each of the fixed triple and tiotropium groups, and 516 in the open triple group) would be required, considering non-assessable rates of approximately 13%, 16·5% and 20% at Weeks 12, 26 and 52, respectively. With the use of a two-sided significance level of 0·05, this sample size provided an overall study power of 80%, and in particular: (1) 93·3% power to detect a rate ratio of 0·8 for moderate-to-severe COPD exacerbations between the fixed triple and tiotropium groups, using a negative binomial model and assuming a rate of 0·9 exacerbations per patient per year in the tiotropium group and an over-dispersion parameter of the negative binomial

distribution of 0·56; (2) 99·7% power to detect a mean difference of 60 mL between fixed triple and tiotropium in pre-dose FEV_1 at Week 52, assuming a standard deviation (SD) of 260 mL; (3) assuming 9% of completed patients with major protocol deviations, 86·0% power to demonstrate the non-inferiority of fixed triple relative to open triple in pre-dose FEV_1 at Week 52 in the per protocol population, with a non-inferiority margin of –50 mL and assuming no difference between treatments and a SD of 260 mL (one-sided significance level of 0·025).

The number of moderate-to-severe COPD exacerbations (primary endpoint) 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 at screening as fixed effects, and log-time on study as an offset. Two COPD exacerbations were considered as a single episode in the statistical analysis if the second exacerbation started less than 10 days after the end of the systemic corticosteroids and/or antibiotics intake for the previous exacerbation. The change from baseline in pre-dose FEV_1 (key secondary endpoint) was analysed 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.

To deal with multiplicity, the primary and the key secondary comparisons were performed in the following prespecified hierarchical order: (1) superiority of fixed triple over tiotropium in terms of moderate-to-severe COPD exacerbation rate; (2) superiority of fixed triple over tiotropium in terms of pre-dose FEV_1; (3) non-inferiority of fixed triple relative to open triple in terms of pre-dose FEV_1. At each step of the procedure, no confirmatory claims were to be made unless the objectives were met in all the preceding steps. No multiplicity adjustments were applied in the analysis of secondary endpoints, and for these variables p-values were interpreted descriptively. Subgroup analyses of the primary and key secondary endpoints

were prespecified, with patients grouped according to severity of airflow limitation, smoking status, sex, reversibility to salbutamol, COPD phenotype (chronic bronchitis, emphysema, or mixed), blood eosinophil concentration at screening, and age, with the primary endpoint also analysed according to presence of cardiovascular comorbidities and number of exacerbations in the previous 12 months. Sensitivity analyses were performed on the primary and key secondary endpoints to assess the potential impact of missing data, as described in the appendix.

The severe and moderate exacerbation rates were analysed using the same model as the primary endpoint. The times to first exacerbation were analysed using a Cox proportional hazards model, and the responder analyses for FEV_1 and SGRQ were conducted using a logistic model. In these models, the same fixed effects as in the analysis of the primary endpoint were included, with the baseline value also considered in the responder analyses. The changes from baseline in pre-dose IC, SGRQ total score and rescue medication use endpoints were analysed using a similar MMRM model as for the key secondary endpoint.

Primary, key secondary, and other secondary endpoints were analysed in the intention-to-treat population classified as all randomly assigned patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment. Non-inferiority of the key secondary endpoint was also tested in the per-protocol population, classified as all patients in the intention-to-treat population with no major protocol deviations. Safety outcomes were analysed in the safety population, which was classified as all randomly assigned patients who received at least one dose of study drug. An independent Data Safety Monitoring Board, composed of three independent clinicians and one independent biostatistician, provided a quarterly independent scrutiny of the study. All analyses presented in this manuscript were done with SAS software, version 9·2. The study is registered with ClinicalTrials.gov, number NCT01911364.

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 (JV) responsible for the decision to submit for publication.

Results

The study ran between January 21, 2014, and March 18, 2016. We recruited 3433 patients to the study, of whom 2691 were randomly assigned to one of the treatment groups (1078 to fixed triple, 1075 to tiotropium and 538 to open triple), with 986 (91·5%) completing the study in the fixed triple group, 914 (85·0%) in the tiotropium group, and 496 (92·2%) in the open triple group, see Figure 1. Patients in the tiotropium group were significantly more likely to prematurely withdraw from the study than either of the other two groups (p<0·0001). Compliance to treatment was high, with a median of 94·6%, 94·3% and 94·9% of doses taken in the fixed triple, tiotropium and open triple groups, respectively. Median exposure in all three groups was 365·0 days, with ranges of 3–402, 1–403 and 4–399 for fixed triple, tiotropium and open triple, respectively. Baseline characteristics of the recruited patients are shown in Table 1. More than 83% of patients had at least one concomitant disease. Cardiac disorders were reported in 41% of the patients in the fixed triple group, 43% of the patients in the tiotropium group and 40% of the patients in the open triple group.

Table 1. Baseline characteristics (Safety population)

	Fixed triple (N=1077)	**Tiotropium (N=1076)**	**Open triple (N=537)**
Sex, n (%)			
Male	829 (77·0)	830 (77·1)	397 (73·9)
Female	248 (23·0)	246 (22·9)	140 (26·1)
Race, n (%)			
White	1067 (99·1)	1071 (99·5)	532 (99·1)
Black/African American	1 (0·1)	0 (0·0)	0 (0·0)
Other	9 (0·8)	5 (0·5)	5 (0·9)
Age (years), mean (SD)	63·4 (8·7)	63·3 (8·4)	62·6 (8·9)
Body-mass index (kg/m²), mean (SD)	26·4 (5·1)	26·2 (4·7)	26·3 (5·3)
Blood leukocyte concentration (10^9/L), mean (SD)	7·68 (2·19)	7·71 (2·09)	7·83 (2·32)
Blood eosinophil concentration (10^9/L), mean (SD)	0·20 (0·17)	0·20 (0·17)	0·20 (0·17)
Blood eosinophil proportion (%)	2·63 (2·19)	2·67 (2·24)	2·66 (2·17)
Smoking status, n (%)			
Ex-smoker	560 (52·0)	573 (53·3)	271 (50·5)

	Fixed triple (N=1077)	Tiotropium (N=1076)	Open triple (N=537)
Current smoker	517 (48·0)	503 (46·7)	266 (49·5)
Time since first COPD diagnosis (years), mean (SD)	7·9 (5·6)	8·2 (6·1)	7·8 (5·4)
FEV_1 (L), mean (SD)*	1·117 (0·330)	1·119 (0·312)	1·127 (0·331)
FEV_1 % of predicted normal value, mean (SD)*	36·6 (8·3)	36·6 (8·1)	36·7 (8·3)
<30%, n (%)	228 (21·2)	229 (21·3)	113 (21·0)
≥30% and <50%, n (%)	849 (78·8)	847 (78·7)	424 (79·0)
FVC (L), mean (SD)*	2·713 (0·774)	2·716 (0·763)	2·743 (0·790)
FEV_1/FVC ratio*, mean (SD)	0·42 (0·10)	0·43 (0·11)	0·42 (0·10)
Reversibility (%), mean (SD)	7·8 (14·0)	7·3 (13·6)	8·6 (14·7)
Inspiratory capacity (L), mean (SD)	1·975 (0·585)	1·962 (0·588)	1·948 (0·589)
Chronic bronchitis†, n (%)	772 (71·7)	781 (72·6)	383 (71·3)
Exacerbation rate in the previous year (range)	1·3 (1, 11)	1·3 (1, 5)	1·2 (1, 7)
CAT total score, mean (SD)	21·5 (5·8)	21·6 (5·8)	21·7 (6·0)
COPD medication at study entry, n (%)			
ICS/LABA	802 (74·5)	804 (74·7)	378 (70·4)
ICS/LAMA	37 (3·4)	30 (2·8)	18 (3·4)
LABA/LAMA	125 (11·6)	124 (11·5)	74 (13·8)
LAMA	113 (10·5)	118 (11·0)	67 (12·5)
Spacer use during the study, n (%)	207 (19·2)	211 (19·6)	112 (20·9)
Patients with at least one concomitant disease, n (%)‡	904 (83·9)	900 (83·6)	446 (83·1)
Hypertension	616 (57·2)	608 (56·5)	293 (54·6)
Ischaemic heart disease	331 (30·7)	351 (32·6)	157 (29·2)
Myocardial ischaemia	187 (17·4)	194 (18·0)	86 (16·0)
Coronary artery disease	119 (11·0)	134 (12·5)	65 (12·1)
Angina pectoris	47 (4·4)	48 (4·5)	22 (4·1)
Ischaemic cardiomyopathy	5 (0·5)	9 (0·8)	0 (0·0)
Myocardial infarction	2 (0·2)	1 (0·1)	4 (0·7)
Cardiac failure	201 (18·7)	197 (18·3)	92 (17·1)
Diabetes mellitus	109 (10·1)	102 (9·5)	61 (11·4)
Arteriosclerosis coronary artery	86 (8·0)	83 (7·7)	43 (8·0)
Osteochondrosis	53 (4·9)	59 (5·5)	28 (5·2)
Cholecystitis chronic	49 (4·5)	49 (4·6)	27 (5·0)
Obesity	53 (4·9)	40 (3·7)	30 (5·6)

FEV_1 = 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. *Measured after salbutamol was administered. †Includes patients with a mixed chronic bronchitis and emphysema phenotype. ‡Only diseases where 5% of patients or more were affected in any group are included here.

The rates of moderate-to-severe COPD exacerbations were 0·46, 0·57 and 0·45 per patient per year for fixed triple, tiotropium and open triple, respectively (Figure 2a). Extrafine fixed triple was superior to tiotropium, with an adjusted rate ratio of 0·80 (95% CI 0·69, 0·92; p=0·003), indicating a significant 20% reduction in the rate with fixed triple (Figure 2a). The rates of moderate-to-severe exacerbations were similar with fixed triple and open triple, with an adjusted rate ratio of 1·01 (95% CI 0·85, 1·21; p=0·887) (Figure 2a). The results of the subgroup analyses are shown in the appendix. Of note, compared with tiotropium monotherapy, the effect of the two triple therapies on exacerbation rate was greater in the subgroups with higher eosinophil concentrations ~~and with severe airflow limitation~~. In the subgroup with eosinophil count ≥2%, the triple therapies significantly reduced exacerbation rates vs tiotropium by 30% (rate ratio: 0·70 [95% CI: 0·58, 0·85]) and 31% (0·69 [0·55, 0·87]) for fixed and open triple, respectively; corresponding reductions in the <2% subgroup were 7% (0·93 [0·75, 1·17]) and 9% (0·91 [0·69, 1·20]). In the subgroup with eosinophil count ≥$0{\cdot}2 \times 10^9$ cells/L, the reductions were 36% (0·64 [0·51, 0·81]) and 38% (0·62 [0·47, 0·83]) for fixed and open triple, respectively; in the <$0{\cdot}2 \times 10^9$ cells/L subgroup, reductions were 8% (0·92 [0·77, 1·10]) and 9% (0·91 [0·72, 1·14]). In addition, compared with open triple, fixed triple significantly reduced the rate of moderate-to-severe exacerbations in the subgroup of patients with more than one exacerbation in the previous 12 months (0·71 [0·51, 0·995]).

The time to first moderate-to-severe exacerbation was significantly extended with fixed triple vs tiotropium, with a hazard ratio (HR) of 0·84 (95% CI 0·72, 0·97; p=0·015; Figure 2b). Fixed triple and open triple showed similar effects on this variable (HR 1·06 [95% CI 0·88, 1·27]; p=0·569). Fixed triple significantly reduced the rate of severe exacerbations compared with tiotropium by 32%, and of moderate exacerbations by 16%, with similar rates to open triple (Figure 2c). The time to first severe exacerbation was significantly prolonged with fixed

297 triple compared with tiotropium (HR 0·70 [95% CI 0·52, 0·95]; p=0·021), and was similar for
298 fixed triple and open triple (HR 1·05 [95% CI 0·70, 1·57]; p=0·822).

299 The adjusted mean changes from baseline in pre-dose FEV_1 at Week 52 (the key secondary
300 efficacy variable) were 0·082 L (95% CI 0·065, 0·100), 0·021 L (0·003, 0·039) and 0·085 L
301 (0·061, 0·110) for fixed triple, tiotropium and open triple, respectively. Both of the key
302 secondary objectives were met, with fixed triple superior to tiotropium (adjusted mean
303 difference 0·061 L [95% CI 0·037, 0·086]; p<0·0001) and non-inferior to open triple (–0·003
304 L [–0·033, 0·027]; p=0·852) in pre-dose FEV_1 at Week 52. Non-inferiority between fixed
305 triple and open triple was confirmed in the per-protocol population. The results of the
306 subgroup analyses were broadly consistent with the overall results (appendix). For this
307 endpoint, eosinophil levels did not consistently influence the results.

308 For pre-dose FEV_1 at all other visits and averaged over the treatment period, fixed triple was
309 superior to tiotropium and similar to open triple (Figure 3a). Averaged over the treatment
310 period, the adjusted mean changes from baseline in pre-dose FEV_1 were 0·080 L (0·067,
311 0·093), 0·022 L (0·009, 0·036) and 0·091 L (0·073, 0·110) with fixed triple, tiotropium and
312 open triple, respectively. The adjusted mean difference between fixed triple and tiotropium
313 was statistically significant (0·058 L [0·039, 0·077]; p<0·0001), whereas the values were
314 similar for fixed triple and open triple (difference –0·011 L [–0·034, 0·012]; p=0·337). In
315 terms of FEV_1 change from baseline, patients were more likely to respond (response defined
316 as ≥100 mL increase) to fixed triple than to tiotropium at both Weeks 26 and 52 (Table 2),
317 with a similar percentage of responders in the fixed triple and open triple groups. Fixed triple
318 was also superior to tiotropium for change from baseline in pre-dose IC; and was similar to
319 open triple at all visits except Week 12 (Figure 3b).

Table 2. FEV_1 and SGRQ responder analysis (intention-to-treat population)

	Responders, n (%)			Odds ratio (95% CI)		
	Fixed triple (N=1077)	**Tiotropium (N=1074)**	**Open triple (N=538)**	**Fixed triple vs tiotropium**	**Fixed triple vs open triple**	**Open triple vs tiotropium**
FEV_1[a]						
Week 26	421 (39·1)	306 (28·5)	204 (37·9)	1·61 (1·34, 1·93); p<0·0001	1·04 (0·84, 1·30); p=0·694	1·54 (1·23, 1·92); p=0·0001
Week 52	408 (37·9)	295 (27·5)	210 (39·0)	1·62 (1·35, 1·95); p<0·0001	0·95 (0·76, 1·18); p=0·627	1·71 (1·37, 2·13); p<0·0001
SGRQ[b]						
Week 26	508 (47·2)	438 (40·8)	276 (51·3)	1·32 (1·10, 1·57); p=0·002	0·81 (0·65, 1·00); p=0·049	1·63 (1·32, 2·02); p<0·0001
Week 52	494 (45·9)	423 (39·4)	254 (47·2)	1·33 (1·11, 1·59); p=0·002	0·91 (0·73, 1·13); p=0·373	1·47 (1·18, 1·83); p=0·0006

a. Response defined as ≥100 mL increase from baseline; b. Response defined as ≥4 units decease from baseline. SGRQ = St George's Respiratory Questionnaire.

More patients on fixed triple than on tiotropium alone were responders in terms of SGRQ total score (decrease from baseline ≥4 units) at both Weeks 26 and 52, with a similar percentage of responders in the two triple therapy groups at the end of the study (Table 2). Fixed triple was associated with a significantly greater improvement in mean SGRQ total score than tiotropium at all time points except Week 26, and a similar mean change from baseline in SGRQ total score to open triple at most timepoints, with the exception of Weeks 26 and 52 (appendix). Compared with the group of patients receiving fixed triple, those receiving tiotropium required significantly more rescue medication, both when analysed in terms of puffs per day and the percentage of days with no use, with rescue medication use similar in the fixed triple and open triple groups (appendix).

A similar proportion of patients had adverse events in the three groups (Table 3). Most events were mild or moderate in severity. Pneumonia was reported in a small number of patients, with similar incidence in the three treatment groups (2·6%, 1·8% and 2·2% for fixed

triple, tiotropium and open triple, respectively). One serious adverse event occurred in one (0·1%) patient in the tiotropium group. This was an episode of angina pectoris, considered moderate in severity, and although the patient fully recovered it resulted in withdrawal from the study. Fewer patients experienced adverse events leading to discontinuation of study drug in the two triple therapy groups than in the tiotropium group. The most common adverse event leading to study drug discontinuation was COPD exacerbation (8 [0·7%], 14 [1·3%] and 5 [0·9%] patients in the fixed triple, tiotropium and open triple groups, respectively). Adverse events resulted in a total of 57 deaths, with the highest percentage of patients with fatal events in the tiotropium group, and similar percentages in the two triple therapy groups. None of the deaths were considered related to study treatment.

Table 3. Adverse events and serious adverse events (≥2% in any group for adverse events and ≥0·5% in any group for serious adverse events and treatment-related adverse events) (Safety population).

Number (%) of patients	**Fixed triple (N=1077)**	**Tiotropium (N=1076)**	**Open triple (N=537)**
Adverse events	594 (55·2)	622 (57·8)	309 (57·5)
COPD	351 (32·6)	383 (35·6)	167 (31·1)
Nasopharyngitis	57 (5·3)	66 (6·1)	20 (3·7)
Headache	43 (4·0)	41 (3·8)	18 (3·4)
Dyspnoea	23 (2·1)	37 (3·4)	8 (1·5)
Pneumonia	28 (2·6)	19 (1·8)	12 (2·2)
Ischaemic heart disease	22 (2·0)	22 (2·0)	9 (1·7)
Angina pectoris	10 (0·9)	8 (0·7)	5 (0·9)
Myocardial ischaemia	6 (0·6)	3 (0·3)	3 (0·6)
Coronary artery disease	3 (0·3)	5 (0·5)	1 (0·2)
Myocardial infarction	4 (0·4)	3 (0·3)	0 (0·0)
Acute coronary syndrome	0 (0·0)	1 (0·1)	0 (0·0)
Coronary artery insufficiency	0 (0·0)	1 (0·1)	0 (0·0)
Ischaemic cardiomyopathy	0 (0·0)	1 (0·1)	0 (0·0)
Cough	18 (1·7)	23 (2·1)	9 (1·7)
Respiratory tract infection, viral	15 (1·4)	15 (1·4)	13 (2·4)
Serious adverse events	140 (13·0)	164 (15·2)	68 (12·7)

Number (%) of patients	**Fixed triple (N=1077)**	**Tiotropium (N=1076)**	**Open triple (N=537)**
COPD	76 (7·1)	100 (9·3)	35 (6·5)
Pneumonia	21 (1·9)	14 (1·3)	9 (1·7)
Ischaemic heart disease	10 (0·9)	11 (1·0)	4 (0·7)
Myocardial infarction	4 (0·4)	3 (0·3)	0 (0·0)
Myocardial ischaemia	3 (0·3)	1 (0·1)	3 (0·6)
Coronary artery disease	2 (0·2)	4 (0·4)	0 (0·0)
Angina pectoris	1 (0·1)	2 (0·2)	1 (0·2)
Acute coronary syndrome	0 (0·0)	1 (0·1)	0 (0·0)
Cardiac failure	5 (0·5)	11 (1·0)	3 (0·6)
Treatment-related adverse events	25 (2·3)	33 (3·1)	27 (5·0)
Dry mouth	5 (0·5)	10 (0·9)	10 (1·9)
Muscle spasms	6 (0·6)	0 (0·0)	3 (0·6)
Dysphonia	3 (0·3)	2 (0·2)	3 (0·6)
Oral candidiasis	3 (0·3)	2 (0·2)	3 (0·6)
Treatment-related serious adverse events	0 (0·0)	1 (0·1)	0 (0·0)
Severe adverse events	91 (8·4)	100 (9·3)	34 (6·3)
Adverse events leading to study drug discontinuation	33 (3·1)	62 (5·8)	15 (2·8)
Adverse events leading to death	20 (1·9)	29 (2·7)	8 (1·5)
All MACEs	20 (1·9)	23 (2·1)	7 (1·3)

COPD = chronic obstructive pulmonary disease exacerbations. MACE = major adverse cardiovascular events, including acute myocardial infarction, arrhythmias, cardiovascular death, heart failure and stroke.

Mean changes in blood pressure, heart rate and Fridericia's corrected QT (QTcF) interval were small, with no clinically relevant differences between the three groups (treatment differences in change from screening to pre-dose and post-dose at Weeks 26 and 52 are shown in the appendix [Tables 2 and 4], together with the comparisons between pre-dose and post-dose values [Tables 3 and 5] and the largest changes in blood pressure). The percentages of abnormal QTcF interval absolute values and changes were similar in all groups (appendix).

Discussion

The study met the primary and both key secondary endpoints. Extrafine fixed triple resulted in a 20% reduction in the rate of moderate-to-severe COPD exacerbations compared with tiotropium, together with a 0·061 L mean improvement in pre-dose FEV_1. Furthermore, the non-inferiority of fixed triple relative to open triple was demonstrated for pre-dose FEV_1. Fixed triple reduced both moderate and severe exacerbation rates, hyperinflation (as measured by IC) and rescue medication use, with a greater percentage of SGRQ responders compared to tiotropium, and effects generally similar to open triple.

The 20% improvement in exacerbation rates with fixed triple over tiotropium (a first-line treatment in this population[1]) is consistent with the suggested minimum clinically important difference.[12] This is especially notable given the relatively low rate of moderate-to-severe exacerbations in all three groups (0·45 to 0·57 exacerbations per patient per year). We recruited a population that was both symptomatic and at high risk of exacerbations, with a history of approximately 1·3 exacerbations per patient in the year prior to entry. We would therefore anticipate that a high proportion of patients would experience an exacerbation during the study. However, lower than anticipated exacerbation rates have also been seen in other recent trials,[14–18] perhaps because patients often receive improved care in interventional trials with regular, detailed clinic visits. In addition, the treatment adherence in clinical trials is far higher than usually seen in clinical practice.

As mentioned earlier, limited evidence is available for an effect of triple therapy on exacerbations – and indeed, this is the first long-term study to compare a fixed triple with a long-acting muscarinic antagonist. Studies have generally been of short duration, and have generally 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.[10] The study suffered with a small sample size and a high drop-out rate, and low statistical power is likely the explanation why the lower exacerbation rate with triple therapy compared to LAMA monotherapy was not

statistically significant. In contrast, 12-week studies have shown a significant 62% reduction in the rate of severe exacerbations ($p<0{\cdot}001$) and a 41% reduction in the rate of moderate-to-severe exacerbations ($p=0{\cdot}0032$) with triple therapy compared with LAMA monotherapy.[7,8]

The results of the current study add to those from the 12-month TRILOGY study, in which this fixed triple combination resulted in a 23% reduction in the rate of moderate-to-severe exacerbations compared with BDP/FF.[23] In addition, we believe that the significant reduction of 32% in the rate of severe exacerbations (those leading to hospitalization or death) with the fixed triple vs tiotropium in TRINITY is particularly important. It is notable that the clinical response to triple therapy (in terms of exacerbation reduction) is consistent and clinically relevant irrespective of whether the use of triple follows an escalation of therapy from inhaled corticosteroid plus long-acting β_2-agonist or from long-acting muscarinic antagonist. More specifically, the two studies together show that triple therapy reduces exacerbation rates and improves lung function compared with either ICS/LABA or LAMA monotherapy.

A recent advance in the management of COPD is the availability of combination inhalers containing a long-acting β_2-agonist and a long-acting muscarinic antagonist. Such bronchodilator combination inhalers have a role in the management of COPD – especially since the recent FLAME study suggested that compared with an inhaled corticosteroid/long-acting β_2-agonist combination, a long-acting muscarinic antagonist/ long-acting β_2-agonist combination reduced the rate of COPD exacerbations and improved both lung function and health-related quality of life.[24] Neither TRINITY nor TRILOGY [23] can directly answer the question of the value of adding an inhaled corticosteroid to a long-acting β_2-agonist plus long-acting muscarinic antagonist combination. Furthermore, currently the addition of inhaled corticosteroids to maintenance therapy with the combination of two long-acting bronchodilators is not the most common route to triple therapy.[25]

Previous *post-hoc* analyses have shown that eosinophil levels can predict response to inhaled corticosteroids in COPD,[19–21] although the exact cut-points to be used are uncertain.[22] Using a 2% cut-point we found better efficacy in the high eosinophil group

regarding the primary outcome, with a 30% reduction in the moderate-to-severe exacerbation rate for fixed triple vs tiotropium, and similar results for the 0·2x10^9 cells/L cut-point. It is worth noting that in the low eosinophil groups we also found 7–8% rate reductions, although these were not statistically significant.

This triple therapy approach did not result in any safety findings, with no relevant differences between the three groups. Of particular note, few patients experienced pneumonia, an event that has been associated with ICS use in COPD.[28] In particular, the incidence of pneumonia in this study was lower than that observed in FLAME,[24] where the incidence of pneumonia was 3·2% in the group that received only dual bronchodilator treatment and 4·8% in those who received ICS/LABA.

The main limitations of TRINITY are the lower than expected rate of exacerbations, as discussed earlier, together with the potential narrowing of the recruited population due to the inclusion and exclusion criteria that we applied. The recruitment criteria are typical of this type of efficacy study, and it is important to recognise that despite them, a population was recruited with a high prevalence of comorbidities, including more than 40% of patients with cardiac disorders.

In conclusion, in TRINITY treatment with extrafine fixed triple therapy had clinically beneficial effects compared to LAMA monotherapy on different components of COPD, namely exacerbations, FEV_1, hyperinflation and health-related quality of life. This consistent improvement in different disease domains increases the chance that stepping up a patient from LAMA to triple therapy will have a clinically meaningful impact.

Research in context

Evidence before this study

We searched PubMed for articles published before 13 September 2016, using the search term *"Drug Therapy, Combination"[MeSH Terms] OR triple AND COPD AND trial*, with no limits applied. Of the 524 hits, 18 presented data from clinical trials evaluating the efficacy of triple therapy with an inhaled corticosteroid plus a long-acting β_2-agonist plus a long-acting muscarinic antagonist, with one further manuscript presenting data from a retrospective cohort analysis. Of these, six studies compared triple therapy with a long-acting muscarinic antagonist therapy; five compared triple therapy with both long-acting muscarinic antagonist and inhaled corticosteroid plus a long-acting β_2-agonist. Although most studies were of short duration (mostly 12 to 24 weeks), a number showed a reduction in the rate of exacerbations for triple therapy vs long-acting muscarinic antagonist, together with a consistent improvement in bronchodilation. However, results were more variable for the other endpoints, including health-related quality of life, and none of these studies used a single inhaler triple combination.

Added value of this study

This is the first long-term study specifically designed to evaluate the effect of a single inhaler triple therapy versus long-acting muscarinic antagonist therapy on the rate of exacerbations in a population at high exacerbation risk.

Implications of all the available evidence

In comparison to long-acting muscarinic antagonist alone, triple therapy with an inhaled corticosteroid, a long-acting β_2-agonist and a long-acting muscarinic antagonist in a single inhaler reduces the rate of COPD exacerbations in this high risk population, together with improvements in lung function, and in a range of other clinically relevant measures.

Contributors

Jørgen Vestbo contributed to the conception and design of the study, and 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.

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 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.

Viktor Blazhko substantially contributed to the acquisition and interpretation of data for the work, 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, 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.

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.

Declaration of interests

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.

Alberto Papi has nothing to disclose related to the work under consideration for publication. Outside the submitted work, Dr Papi reports grants, personal fees, non-financial support and other from Chiesi, Astrazeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Takeda, Mundipharma and TEVA, personal fees and non-financial support from Menarini, Novartis and Zambon, and grants from Sanofi.

Massimo Corradi received honoraria for consultancy from Chiesi Farmaceutici SpA, the sponsor of the study.

Viktor Blazhko has nothing to disclose.

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.

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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Figure legends

Figure 1. Patient disposition

*One patient randomised to tiotropium received the first dose of study medication, but then withdrew consent before providing any post-baseline data, and so is included in the safety population but not the intention-to-treat population. †One patient randomised to the open triple arm received only tiotropium until discontinuation, and so was included in the tiotropium group for the safety analyses, but the open triple group for the efficacy analyses.

Figure 2a. Adjusted annual rate of moderate-to-severe COPD exacerbations (intention-to-treat population).

Error bars and values in brackets are 95% confidence intervals.

Figure 2b. Time to first moderate-to-severe COPD exacerbation (intention-to-treat population)

Figure 2c. Adjusted annual rate of severe and moderate COPD exacerbations (intention-to-treat population)

Error bars and values in brackets are 95% confidence intervals.

*Figure 3a. Adjusted mean change from baseline in pre-dose FEV_1 (intention-to-treat population). ***p<0·001 vs tiotropium*

FEV_1 = forced expiratory volume in 1 second. Error bars are 95% confidence intervals.

*Figure 3b. Adjusted mean change from baseline in pre-dose IC (intention-to-treat population). *p<0·05, **p<0·01, ***p<0·001 vs tiotropium; ††p<0·01 vs open triple.*

IC = inspiratory capacity. Error bars are 95% confidence intervals.

***Reply to Reviewers Comments**

Comment	Response
Editor	
Might you please add a brief paragraph to the discussion outlining the limitations of the study?	Added, as requested (Lines 423–428).
Additionally, we will be unable to accept the manuscript without completion of some formatting details. Might you please include number of events/mean (SD) values in the abstract and the text for all outcomes? Clarification email from Jennifer Sargent: Might I ask that in the abstract you report the exacerbation rates for each group with the CIs (as appear in figure 2a) in addition to the rate ratios and differences that are included in the abstract already. Please can you also add the numeric values for the CIs to figures 2a and 2c? As these values are/will be in the figures, no need to add them to the main text.	Our thanks for the clarification. The exacerbation rates have been added to the abstract, as requested, and the confidence intervals have been added to Figures 2a and 2c. We have then edited the abstract down to the 300 word limit.
Please also can you confirm that you have written permission from David Young, the medical writer, that he is happy to be acknowledged in the manuscript.	Yes, he is. The confirmation letters from both Jørgen Vestbo and David Young have been uploaded.
Reviewer #3	
Thank you for providing the tests for interaction and for replacing the within-subgroup p-values with confidence intervals. The statement on line 279 that the effect of the two triple therapies was greater in the subgroup with sever airflow limitation does not appear to be supported by the p-value for interaction (0.735), so I suggest "and with severe airflow limitation" is deleted.	Deleted, as requested.

Figure 1

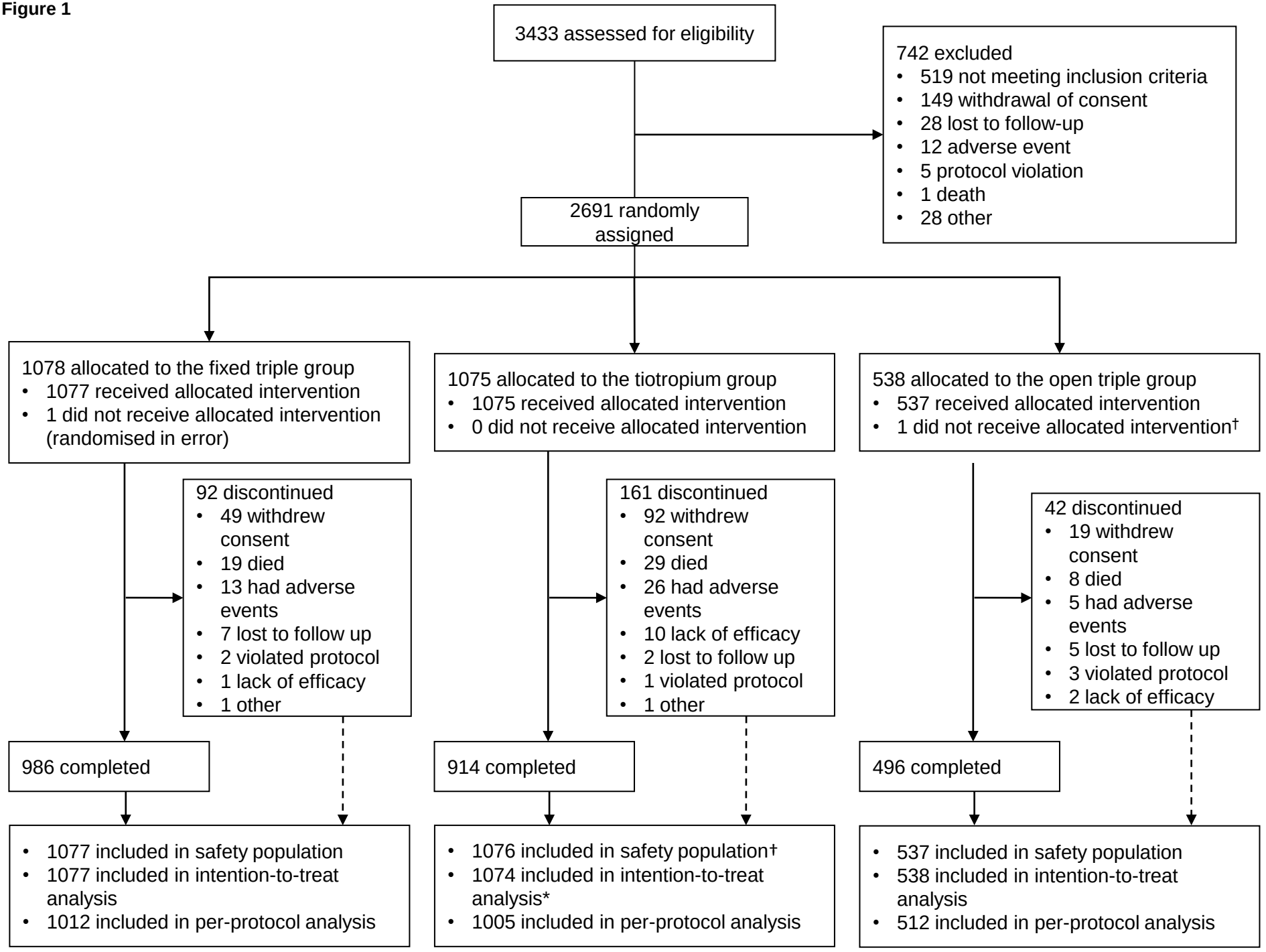

3433 assessed for eligibility
742 excluded
• 519 not meeting inclusion criteria
• 149 withdrawal of consent
• 28 lost to follow-up
• 12 adverse event
• 5 protocol violation
• 1 death
• 28 other
2691 randomly assigned
1078 allocated to the fixed triple group
• 1077 received allocated intervention
• 1 did not receive allocated intervention (randomised in error)
1075 allocated to the tiotropium group
• 1075 received allocated intervention
• 0 did not receive allocated intervention
538 allocated to the open triple group
• 537 received allocated intervention
• 1 did not receive allocated intervention†
92 discontinued
• 49 withdrew consent
• 19 died
• 13 had adverse events
• 7 lost to follow up
• 2 violated protocol
• 1 lack of efficacy
• 1 other
161 discontinued
• 92 withdrew consent
• 29 died
• 26 had adverse events
• 10 lack of efficacy
• 2 lost to follow up
• 1 violated protocol
• 1 other
42 discontinued
• 19 withdrew consent
• 8 died
• 5 had adverse events
• 5 lost to follow up
• 3 violated protocol
• 2 lack of efficacy
986 completed
914 completed
496 completed
• 1077 included in safety population
• 1077 included in intention-to-treat analysis
• 1012 included in per-protocol analysis
• 1076 included in safety population†
• 1074 included in intention-to-treat analysis*
• 1005 included in per-protocol analysis
• 537 included in safety population
• 538 included in intention-to-treat analysis
• 512 included in per-protocol analysis

Figure 2a

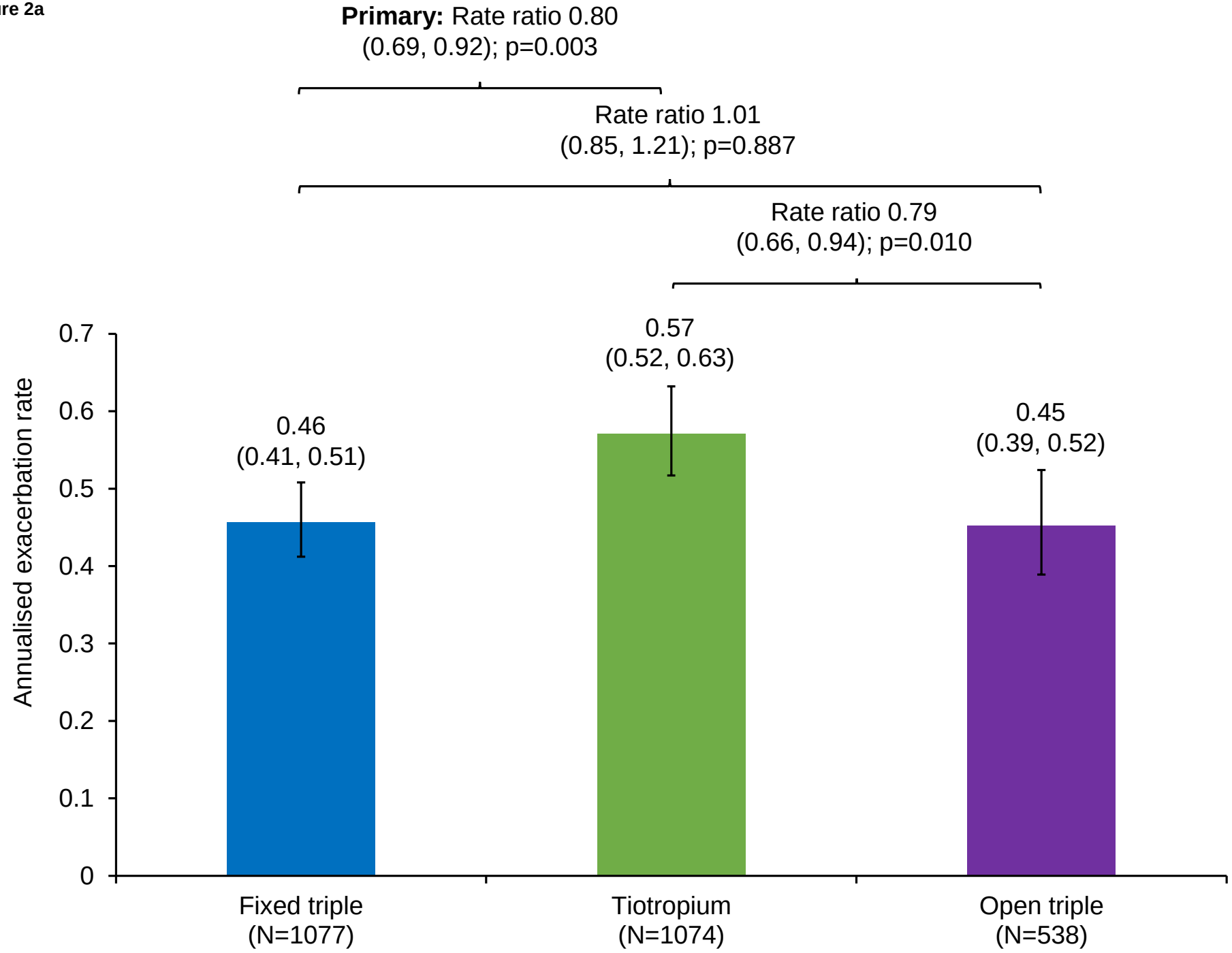
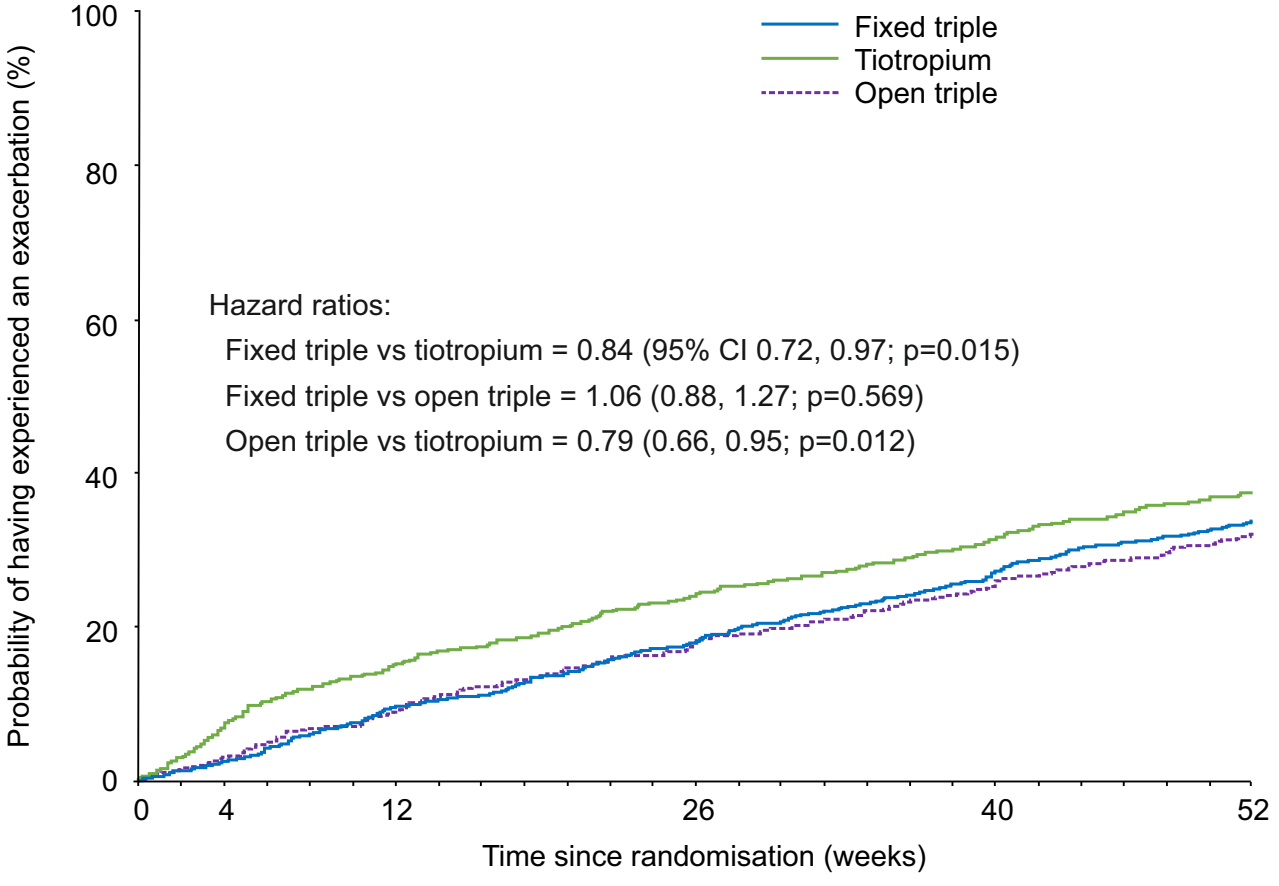

Primary: Rate ratio 0.80
(0.69, 0.92); p=0.003
Rate ratio 1.01
(0.85, 1.21); p=0.887
Rate ratio 0.79
(0.66, 0.94); p=0.010
Annualised exacerbation rate
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.46
(0.41, 0.51)
0.57
(0.52, 0.63)
0.45
(0.39, 0.52)
Fixed triple
(N=1077)
Tiotropium
(N=1074)
Open triple
(N=538)

Figure 2b



Number of patients at risk

Fixed triple	n= 1077	1044	955	851	748	426
Tiotropium	n= 1074	986	875	766	675	374
Open triple	n= 538	520	484	426	381	223

Figure 2c

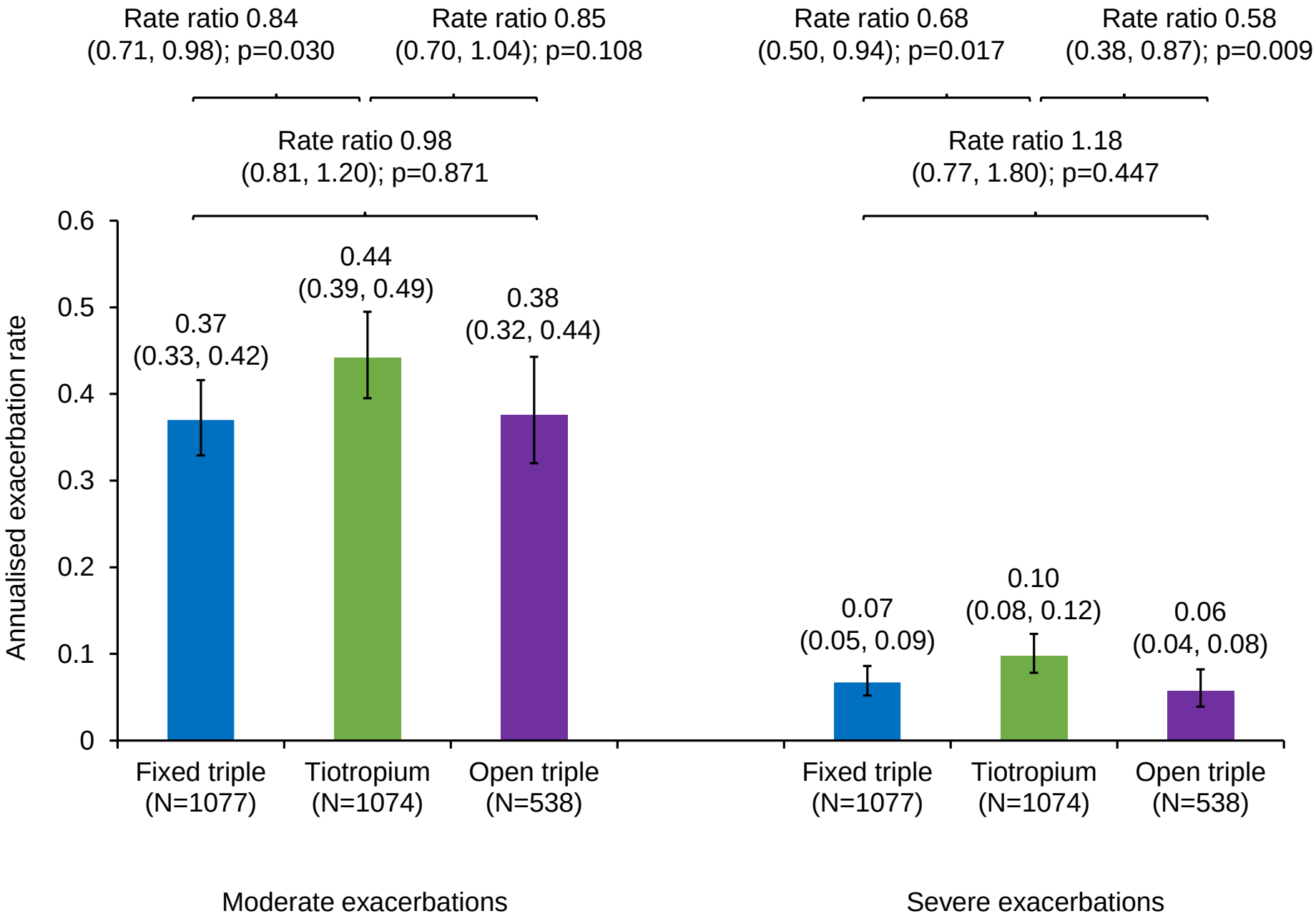
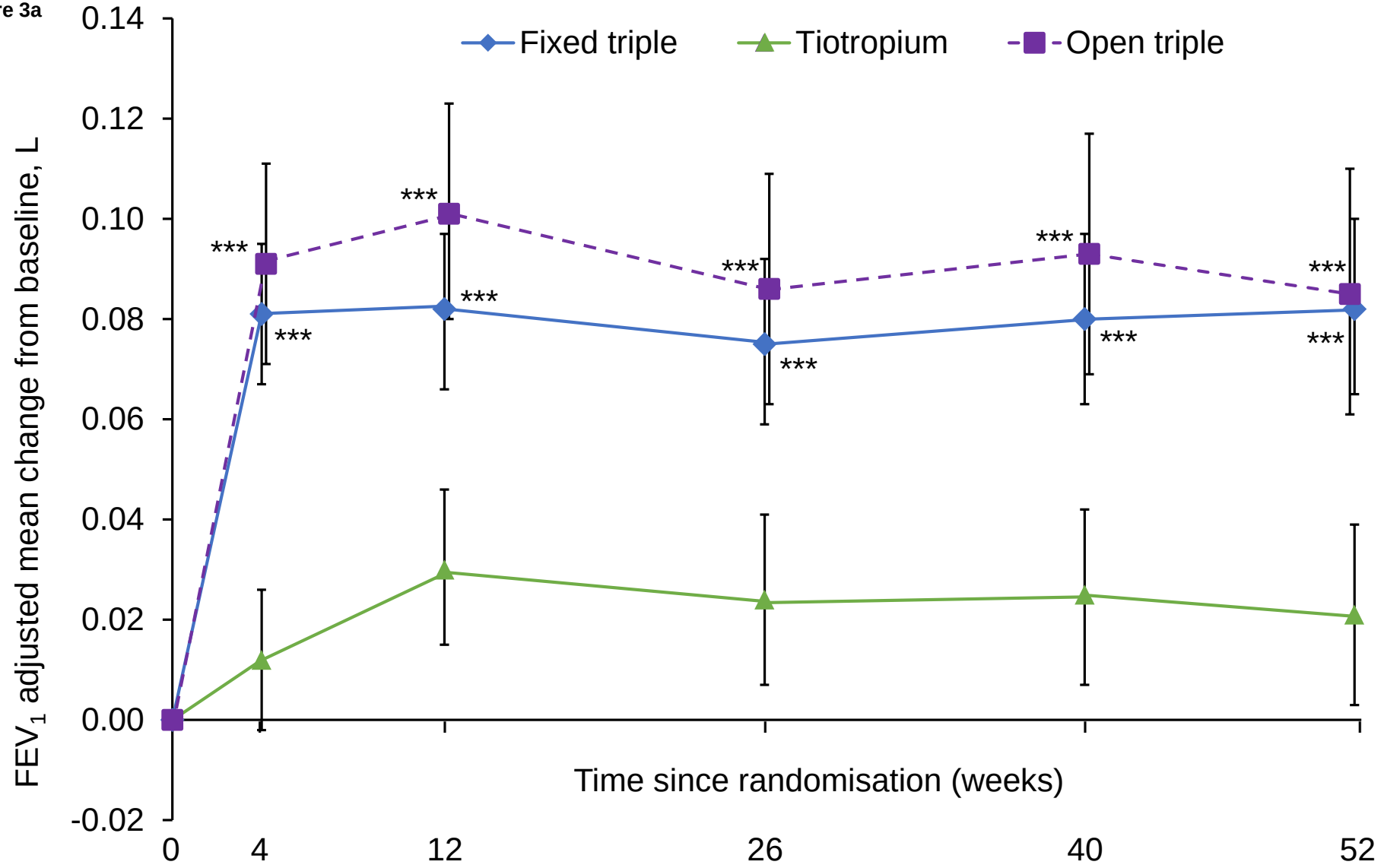
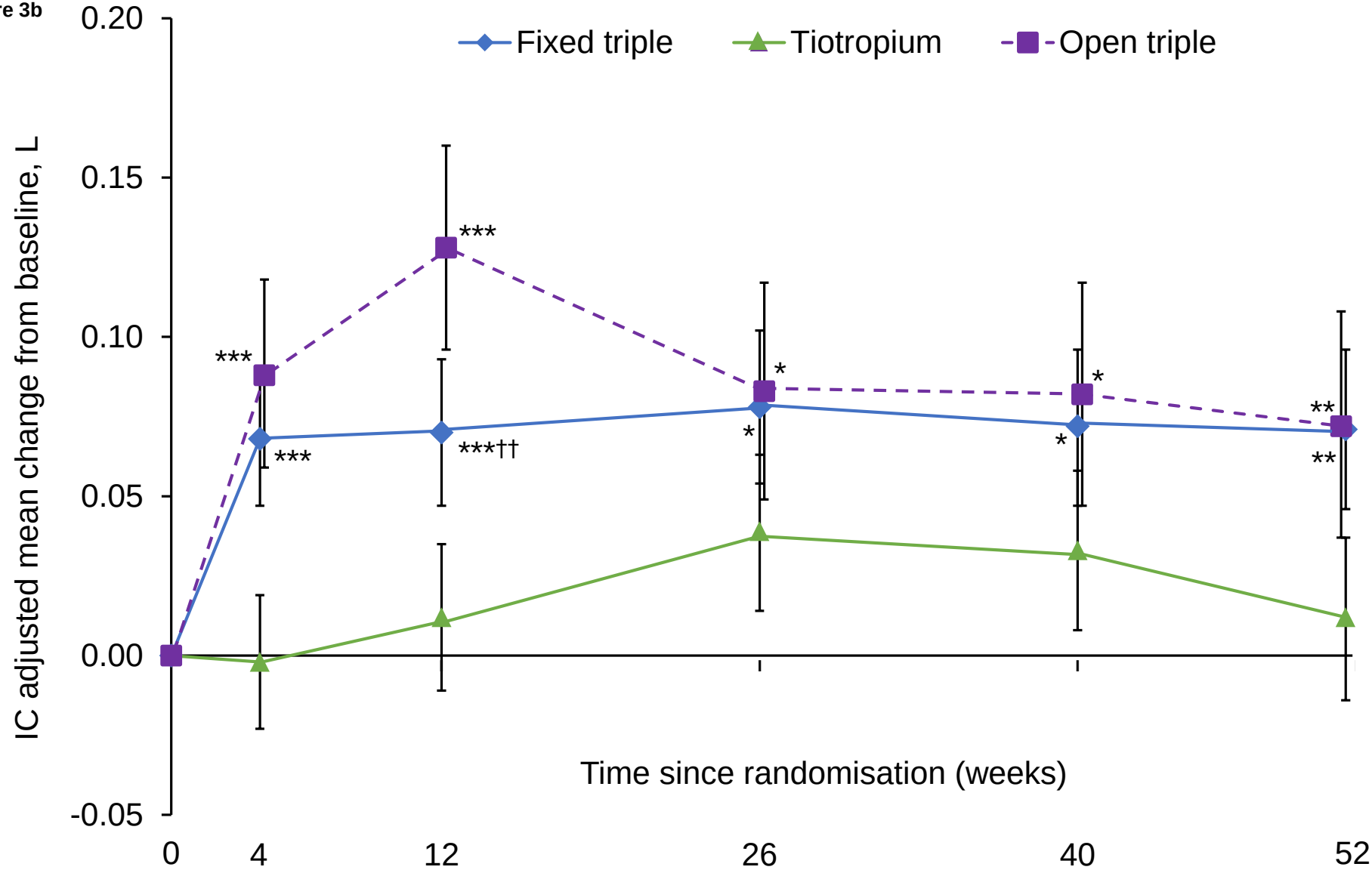

Rate ratio 0.84
(0.71, 0.98); p=0.030
Rate ratio 0.85
(0.70, 1.04); p=0.108
Rate ratio 0.98
(0.81, 1.20); p=0.871
Rate ratio 0.68
(0.50, 0.94); p=0.017
Rate ratio 0.58
(0.38, 0.87); p=0.009
Rate ratio 1.18
(0.77, 1.80); p=0.447
Annualised exacerbation rate
0.6
0.5
0.4
0.3
0.2
0.1
0
0.37
(0.33, 0.42)
0.44
(0.39, 0.49)
0.38
(0.32, 0.44)
0.07
(0.05, 0.09)
0.10
(0.08, 0.12)
0.06
(0.04, 0.08)
Fixed triple
(N=1077)
Tiotropium
(N=1074)
Open triple
(N=538)
Fixed triple
(N=1077)
Tiotropium
(N=1074)
Open triple
(N=538)
Moderate exacerbations
Severe exacerbations

Figure 3a



Number with available measurements						
Fixed triple	n=1077	1067	1047	1027	998	985
Tiotropium	n=1074	1052	1019	977	944	921
Open triple	n=538	536	526	510	502	495

Figure 3b



Number with available measurements						
Fixed triple	n=1072	1060	1043	1022	991	975
Tiotropium	n=1073	1051	1016	973	943	918
Open triple	n=535	533	521	507	500	492

Supplementary Material

Click here to download Web Appendix: TRINITY supplement (8 November 2016).pdf

CCD-1208-PR-0090

CLINICAL STUDY PROTOCOL

EUDRACT No.: 2013-000063-91

A 52-WEEK, DOUBLE BLIND, DOUBLE DUMMY, RANDOMIZED, MULTINATIONAL, MULTICENTRE, 3-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 TIOTROPIUM BROMIDE AND VERSUS FIXED COMBINATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE ADMINISTERED VIA PMDI AND TIOTROPIUM BROMIDE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Version No.: 1.0
Date: 25 July 2013

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma - Italy

GENERAL INFORMATION

SPONSOR:	Chiesi Farmaceutici S.p.A.* Via Palermo 26/A 43122 Parma - Italy + 39 0521 2791 *also reported as Chiesi throughout the text
CLINICAL STUDY MANAGER:	**Géraldine COHUET, MSc** Tel.: +33 1 47 68 41 46 Fax: +33 1 47 68 49 04 E-mail: g.cohuet@chiesifrance.com
CLINICAL RESEARCH PHYSICIAN	**Massimo CORRADI, MD** Consultant Chiesi Farmaceutici S.p.A. Tel.: +39 0521 279 771Fax: +39 0521 279 333 E-mail : m.corradi@chiesi.com Available in case of medical questions
CLINICAL PHARMACOLOGIST	**Fabrizia MARIOTTI, MSc** Tel. +39 0521 279 808 E-mail: f.mariotti@chiesi.com
CORPORATE CARDIAC LEADER	**Antonio FERRARI, MD** Tel. +39 0521 279 794 Mob. +39 349 754 8216 E-mail: an.ferrari@chiesi.com
INTERNATIONAL COORDINATOR	**Prof. Jorgen VESTBO** Professor in Respiratory Medicine Respiratory Research Group Education and Research Centre Wythenshawe Hospital M23 9LT Southmoor Road Manchester Great Britain
MONITORING CRO	**Chiltern International SARL** 37, bis rue de Villiers 92200 Neuilly sur Seine France

A 52-WEEK, DOUBLE BLIND, DOUBLE DUMMY, RANDOMIZED, MULTINATIONAL, MULTICENTRE, 3-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 TIOTROPIUM BROMIDE AND VERSUS FIXED COMBINATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE ADMINISTERED VIA PMDI AND TIOTROPIUM BROMIDE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Product: CHF 5993 100/6/12.5 mcg (extrafine fixed combination of beclometasone dipropionate 100mcg plus formoterol fumarate 6mcg plus glycopyrrolate bromide 12.5 mcg / metered dose)

Pharmaceutical Form: spray aerosol via pMDI HFA-134a propellant

Approval of the Clinical Study Protocol by the Sponsor's Representative:

Clinical Program Leader Caterina Brindicci Date: 26/07/2013
Caterina BRINDICCI, MD, PhD

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma – Italy

A 52-WEEK, DOUBLE BLIND, DOUBLE DUMMY, RANDOMIZED, MULTINATIONAL, MULTICENTRE, 3-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 TIOTROPIUM BROMIDE AND VERSUS FIXED COMBINATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE ADMINISTERED VIA PMDI AND TIOTROPIUM BROMIDE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Product: CHF 5993 100/6/12.5 mcg (extrafine fixed combination of beclometasone dipropionate 100mcg plus formoterol fumarate 6 mcg plus glycopyrrolate bromide 12.5 mcg / metered dose)

Pharmaceutical Form: spray aerosol via pMDI HFA-134a propellant

Approval of Clinical Study Protocol by the Coordinating Investigator:

I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

I understand that this trial will not be initiated without Ethics Committee/Institutional Review Board approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

Informed written consent will be obtained from all participating patients and appropriately documented, prior to their enrolment in the study.

The undersigned agrees that the trial will be carried out in conformity with the Code of Federal Regulations (21 CFR 50) and the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in patients.

International Coordinating Investigator's Name: Professor Jorgen VESTBO, MD

Centre No. : _____

Signature

07 Aug 2013
Date

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma – Italy

A 52-WEEK, DOUBLE BLIND, DOUBLE DUMMY, RANDOMIZED, MULTINATIONAL, MULTICENTRE, 3-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 TIOTROPIUM BROMIDE AND VERSUS FIXED COMBINATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE ADMINISTERED VIA PMDI AND TIOTROPIUM BROMIDE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Product: CHF 5993 100/6/12.5 mcg (extrafine fixed combination of beclometasone dipropionate 100 mcg plus formoterol fumarate 6 mcg plus glycopyrrolate bromide 12.5 mcg / metered dose)

Pharmaceutical Form: spray aerosol via pMDI HFA-134a propellant

Approval of Clinical Study Protocol by the Principal Investigator:

I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

I understand that this trial will not be initiated without Ethics Committee/Institutional Review Board approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

Informed written consent will be obtained from all participating patients and appropriately documented, prior to their enrolment in the study.

The undersigned agrees that the trial will be carried out in conformity with the Code of Federal Regulations (21 CFR 50) and the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in patients.

Principal Investigator's Name: _____ , MD

Centre No. : _____

_____ _____
Signature Date

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma - Italy

PROTOCOL OUTLINE

Study title	A 52-week, Double Blind, Double dummy, Randomized, Multinational, Multicentre, 3-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 tiotropium bromide and versus fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI and tiotropium bromide in patients with Chronic Obstructive Pulmonary Disease
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF 5993 (pMDI)
Centre(s)	Multicenter, in approximatively 200 sites
Indication	Chronic Obstructive Pulmonary Disease (COPD)
Study design	Double-blind, double-dummy, randomized, multinational, multicentre, 3-arm parallel-group, active-controlled study
Study phase	III
Objectives	***Primary objective*** To demonstrate the superiority of CHF 5993 pMDI over Tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment. ***Key secondary objectives*** To demonstrate the superiority of CHF 5993 pMDI over Tiotropium in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 at Week 52). To demonstrate the non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI+Tiotropium in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 at Week 52). ***Secondary objectives*** To evaluate the effect of CHF 5993 pMDI on other lung function parameters, patient's health status and clinical outcome measures. To perform a population PK analysis (in a subset of patients treated with CHF 5993 pMDI) investigating the inter-subject variability in the drug exposure and the effects of selected covariates on PK parameters of B17MP, FF and GB. 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.
Treatment duration	A 2-week open-label run-in period under Tiotropium followed by a 52-week randomised treatment period.
Test product dose/route/regimen	**CHF 5993 pMDI**: Fixed combination of beclometasone dipropionate 100 mcg plus formoterol fumarate 6 mcg plus glycopyrrolate bromide 12.5 mcg per metered dose (BDP/FF/GB) administered via metered dose inhaler (pMDI).

	Dose regimen: BDP/FF/GB, 100/6/12.5 mcg per inhalation, 2 inhalations bid. **Administration:** pressurised metered dose inhaler (pMDI) Patients used to inhale their COPD pMDI medications with a spacer shall continue using a spacer (AeroChamber Plus™ Flow-Vu antistatic) to take the pMDI study drugs.
Reference product dose/route/regimen	**Tiotropium Bromide (Spiriva®):**18 mcg inhalation powder, hard capsule, one capsule once daily **Dose regimen:** 18 mcg per capsule, one capsule once daily **Administration:** HandiHaler® inhaler **CHF 1535 pMDI + Tiotropium Bromide**: Free combination of beclometasone dipropionate 100 mcg/unit dose plus formoterol fumarate 6 mcg/unit dose (BDP/FF) administered via metered dose inhaler (pMDI) + Tiotropium bromide 18 mcg inhalation powder, hard capsule, one capsule once daily **Dose regimen:** BDP/FF, 100/6 mcg per inhalation, 2 inhalations bid + Tiotropium bromide 18 mcg per capsule, one capsule once daily. **Administration:** pressurised metered dose inhaler (pMDI) + HandiHaler® inhaler. Patients used to inhale their COPD pMDI medications with a spacer shall continue using a spacer (AeroChamber Plus™ Flow-Vu antistatic) to take the pMDI study drugs.
Number of patients	A total of 2580 patients (1032 in each of the CHF 5993 pMDI and Tiotropium groups and 516 in the CHF 1535 pMDI + Tiotropium group) will be randomised in order to reach a total of 2062 completed and evaluable patients (825 / 825 / 412 per group), considering a non-evaluable rate of approximately 20% at Week 52. At least 20 % of patients with very severe airflow limitation (post bronchodilator FEV_1 at screening <30% predicted normal value) will be randomised in the study. A total of 550 randomised patients (220 expected in each of the CHF 5993 pMDI and Tiotropium groups and 110 expected in the CHF 1535 pMDI + Tiotropium group) will be selected for the evaluation of PK in order to reach a total of 200 evaluable patients in the CHF 5993 pMDI group at Week 4, considering a non-evaluable rate of approximately 9% at this time point.
Study population	Patients with severe to very severe COPD
Inclusion/exclusion criteria	**INCLUSION CRITERIA** Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study: 1. Male and 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, updated February 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 ratio < 0.7 within 30 min after 4 puffs (4 x 100 mcg) 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 patient at screening with a CAT score ≥ 10.

8. A cooperative attitude and ability to be trained to use correctly the pMDI inhalers and HandiHaler® inhalers.

9. A cooperative attitude and ability to be trained to use correctly the spacer AeroChamber Plus™ Flow-Vu antistatic. The criterion on spacer applies only to patients who are using a spacer for the administration of their COPD medications at screening.

10. A cooperative attitude and ability to be trained to use correctly electronic devices with COPD questionnaire.

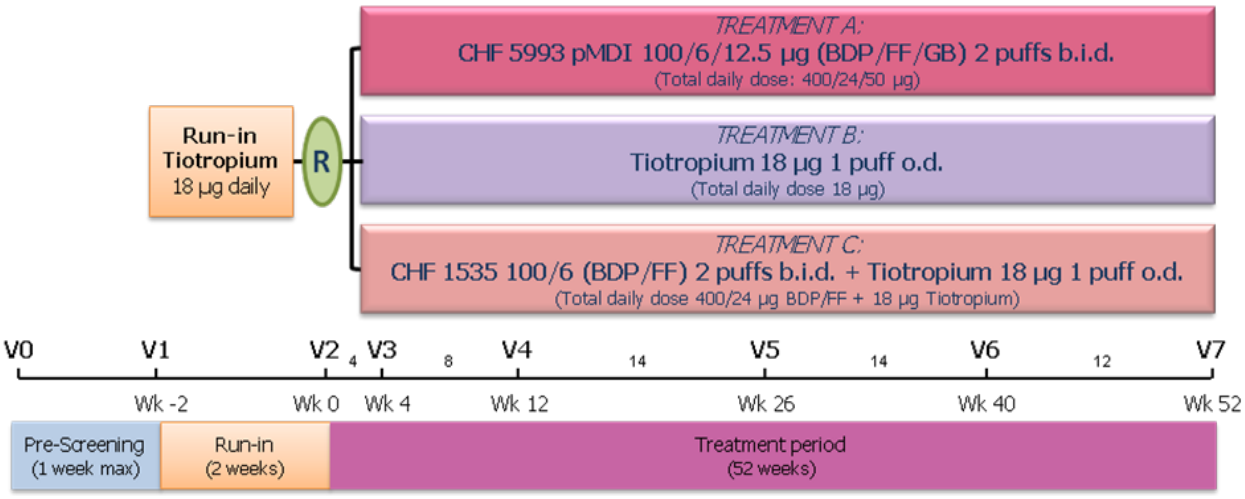
EXCLUSION CRITERIA

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 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 visits except V7. 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, history of allergic rhinitis or atopy (atopy which may raise contra-indications or impact the efficacy of the study according to investigator's judgment). 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. PDE4 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 the investigator's judgment. 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 in consultation with the Corporate Cardiac Leader's opinion. Patients whose electrocardiogram (ECG) (12 lead) shows QTcF >450 ms for males or QTcF >470 ms for females at screening visit are not eligible. 12. Medical diagnosis of narrow-angle glaucoma, clinically relevant 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 contra-indications 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; uncontrolled gastrointestinal disease (e.g. active peptic ulcer); uncontrolled neurological disease; uncontrolled haematological disease; uncontrolled autoimmune disorders, or other which may impact the feasibility of the results of the study according to investigator's judgment. 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.

	Patients included in the subset for PK assessment 19. Patients with unsuitable veins for repeated venipuncture. 20. Blood donation (equal or more than 450 mL) or blood loss in the 4 weeks before randomization.
Study plan	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, to obtain the written informed consent from the patient and to instruct the patient on screening visit procedures (such as medication restrictions and fasting conditions) - 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 receive Tiotropium 18 mcg per day. - After the randomisation (V2), patients will be assessed after 4, 12, 26, 40 and 52 weeks of treatment (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 compliance to the study medications daily in the digital platform configured for the study. AEs/SAEs and COPD exacerbations will be monitored throughout the study.
	
Most relevant allowed concomitant treatments	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 medications 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.
Most relevant forbidden concomitant treatments	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 steroid (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 antagonist. 7. Inhaled short acting β_2-agonists (other than salbutamol) (Short course 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. Oral xanthine derivatives (e.g. theophylline) 7 days prior to screening visit or during the study period. 13. PDE4 inhibitors (e.g. roflumilast) 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 antagonist: 12 hours • Inhaled SABA/SAMA fixed combinations: 12 hours • Inhaled long-acting β_2-agonists: 12 hours

	• Inhaled long acting muscarinic antagonist : 72 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 antagonist: 12 hours • Inhaled SABA/SAMA fixed combinations: 12 hours • Nebulised corticosteroids: 12 hours
Efficacy variables	**Primary efficacy variable** • Moderate and severe COPD exacerbation rate over 52 weeks of treatment. **Key secondary efficacy variable** • Change from baseline in pre-dose morning FEV_1 at Week 52. **Secondary efficacy variables** • Time to first moderate or severe COPD exacerbation. • Rate of severe COPD exacerbations over 52 weeks of treatment. • Time to first severe COPD exacerbation. • Rate of moderate COPD exacerbations over 52 weeks of treatment. • Change from baseline in pre-dose morning FEV_1 at all the other clinic visits. • Change from baseline to the average over the treatment period in pre-dose morning FEV_1. • FEV_1 response (change from baseline in pre-dose morning $FEV_1 \geq$ 100 ml) at Week 26 and Week 52. • Change from baseline in pre-dose morning IC at all clinic visits. • 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). **Exploratory efficacy variables** • Change from baseline in pre-dose morning 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: o family practitioner o specialist outpatients setting o 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.
Pharmacokinetic variables	Clearances and volumes of distribution will be estimated by population PK analysis starting from B17MP, FF and GB plasma levels measured in a subset of patients in the CHF 5993 pMDI group at steady state (Week 4). Other pharmacokinetic parameters of interest could also be reported like for example AUCtau (AUC during a dosing interval at steady state).
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 • Standard Haematology and Blood Chemistry
Sample size calculation	The sample size has been calculated to demonstrate the superiority of CHF 5993 pMDI over Tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment and change from baseline in pre-dose morning FEV_1 at Week 52, and the non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium in terms of change from baseline in pre-dose morning FEV_1 at Week 52. A total of 2580 patients will be randomised according to a 2:2:1 ratio to the CHF 5993 pMDI (1032 patients), Tiotropium (1032 patients) and CHF 1535 pMDI + Tiotropium groups (516 patients). A log-normal distribution is assumed for drop-out times, with drop-out rates of approximately 13%, 16.5% and 20% at Week 12, Week 26 and Week 52, respectively. A percentage of completed and evaluable patients with major protocol deviations of 9% is assumed. • This sample size will provide approximately 93.3% power to detect a rate ratio of 0.8 between CHF 5993 pMDI and Tiotropium at a two-sided significance level of 0.05, using a negative binomial model and assuming a rate of 0.9 exacerbations per patient per year in the Tiotropium group and an overdispersion parameter of the negative binomial distribution of 0.56. • At Week 52, 825 evaluable patients per group in the CHF 5993 pMDI and Tiotropium arms will provide approximately 99.7% power to detect a mean difference of 60 ml in terms of change from baseline in FEV_1 at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 260 ml. • At Week 52, 751 evaluable patients in the CHF 5993 pMDI group

	and 375 evaluable patients in the CHF 1535 pMDI + Tiotropium group with no major protocol deviations will provide approximately 86.0% power to demonstrate the non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium in terms of change from baseline in FEV_1 at a one-sided significance level of 0.025, with a non-inferiority margin of -50 ml and assuming no difference between treatments and a SD of 260 ml. An overall study power of approximately 80% will therefore be ensured. At least 20 % of patients with very severe airflow limitation (post-bronchodilator FEV_1 at screening < 30% of predicted normal value) will be randomised in the study. A total of 550 randomised patients (220 expected in each of the CHF 5993 pMDI and Tiotropium groups and 110 expected in the CHF 1535 pMDI + Tiotropium group) will be selected for the evaluation of PK in order to reach a total of 200 evaluable patients in the CHF 5993 pMDI group at Week 4, considering a non-evaluable rate of approximately 9% at this time point.This sample size is based on an evaluation of historical PK data and it is considered sufficient to properly conduct the planned population PK analysis.
Statistical methods	The comparisons between treatments will be conducted according to a hierarchical testing procedure. The primary and the key secondary efficacy comparisons will be considered in the following order: 1. superiority testing of CHF 5993 pMDI vs. Tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment (primary efficacy variable); 2. superiority testing of CHF 5993 pMDI vs. Tiotropium in terms of change from baseline in pre-dose morning FEV_1 at Week 52 (key secondary efficacy variable); 3. non-inferiority testing of CHF 5993 pMDI vs. CHF 1535 pMDI + Tiotropium in terms of change from baseline in pre-dose morning FEV_1 at Week 52 (key secondary efficacy variable). At each step of the procedure, no confirmatory claims will be made unless the objectives will be met in all the preceding steps. ***Primary efficacy variable*** 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 (1 or >1), severity of airflow limitation (post-bronchodilator FEV_1 at screening < or ≥ 30% of predicted normal value) 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 ratios with their 95% confidence intervals (CIs) will be estimated by the model. Superiority of CHF 5993 pMDI over Tiotropium will be demonstrated by a statistically significant rate ratio (defined as $p<0.05$) favouring CHF 5993 pMDI. The comparison CHF 5993 pMDI vs. CHF 1535 pMDI + Tiotropium will be considered as a secondary efficacy analysis. ***Key secondary efficacy variable*** Change from baseline (Visit 2) in pre-dose morning FEV_1 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, severity of airflow limitation 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 differences between treatments and their 95% CIs at Week 52 will be estimated by the model. Superiority of CHF 5993 pMDI over Tiotropium will be demonstrated by a statistically significant difference between treatments at Week 52 favouring CHF 5993 pMDI. Non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium will be demonstrated if the 95% CI of the adjusted mean difference between treatments at Week 52 will lie entirely to the right of the pre-defined non-inferiority margin of -50 ml. ***Secondary efficacy variables*** • 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. • The same analyses above defined for all moderate and severe COPD exacerbations will be performed separately on the number of severe and moderate COPD exacerbations during the treatment period and on the time to first severe COPD exacerbation. • For change from baseline in pre-dose morning FEV_1, 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 key secondary efficacy analysis. In the estimation of the averages over the treatment period equal weights will be assigned to the clinic visits. • FEV_1 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 • Change from baseline in pre-dose morning IC at all clinic visits will be analysed using a similar model as for the key secondary efficacy variable. • Change from baseline (Visit 2) in the SGRQ total score and domain scores at all clinic visits will be analysed using a similar model as for the key secondary efficacy variable. • SGRQ response at Week 26 and Week 52 will be compared between treatment groups using a similar model as for FEV_1 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 key secondary efficacy variable. 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.

	Exploratory efficacy variables • Change from baseline in pre-dose morning FVC at all clinic visits will be analysed using a similar model as for the key secondary efficacy variable. • 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. ***Pharmacokinetic variables*** • Individual plasma concentration data of BDP, B17MP, FF and GB will be tabulated vs. the scheduled sampling times. Concentrations will be summarized scheduled sampling time using descriptive statistics. Mean plasma concentration vs. time profiles will be presented in linear/linear and log/linear scales. • The plasma concentration data of B17MP, FF and GB will be subjected to a population PK analysis. For this analysis the data may be combined with results from previous studies (or analysis). The aim of the population PK analysis is to develop a compartmental model of the plasma concentration vs. time profiles, which will provide a good understanding of the inter-subject and intra-subject (if possible) variability in the drug exposure. In addition the effects of selected covariates on PK parameters will be evaluated, e.g. age, sex, race, smoking status, BMI, concomitant medications, renal and hepatic impairment. • Information regarding the population PK analysis will be described in the separate population PK Analysis Plan. The results and the model development will be described in detail in a separate PK Report. ***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 screening in pre-dose 12-lead ECG parameters (HR, QTcF, PR and QRS) will be analysed using a similar model as for the key secondary efficacy variable. 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 screening in post-dose 12-lead ECG parameters (HR, QTcF, PR and QRS). • At Week 26 and Week 52, the change from pre-dose to post-dose in the 12-lead ECG parameters 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 o QTcF >450 ms, >480 ms and >500 ms o change from screening in QTcF >30 ms and >60 ms o 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. • 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.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ANCOVA	ANalysis of COVAriance
BDP	Beclometasone DiPropionate
b.i.d	Bis in diem (twice a day)
B17MP	Beclometasone-17-monopropionate
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
(e-) CRF	(Electronic) Case Report Form
CRO	Contract Research Organization
ECG	ElectroCardioGram
EMA	European Medicine Agency
EXACT(-PRO)	EXAcerbations of Chronic pulmonary disease Tool
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in the 1st second
FF	Formoterol Fumarate
FPFV	First Patient First Visit
GB	Glycopyrrolate Bromide
GFR	Glomerular Filtration Rate
HCRU	Health Care Resources Utilisation
HE	Hepatic encephalopathy
HR	Heart Rate
IC	Inspiratory Capacity
ICH	International Conference on Harmonization
ICS	Inhaled CorticoSteroid
IM	IntraMuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention to Treat
IU (D or S)	Intra Uterine (Device or System)
IV	IntraVenous
LABA	Long Acting β_2 agonist
LAMA	Long Acting Muscarinic Antagonist
LPLV	Last Patient Last Visit
MACE	Major Adverse Cardiovascular Event
MAOI	MonoAmine Oxidase Inhibitor
mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
o.d.	Once daily
PDE	PhosphoDiEsterase
PK	Pharmacokinetics
pMDI	Pressurised Metered Dose Inhaler
PP	Per-Protocol
PRN	Pro re nata (as-needed)
PRO	Patient Related Outcome
SABA	Short Acting β_2 agonist

SAMA	Short Acting Muscarinic Antagonist
SAE	Serious Adverse Event
SAMA	Short Acting Muscarinic Antagonist
SGRQ	Saint George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SSRI	Selective Serotonin Re-uptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
VC (SVC / FVC)	Vital Capacity (Slow /Forced)
WHO	World Health Organisation

CONTENTS

APPENDICES

1. BACKGROUND INFORMATION AND STUDY RATIONALE

Chronic Obstructive Pulmonary Disease is a multi-component respiratory inflammatory disorder characterised by progressively partially reversible airway obstruction and hyperinflation and increasing frequency of exacerbations. The aim of pharmacological therapy for COPD is to slow down disease progression, control symptoms, improve health status and reduce frequency of exacerbations. International guidelines [1] advocate combining different classes of long acting bronchodilators or inhaled corticosteroids to achieve these goals.

Chiesi CHF 1535 100/6 mcg pressurised inhalation solution is a fixed dose combination (FDC) of Beclometasone Dipropionate (BDP 100 mcg/actuation) and of Formoterol Fumarate (FF 6 mcg/actuation developed as a hydrofluoroalkane (HFA) pressurised metered dose inhaler (pMDI). Glycopyrrolate Bromide (GB) is a synthetic quaternary ammonium compound that acts as a competitive antagonist of muscarinic acetylcholine receptors. The compound is being developed by Chiesi as hydrofluoroalkane (HFA) pressurised metered dose inhaler (pMDI) (CHF 5259) using the same formulation as CHF 1535.

The CHF 1535 FDC is named also BDP/FF 100/6 mcg or Beclomethasone Dipropionate/Formoterol Fumarate within this document.

Chiesi is now developing a triple fixed dose combination (FDC) by combining CHF 1535 pMDI with Glycopyrrolate Bromide (GB) using the same formulation for the indication of COPD. The code of triple FDC is CHF 5993 pMDI. The FDC is named CHF 5993 pMDI or BDP/FF/GB 100/6/12.5 mcg or Beclomethasone Dipropionate/Formoterol Fumarate/Glycopyrrolate Bromide within this document.

CHF1535 pMDI 100/6 mcg has been approved for the indication of asthma in EU and extra-EU countries since 2006 and its efficacy and safety shown in moderate asthma patients with a greater effect on lung function and asthma control over BDP CFC alone and similar effect to that of Symbicort and Seretide. CHF 1535 pMDI is currently being evaluated in COPD patients.
Antimuscarinics are a well established class of drugs, and there is extensive experience with the use of Glycopyrrolate by injection as well as orally (Robinul®, or generic equivalents). The injectable form (given intravenously [i.v.] or intramuscularly [i.m.]) is used predominantly during preoperative anesthesia to reduce salivary, tracheobronchial and pharyngeal secretions. Inhaled Glycopyrrolate has been shown to cause prolonged bronchodilation in patients with asthma and has been found to be an effective bronchodilator in patients with COPD [2,3].

The choice of therapeutic agents is based on disease stage, individual response and side effects profile. Inhaled corticosteroids (ICS) and long acting β2-agonists (LABA) combination products have been shown to improve lung function, symptoms and health status and to reduce exacerbations in patients with moderate to severe COPD [4,5]. Combining more than one class of bronchodilators such as a muscarinic antagonist with a LABA is more effective than the use of single agents with respect to improvement in lung function and symptoms [6,7,8]. Considering the different molecular mechanisms of action of these drugs, there is a scientific rationale for combining them together. The activation of various muscarinic receptors by acetylcholine causes airway constriction via the parasympathetic system. Conversely, activation of sympathetic β2-receptors leads to airway relaxation, allowing both muscarinic inhibition and β2-agonists to be targets for COPD treatment [9]. Besides adrenergic and muscarinic targets, inflammation also plays a role in the pathophysiology of COPD. Patients with COPD have infiltration of T cells, macrophages and neutrophils within the airway mucosa and lung parenchyma. The effects of corticosteroids on the

inflammatory pathway of COPD are minimal. However, in combination, corticosteroids may increase the number of β2-adrenoreceptors while β2-agonists may induce glucocorticoid receptor (GR) nuclear translocation [10]. Therefore, corticosteroid combination therapy may exhibit synergistic pharmacologic properties that anticholinergic, β2-agonist combinations.

Therefore adding a long acting muscarinic antagonist (LAMA) to a LABA/ ICS combination is an attractive alternative for patients with more severe disease and is widely used in clinical practice. Several clinical studies have investigated this treatment approach and showed that « triple therapy » is more effective therapy in terms of pulmonary function improvement and symptoms control as compared to bronchodilator monotherapy or ICS/LABA [11, 12, 13].

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

The aim of the present study is to evaluate the superiority of the fixed triple therapy with BDP/FF/GB at a daily dose of 400/24/50 mcg respectively with that of tiotropium monotherapy at a daily dose of 18 mcg and the non inferiority versus free triple therapy BDP/FF+tiotropium in COPD patients.

Tiotropium bromide is also named Tio or Tiotropium or Spiriva® within this document.

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 Objective

To demonstrate the superiority of CHF 5993 pMDI over Tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment.

2.2 Key Secondary Objectives

To demonstrate the superiority of CHF 5993 pMDI over Tiotropium in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 at Week 52).

To demonstrate the non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 at Week 52).

2.3 Secondary Objectives

To evaluate the effect of CHF 5993 pMDI on other lung function parameters, patient's health status and clinical outcome measures.

To collect data in order to assess the impact of study treatments on health economic outcomes.

To perform a population PK analysis (in a subset of patients treated with CHF 5993 pMDI) investigating the inter-subject variability in the drug exposure and the effects of selected covariates on PK parameters of B17MP, FF and GB.

To assess the safety and the tolerability of the study treatments.

3. STUDY DESIGN

This is a phase III, double-blind, double-dummy, randomized, multinational, multicentre, 3-arm parallel-group, active-controlled study in approximately 2580 randomised patients. Approximately 200 sites will be involved.

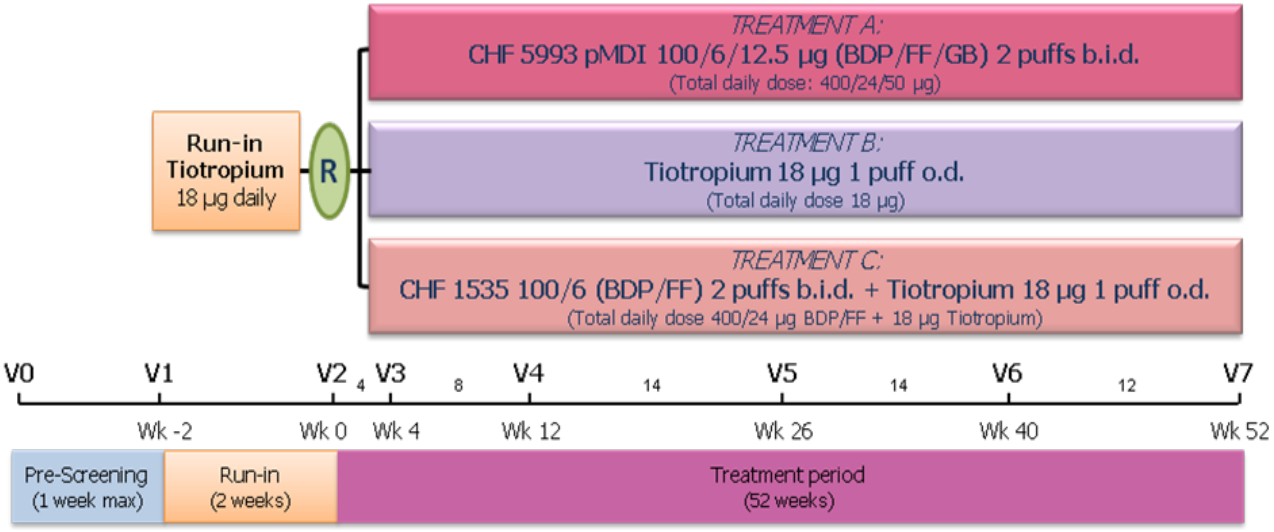
A total of 8 clinic visits (Visit 0 to Visit 7) will take place during the study:

- A pre-screening visit (Visit 0) will be carried out in order to fully explain the study to potential patients, to obtain their written informed consent and to instruct them on screening visit procedures (such as medication restrictions and fasting)
- A screening visit (Visit 1 no more than 7 days after V0, Week -2 before randomisation) will help establish the eligibility of patients for inclusion in the study. All previous treatments shall then be stopped accordingly to the non-permitted concomittant medications section (section 5.2). This visit will be followed by a 2-week open-label run-in period on Tiotropium (18 mcg daily);
- A randomisation visit (Visit 2, Week 0) where patients will be randomised to one of the three treatment arms.
- 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.

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

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

A total of 2580 patients (1032 in each of the CHF 5993 pMDI and Tiotropium groups and 516 in the CHF 1535 pMDI + Tiotropium group) will be randomised in order to reach a total of 2062 completed and evaluable patients (825 / 825 / 412 per group), considering a non-evaluable rate of approximately 20% at Week 52.

At least 20 % of patients with very severe airflow limitation (post-bronchodilator FEV_1 at screening < 30% of predicted normal value) will be randomised in the study.

A total of 550 randomised patients (220 expected in each of the CHF 5993 pMDI and Tiotropium groups and 110 expected in the CHF 1535 pMDI + Tiotropium group) will be selected for the evaluation of PK in order to reach a total of 200 evaluable patients in the CHF 5993 pMDI group at Week 4, considering a non-evaluable rate of approximately 9% at this time point.

The subset of patients who will undergo the PK evaluation will be selected in some sites which will be preselected in some involved countries. All the patients in these preselected sites will be involved in the blood sample collection for the PK analysis.

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 and 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, updated February 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 ratio < 0.7 within 30 min after 4 puffs (4 x 100 mcg) 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 patient at screening with a CAT score ≥ 10.

8. A cooperative attitude and ability to be trained to use correctly the pMDI inhalers and HandiHaler® inhalers.

9. A cooperative attitude and ability to be trained to use correctly the spacer AeroChamber Plus™ Flow-Vu antistatic. The criterion on spacer applies only to patients who are using a spacer for the administration of their COPD medications at screening.

10. 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 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 visits except V7.
   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, history of allergic rhinitis or atopy (atopy which may raise contra-indications or impact the efficacy of the study according to investigator's judgment).

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. PDE4 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 the investigator's judgment. 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 in consultation with the Corporate Cardiac Leader's opinion.
    Patients whose electrocardiogram (ECG) (12 lead) shows QTcF >450 ms for males or QTcF >470 ms for females at screening visit are not eligible.

12. Medical diagnosis of narrow-angle glaucoma, clinically relevant 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 contra-indications or impact the efficacy of the study drug according to the investgator'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; uncontrolled gastrointestinal disease (e.g. active peptic ulcer); uncontrolled neurological disease; uncontrolled haematological disease; uncontrolled autoimmune disorders, or other which may impact the feasibility of the results of the study according to investigator's judgment.

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.

Patients included in the subset for PK assessment

19. Patients with unsuitable veins for repeated venipuncture.
20. Blood donation (equal or more than 450 mL) or blood loss in the 4 weeks before randomization.

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 not interpretable; 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 nor 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 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.
The Investigator must fill in the Study Termination form in the eCRF explaining the primary reason for withdrawal and including the assessments performed (see section 7.1.9).

If a patient is withdrawn/drops-out of the study after receiving the test treatment, the patient study number and corresponding test treatments will 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 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 CRF.

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 medications 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-2agonists, 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 antagonist.
7. Inhaled short acting β_2-agonists (other than salbutamol) (Short course 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. Oral xanthine derivatives (e.g. theophylline) in 7 days prior to screening visit or during the study period.
13. PDE4 inhibitors (e.g. roflumilast)
14. Leukotriene modifiers
15. Non- potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug).

Prior to screening, 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 antagonist: 12 hours
- Inhaled SABA/SAMA fixed combinations: 12 hours
- Inhaled long-acting β_2-agonists: 12 hours
- Inhaled long acting muscarinic antagonist : 72 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 antagonist: 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 mcg***
  Active ingredient: Beclometasone dipropionate/Formoterol Fumarate/Glycopyrrolate Bromide 100/6/12.5 mcg per metered dose
  Excipients: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
  Presentation: canister containing 120 doses plus white actuator

- ***CHF 1535 pMDI 100+6 mcg (Foster®)***
  Active ingredient: Beclometasone dipropionate/Formoterol Fumarate 100/6 mcg per metered dose
  Excipients: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
  Presentation: canister containing 120 doses plus white actuator

- ***CHF 5993 pMDI placebo (*)***
  Excipients: HFA-134a propellant, ethanol anhydrous
  Presentation: canister containing 120 doses plus white actuator

- ***Tiotropium 18 mcg, powder for inhalation (Spiriva®)***
  Active ingredient: Tiotropium bromide 18mcg per capsule
  Excipients: Lactose monohydrate
  Presentation: Blister containing 10 capsules of Tiotropium bromide 18 mcg

- ***Tiotropium matched placebo, powder for inhalation (*)***
  Excipients: Lactose monohydrate
  Presentation: Blister containing 10 capsules of Tiotropium matched placebo

(*) The placebo pMDI and the matched placebo powder for inhalation will be used also for training.

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

6.2.2 Dosage

6.2.2.1 Run-in period:

Tiotropium bromide 18 mcg:

- **1 capsule o.d** via HandiHaler® inhaler (Total daily dose: Tiotropium 18 mcg)

6.2.2.2 Randomised Treatment period:

➢ **Treatment A (CHF 5993 pMDI arm)**:

CHF 5993 pMDI 100/6/12.5 mcg

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

➢ **Treatment B (Tiotropium arm)**:

Tiotropium bromide 18 mcg

- **1 capsule o.d** via HandiHaler® inhaler (Total daily dose: Tiotropium 18 mcg)

➢ **Treatment C (CHF 1535 pMDI +Tiotropium arm)**:

CHF 1535 pMDI 100/6 mcg

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

PLUS

Tiotropium bromide 18 mcg

- **1 capsule o.d** via HandiHaler® inhaler (Total daily dose: Tiotropium 18 mcg)

6.2.3 Administration

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

All previous COPD medications will have to be withdrawn during the course of the study except as described in section 5.

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

At Visit 1 (screening visit), each eligible patient will receive the medication to cover the 2-week run-in:

- One run-in box containing 3 blisters of 10 capsules each of tiotropium bromide powder for inhalation and 1 HandiHaler® inhaler.

Tiotropium bromide will be administered once a day in the morning: one hard capsule containing Tio 18 mcg using the HandiHaler® inhaler.

Ventolin® used as rescue medication will be taken as needed in response to symptoms.

6.2.3.2 Randomised period (from Visit 2 to 7):

Each patient will receive three boxes at V2, V4, V5 and V6 to cover the treatment duration between 2 visits with dispensation.

- One box containing 4 pMDI inhalers of CHF 5993 pMDI 100/6/12.5 mcg **or** 4 pMDI inhalers of placebo **or** 4 pMDI inhalers of CHF 1535 pMDI 100/6 mcg
- One box containing 12 blisters of 10 capsules each of Tiotropium bromide 18 mcg **or** matched placebo
- One box containing 1 HandiHaler® inhaler to inhale dry powder in capsule

If the patient is used to take COPD pMDI medication via a spacer, he/she shall use the AeroChamber Plus™ Flow-Vu antistatic provided at V2. He/she will receive a new AeroChamber Plus™ Flow-Vu antistatic at V4, V5 and V6.

The first administration of the study drug will take place in the morning at clinic visit under medical supervision.

The study treatments (CHF 5993 pMDI or Tiotropium or CHF 1535 pMDI+Tiotropium) will be administered daily. In order to ensure the double dummy design of the trial, patients randomised to

receive CHF 5993 pMDI will be administered Tiotropium matched placebo and patients randomised to receive Tiotropium will be administered pMDI placebo, as detailed in the scheme below:

Treatment Administration scheme	**CHF 5993 pMDI Arm**	**Tiotropium Arm**	**CHF 1535 pMDI +Tiotropium Arm**
pMDI	Two puffs in the morning and two puffs in the evening of CHF 5993 100/6/12.5 mcg	Two puffs in the morning and two puffs in the evening of pMDI Placebo	Two puffs in the morning and two puffs in the evening of CHF 1535 100/6 mcg
Dry powder for inhalation	One capsule containing Tiotropium matched placebo in the morning using the HandiHaler® inhaler	One capsule containing Tiotropium 18 mcg in the morning using the HandiHaler® inhaler	One capsule containing Tiotropium 18 mcg in the morning using the HandiHaler® inhaler

Administration will be done according to the package instruction leaflets. A package leaflet will be included with study medications in local language (see Appendices II and III).

Administration via a spacer device (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 (during the randomised period). The spacer device to be used in the study, the **AeroChamber Plus™** Flow-Vu antistatic (refered as AeroChamber Plus™ in the rest of the document), will be assigned to the patient by the Investigator (one spacer at visits: V1, V4, V5, V6). For these patients, **each inhalation** (from the pMDI) **must be performed via AeroChamber Plus™. For each puff, 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 IV.

Ventolin® used as rescue medication will be taken as needed in response to symptoms.

6.2.3.3 Use of dry powder for inhalation in capsules via HandiHaler® inhaler.

Priming is not applicable for HandiHaler® inhaler.

- **Cleaning of the inhaler**

The HandiHaler® inhaler must be cleaned regularly (once a month) by the patient, according to the detailed instructions provided (Appendix III). The inhaler must be completely open and rinsed with warm water. The HandiHaler® inhaler must then be dried thoroughly by tipping excess of water out and air-dry afterwards, leaving the dust cap, mouthpiece and base open. It takes 24 hours to air dry, so it must be cleaned right after the use to be ready for the next dose. If needed, the outside of the mouthpiece may be cleaned with a moist but not wet tissue.

6.2.3.4 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, CHF 1535 pMDI or Placebo 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 detailed instructions provided (Appendix II).

6.2.3.5 Use of a spacer

The intake of study drugs via the spacer must be done according to the AeroChamber Plus™ commercial leaflet (see Appendix IV). The AeroChamber must be washed weekly (at home), according to cleaning instructions of Appendix IV.

6.2.4 Patient Training

During the screening visit, each patient will receive two training kits containing placebo only (see description in section 6.3.1).
Patient will be instructed on how to use the pressurised Meter Dose Inhaler and the HandiHaler® inhaler to inhale the powder in capsule according to the instructions for use (Appendices II and III).
If the patient is used to take COPD pMDI medications via a spacer, he/she will be trained to use AeroChamber Plus™.
The proper use of the inhalers will be checked again at randomisation in all patients (including at V3 in the subset of patients included in the PK analysis) and the proper use of the spacer (if applicable) will be checked again as well. The AeroChamber Plus™ used for training will be dispensed to the patient at V1 and kept at V2, if he/she will enter the randomisation period.
These training kits will be kept at the site by the Investigator (will not be dispensed to the patients).

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 Farmaceutici S.p.A. will supply the study drugs for the run-in period and the randomised treatment period.

6.3.1 Training kits

At visit 1, the investigator will train the eligible patients using placebo, to the proper use of pMDI and HandiHaler® inhaler. The investigator will use two boxes.

One box will contain 1 CHF 5993 pMDI placebo.

- *Primary packaging*: canister plus standard actuator
- *Secondary packaging*: box containing 1 canister plus 1 standard actuator

A second box will contain 2 blisters of 10 hard capsules each of tiotropium matched placebo, dry powder for inhalation (DPI) and 1 HandiHaler® inhaler.

- *Primary packaging*: blister containing 10 hard capsules
- *Secondary packaging*: box containing 2 blisters of 10 hard capsules each and 1 HandiHaler® inhaler

If the patient is used to take COPD pMDI medication via a spacer, he/she will be trained to inhale using 1 AeroChamber Plus™.

- *Secondary packaging*: box containing 1 AeroChamber Plus™ spacer**.**

6.3.2 Run-in period

At visit 1, the investigator will deliver to each eligible patient one ambient box containing 3 blisters of 10 capsules of tiotropium powder for inhalation each and the HandiHaler® inhaler.

- *Primary packaging***:** blister **containing** 10 hard capsules
- *Secondary packaging*: box containing 3 blisters of 10 hard capsules each and 1 HandiHaler® inhaler.

6.3.3 Treatment period

At randomisation (V2) and subsequent visits (V4, 5 and 6, except V7), each patient will be provided with 3 boxes.
The first box will contain 4 pMDI inhalers of CHF 5993 pMDI 100+6+12.5mcg **or** CHF 1535 pMDI 100+6 mcg **or** placebo. 2 of the 4 inhalers will be labelled with a "sun" sticker (plus number 1 or 2) identifying the ones to be used for the morning administration. The remaining 2 inhalers will be labelled with a "moon" sticker (plus number 1 or 2) identifying the ones to be used for the evening administration. Overall, there will be 4 pMDI boxes per patient, from V2 to V6.

- *Primary packaging*: canister plus standard actuator
- *Secondary packaging*: box containing 4 canisters plus 4 standard actuators

The second box will contain 12 blisters of 10 hard capsules each of tiotropium 18mcg or matched placebo, dry powder for inhalation (DPI). Patients will be instructed to inhale the content of 1 capsule each morning. Overall, there will be 4 DPI boxes per patient, from V2 to V6.

- *Primary packaging*: blister containing 10 hard capsules
- *Secondary packaging*: box containing 12 blisters of 10 hard capsules each

The third box will contain 1 HandiHaler® inhaler for the administration of the dry powder in capsules. Overall, there will be 4 HandiHaler® inhalers per patient, from V2 to V6.

- *Secondary packaging***:** box containing 1 HandiHaler® inhaler

If the patient is used to take COPD pMDI medication via a spacer, he/she will be dispensed also with a box containing 1 AeroChamber Plus™. Overall, there will be 4 AeroChamber Plus™ per patient, one at V1 to be used until V4, the second at V4, the third at V5 and the forth at V6.

- *Secondary packaging***:** box containing 1 AeroChamber Plus™ spacer.

6.3.4 Rescue medication: salbutamol

During the study, each centre will receive the necessary quantity of rescue medication purchased locally to cover the 2-week run-in and the 52-week study period. The rescue medication will remain in its commercial packaging.

6.4 Labelling

All labelling of primary/secondary packaging of treatment andrun-in kits and secondary packaging of HandiHaler® and AeroChamber Plus™ will be in local language, with the exclusion of canisters that will be in English.
Labelling of training kits will be in English.

All the supplies will be labelled according to Annex 13 to EU GMP and according to local law and regulatory requirements. Labels will contain at least the following information:

Primary packaging:

- Study code
- Kit number
- Pharmaceutical dosage form, quantity of dosage units
- Route of administration
- Instruction for use
- Storage conditions
- Code/Batch number
- Sponsor

Secondary packaging:

- Study code
- Kit number
- Patient number
- Pharmaceutical dosage form, quantity of dosage units
- Route of administration
- Code/Batch number
- Sponsor
- Instruction for use
- Storage conditions
- For clinical trial use only
- Keep out of reach of children.

Tertiary packaging:

- Study code
- Kit number
- Patient number
- Pharmaceutical dosage form, quantity of dosage units
- Route of administration
- Code/Batch number
- Sponsor
- Instruction for use
- Storage conditions
- For clinical trial use only
- Keep out of reach of children.

The box of run-in kits, treatment kits, HandiHaler® inhalers and AeroChamber Plus™ will have a tear-off portion which will be removed and attached to the specific tracking form at the time the box is dispensed.

6.5 Treatment allocation

A balanced block randomisation scheme stratified by Country and severity of airflow limitation (post-bronchodilator FEV_1 at screening <30% or ≥30% of the predicted normal value) will be prepared via a computerised system. At least 20 % of patients with very severe airflow limitation (post-bronchodilator FEV_1 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 three treatment arms at the end of the run-in period through an Interactive Response Technology (IRT, combination of voice

and web response system). The Investigators at the sites will connect to the IRT to enrol and randomise patients. The IRT will allocate the patient ID, will assign the patient to a certain treatment group using a list-based randomisation algorithm and will 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 patient will be identified by a patient number of nine digits: the 3 first digits correspond to the country code, the next 3 digits will identify the site incrementally and the 3 last digits will be chronologically be assigned to patients within a centre.

The Investigator will connect to the IRT at each visit (from pre-screening to end of treatment) to register the patient status in the system.

6.6 Treatment Code

Study drug will be packaged and uniquely numbered. Each primary packaging in the medication kit will have a numbered label that matches the kit number on the label of the outside packaging. The IRT will be used to assign both initial and subsequent kits in order to have an inventory control and patient dosing tracking. The IRT will also maintain quantities, kit numbers, drug types, batch/code numbers, expiration dates and do not dispense after these dates. The IRT will monitor inventory levels at all sites and manage the study drug re-supply. The IRT will track patient screen failures, discontinuations and withdrawals from the study.

The randomization list will be provided to the labelling 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.

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 separate usernames and passwords 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 V).
The analytical laboratory performing the PK analyses will be unblinded.

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. It is also recommended to protect the study medication from humidity.

Run-in medication:

The boxes containing tiotropium bromide powder in capsules used as study medication for the run-in period must be stored **not above 25˚C** protect from humidity either by Pharmacist/Investigator at the Hospital and by patients at home.

***Study drug for randomized treatment period*:**

pMDI medication: CHF 5993 or CHF 1535 or placebo.

pMDI kits must be stored between 2˚C and 8˚C by Pharmacist/Investigator at the Hospital. At clinic visits, the medication kits should be removed from the refrigerator before patient's administration. If the inhaler has been exposed to severe cold, the canister has to be taken out of the mouthpiece and warmed with the hands for a few minutes before administration to the patient. It must never be warmed by artificial means. The patient should never inhale a cold medication. The canisters contain a pressurised liquid. It must not be exposed to temperatures higher than 50°C. Do not pierce the canister.

Once dispensed, the patients will be instructed to keep the boxes at home at ambient temperature not above 25°C but not in the refrigerator.
At this temperature condition the residual shelf life of the pMDI kits will be four months (**120 days**). 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 dispensing date plus 4 months.** Please note that the use-by-date must not exceed the total shelf life of the product.

DPI medication: Tiotropium or matched placebo

DPI kits must be stored at ambient temperature, not above 25°C and protect from humidity either by Pharmacist/Investigator at the Hospital and by patients at home.

***Medication for training*:**

pMDI training must be kept at site and **not** dispensed to the patients. pMDI training must be stored between 2˚C and 8˚C by Pharmacist/Investigator at the Hospital. At screening, the training kits should be removed from the refrigerator before patient's administration. If the inhaler has been exposed to severe cold, the canister has to be taken out of the mouthpiece and warmed with the hands for a few minutes before administration to the patient. It must never be warmed by artificial means. The patient should never inhale a cold medication. The canisters contain a pressurised liquid. It must not be exposed to temperatures higher than 50°C. Do not pierce the canister.

Once used, the pMDI training must be kept at site at ambient temperature not above 25°C, but not in the refrigerator. At this temperature condition the residual shelf life of the pMDI will be four months (**120 days**). Therefore, **the Pharmacist/Investigator at the Hospital must write the use-**

by-date on the kit labels once the pMDI is removed from the refrigerator, before using it. The **use-by-date corresponds to the dispensing date plus 4 months.** Please note that the use-by-date must not exceed the total shelf life of the product. The same trainng kit will be used by patient at screening and randomisation.

DPI training must be kept at site and **not** dispensed to the patients. DPI training must be stored at ambient temperature, not above 25°C and protect from humidity by Pharmacist/Investigator at the Hospital.

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 for destruction. 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), as follows:

- A **pre-screening visit** (**Visit 0**) to explain the aim of the study to the patients, to obtain their informed written consent and to prepare patients for V1;
- A **screening visit** (**Visit 1**, no more than 7 days after V0, week –2 before randomisation), to verify the patients' eligibility. This visit will be followed by a 2-week run-in period, where the patients will receive open-label tiotropium bromide at the daily dose of 18 mcg;
- A **randomisation visit** (**Visit 2**, Week 0) when patients will be randomised to one of the three treatment arms.
- 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 spirometry and vital signs assessment will be performed at all visits.
- EXACT questionnaire, study medication compliance and rescue medication use will be recorded daily during the run-in and randomised treatment periods using a digital platform.

A subset of patients will undergo blood sample collection in order to perform pharmacokinetic evaluations. The sampling will take place during **V3 (week 4)**, at steady state. The study plan and scheduled tests are summarised in the following flow-chart:

	Pre-screening		Treatment Period					
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7/ET***
Time (Wks)		**-2**	**0**	**4**	**12**	**26**	**40**	**52**
Windows (Days)			**±2d**	**±3d**	**±5d**	**±5d**	**±5d**	**±5d**
Assessments								
Informed consent procedures	✓							
Instructions for the screening visit	✓							
Demographic data collection	✓							
Inclusion/Exclusion criteria		✓						
Medical history/Previous medications		✓						
Concomitant medications		✓	✓	✓	✓	✓	✓	✓
Adverse Events/Serious adverse events		✓	✓	✓	✓	✓	✓	✓
Physical examination		✓	✓	✓	✓	✓	✓	✓
Smoking Status		✓	✓	✓	✓	✓	✓	✓
Weight and height [1]		✓	✓	✓	✓	✓	✓	✓
Vital signs (BP) pre-dose and 10 min post-dose		✓ [2]	✓	✓	✓	✓	✓	✓
12-lead ECG at pre-dose and 10 min post-dose [3]		✓ [2]				✓		✓
Eligibility confirmation for randomisation			✓ [4]					
Pre-dose spirometry [5]		✓	✓	✓	✓	✓	✓	✓
Spirometry after salbutamol		✓ [6]						
COPD Assessment Test (CAT)		✓						
EQ-5D-3L health questionnaire			✓	✓	✓	✓	✓	✓
St George's Respiratory Questionnaire (SGRQ)			✓	✓	✓	✓	✓	✓
Health Economics			✓	✓	✓	✓	✓	✓
Pharmacokinetic evaluations				✓ [7]				
Haematology and blood chemistry		✓				✓		✓
Serum pregnancy test [8]		✓						✓
Urinary pregnancy test [8]		✓	✓	✓	✓	✓	✓	
IRS call	✓	✓	✓	✓	✓	✓	✓	✓
Drug dispensation		✓	✓		✓	✓	✓	
Drug collection			✓		✓	✓	✓	✓
Electronic diary completion (EXACT-PRO questionnaire, treatment compliance, rescue intake)		✓ **(daily)**						
Electronic diary review			✓	✓	✓	✓	✓	✓
Assessment of COPD exacerbations		✓	✓	✓	✓	✓	✓	✓
Training to the use of pMDI inhalers		✓	✓					
Training to the use of HandiHaler® for DPI		✓	✓					
Training to the use of Aerochamber Plus [9]		✓	✓					
Training to questionnaires use on digital platform		✓	✓					

* ET stands for Early Discontinuation (for patients withdrawn from the study prior to week 52)

1- Height only to be recorded at screening

2- Vital signs and ECG at screening will only be performed before salbutamol intake.

3- 12-lead ECG will be recorded in triplicate at screening (see section 7.2.6)
4- Relevant inclusion and exclusion criteria to be confirmed at randomisation
5- Including IC, FEV_1, FVC. Please to verify that wash-out of rescue medication (at least 6h), forbidden and study medications have been respected.
6- After 4x100 mcg salbutamol in order to evaluate the post-bronchodilator FEV_1 % predicted and FEV_1/FVC ratio for patient eligibility
7- Evaluation at steady state on a subset of patients. Blood sample (4 ml/timepoint for the analysis of FF, 4 ml/timepoint for the analysis of GB and 6 ml/timepoint for the analysis of B17MP) will be taken at pre-dose and 5min, 15 min, 1h, 4h and 8h post-dose.
8- For females of childbearing potential only.
9- Training with spacer will be performed only for patients already using 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:

- Collection of the written informed consent signed by the patient, 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 visit (Visit 1) 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 unique patient number. This number will be sequentially assigned.

Before discharge,

- A **patient card** with the Investigator's contact details will be handed out to the patient.
- An **appointment** for the screening visit (Visit 1) will be taken **within 1 week** in the morning. 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 in the 6 hours preceding the next visit, unless absolutely necessary;
➔ Not to take inhaled short acting muscarinic antagonists (SAMA) or SABA/SAMA combination in the 12 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 order to identify eligible consenting patients for the study. The following procedure will take place:

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:

- The medical history and the 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 urine pregnancy test will be performed in women of childbearing potential.
- A full physical examination will be performed.
- Weight and height will be recorded.
- Vital signs [systolic (SPB) and diastolic (DBP) blood pressure] will be measured before salbutamol administration, after 10 minutes of rest (see section 7.2.5).
- A 12-lead ECG will be performed in triplicate before salbutamol administration after 10 minutes of rest (see section 7.2.6). A patient will not be eligible in case of QTcF >450 ms for males or QTcF >470 ms for females (the value will be the average of the 3 recorded 12-lead ECG), 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 in consultation with the Chiesi Corporate Cardiac Leader's opinion.
- A blood sample will be collected before salbutamol administration and after an overnight fasting for the assessments of (see section 7.2.9):
  - 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). Laboratory results will be entered in the eCRF by the investigator.
- Pre-bronchodilator spirometry will be carried out: the patient will have to perform a SVC manoeuvre to assess pre-dose inspiratory capacity (IC) followed by a FVC manoeuvre for other pre-dose parameters (FEV_1, FVC and FEV_1/FVC). (see section 7.2.4)
- Patients will inhale 4 puffs (4 × 100 mcg) of salbutamol
- Post-bronchodilator spirometry (FVC manoeuvre) will be carried out within **30 min** after the inhalation of 400 mcg of salbutamol pMDI to assess FEV_1, FVC and FEV_1/FVC ratio. To be eligible, post salbutamol **FEV_1** must be **<50%** of the patient's predicted normal value **and** post salbutamol **FEV_1/FVC<0.7**. (see section 7.2.4)

  If the criterion is not met, this test can be performed **once more before Visit 2** after an appropriate wash-out from bronchodilators. The criterion must be confirmed before randomisation.
- The CAT questionnaire will be completed to evaluate whether the patient is symptomatic (see section 7.2.2.1). Symptomatic patient with a **CAT score ≥ 10 at screening are eligible**.
- 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 within 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 the patient is not eligible, the investigator will access the IRT to record the status of the patient as screen failure.

- If the patient is eligible, inclusion criteria 8, 9 and 10 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). Patients will also be trained to the proper use of the HandiHaler® inhaler for the inhalation of DPI in capsule (see section 6.2.4 and appendix III). 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 IV).
- Patient will be also instructed on how to report the medications (run-in and rescue) intake as well as their symptoms (EXACT-PRO questionnaire) and on how to transmit the data daily on the digital platform. (see section 7.2.2.2).

- If the training is successful and patient is therefore eligible for inclusion criteria 8, 9 and 10, the investigator will access the IRT in order to obtain the run-in medication (Tiotropium bromide with HandiHaler® inhaler) to be dispensed together with instructions for use. **The first administration of run-in medication will take place at the clinic visit under medical supervision**.
- If the patient is not eligible to criteria 8, 9 and 10, the investigator will access the IRT to record the status of the patient as screen failure.
- Patients will be instructed to withdraw all non-permitted COPD medications in accordance with section 5.2.

- Rescue salbutamol, for as needed use, will be dispensed. 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 will be dispensed to the patient**. The corresponding tear-off label will be stuck to the patient specific dispensation tracking form and the kit number will be recorded in the e-CRF. Patients will be instructed to inhale 1 capsule of 18 mcg tiotropium in the morning.
- **An electronic diary will be dispensed.** Patient must complete and transmit the diary daily 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 within 2 weeks (±2 days) from Visit 1 (at approximately the same time of the day, between 7:00 and 09:00 a.m.). The patient will be instructed to:
  - ➔ To complete and transmit the **daily electronic diary** until visit 2.
  - ➔ **Not to take salbutamol in the 6 hours** preceding the next visit, unless absolutely necessary.
  - ➔ **Not to take the run-in medication for 24h before coming to the clinic visit**. (the last run-in medication intake shall occur in the morning of the day preceding visit 2 date).
  - ➔ **To bring back the run-in and rescue medications (in their boxes)**, the **electronic diary** at the next visit. For patients using a spacer, they will be instructed **to bring back the AeroChamber PLUS™**.

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

The visit 2 will start between 7:00 and 09:00 a.m.

If rescue salbutamol has been inhaled in the previous 6 hours, or run-in medication has been taken later than the morning of the day prior to 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 or if run-in medication wash-out is again not respected, the patient will be discontinued and recorded as screen failure in the IRT.

The following procedures will be performed:

- Medications for the run-in period will be collected as well as the AeroChamber PLUS™;
- 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 it will be given again to the patient.** (see section 7.2.2.2)
- Changes of smoking status will be recorded. Pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication (see section 5.2), the patient will be withdrawn from the study and recorded as screen failure in the IRT and eCRF.
- The occurrence of COPD exacerbations (if any) will be evaluated and data will be recorded in the e-CRF. In case of exacerbation during the run-in, the patient will not be randomised (see also sections 5.1-5.2) and recorded as screen failure in the IRT and eCRF.
- The occurrence of adverse events (if any) will be checked and recorded.

- A urine pregnancy test will be performed in women of childbearing potential
- 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 7.2.5).
- The proper use of pMDI and DPI capsules with HandiHaler® inhaler will be checked and the patient will be trained again using training kits (see section 6.2.4).
- If the patient is used to take COPD pMDI medications via a spacer, the proper use of the AeroChamber Plus™ (see appendix IV) will be checked again with the spacer used at visit 1.
- Eligibility criteria will be reviewed.

For eligible patients:

- The EQ-5D-3L questionnaire will be completed at the visit by the patient (see section 7.2.2.3).
- The St George's Questionnaire (SGRQ) will be completed at the visit by the patient (see section 7.2.2.4).
- Investigator will collect Health economic information as per section 7.2.3
- Pre-dose spirometry measurement will be performed prior to randomisation: the patient will have to perform a SVC manoeuvre to assess pre-dose inspiratory capacity (IC) followed by a

FVC manoeuvre for other pre-dose parameters (FEV_1, FVC). This measurement will constitute the pre-dose baseline values. (see section 7.2.4).

- The patient will be randomised and the treatment will be allocated according to a central randomisation system. Investigator will access the IRT in order to obtain the appropriate kit numbers for a 12-week treatment period plus one HandiHaler inhaler. **The first administration of the study drug will take place at the clinic visit (before 10:00 am) under supervision of the Investigator** as per instructions for use (Appendices II and III) and according to section 6.2.3. For the patient using a spacer, pMDI medication will be taken via the AeroChamber Plus™ as per instructions for use (Appendix IV).
- The corresponding tear-off labels will be stuck in the dispensation tracking form and the kit numbers will be recorded in the e-CRF. For pMDI, the use-by-date must be filled-in on the labels.

- Post-dose (10 min) vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.5).

Before Discharge,

- **Study medication** plus one HandiHaler inhaler will be dispensed to the patient together with instructions for use (Appendices II and III). Drug administration must be explained according to section 6.2.3.
- An **appointment for Visit 3** will be made within 4 weeks (±3 days) from Visit 2 (at approximately the same time as Visit 2, between 7:00 and 09:00 a.m.). The patient will be instructed:
  - ➔ To continue completing **and transmitting the EXACT-PRO and study medication/rescue** intake in the digital platform.
  - ➔ To **bring back** the **electronic diary** and the **study medication** plus the HandiHaler inhaler (in their boxes) at the next visit.
  - ➔ For the patient using a spacer, to bring back the **AeroChamber Plus™**.
  - ➔ To **avoid taking salbutamol in the 6 hours** preceding the next visit, unless absolutely necessary.
  - ➔ **Not to take study medication the morning of the next clinic visit**.
  - ➔ **For the subset of patients selected to perform PK assessment**: To follow **strictly** the restrictions as described in section 7.2.8. (e.g. but not limited to fast for at least 10 hours before the next clinic visit).

7.1.4 Visit 3 (Week 4 of Treatment Period)

The Visit 3 will start between 7:00 and 09:00 a.m.

If rescue salbutamol has been inhaled in the previous 6 hours, or if study and allowed medications has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 1 or 2 days. Only one re-schedule is allowed. If wash-out periods are still not respected at this rescheduled 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 smoking status will be recorded. Pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.

- 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. In case of withdrawal, it will be recorded as discontinued in the IRT and eCRF.
- 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 it will be given again to the patient.** (see section 7.2.2.2)
- The occurrence of COPD exacerbations and other adverse events (if any) will be evaluated and data will be recorded in the e-CRF.
- A urine pregnancy test will be performed in women of childbearing potential
- A full physical examination will be performed.
- Weight will be recorded.

- The EQ-5D-3L questionnaire will be completed at the visit by the patient (see section 7.2.2.3).
- The St George's Questionnaire (SGRQ) will be completed at the visit by the patient (see section 7.2.2.4).
- Investigator will collect Health economic information as per section 7.2.3
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.5).
- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose inspiratory capacity (IC) followed by a FVC manoeuvre for other pre-dose parameters (FEV_1, FVC). Spirometry consists in three acceptable manoeuvres (see section 7.2.4).
- **In a subset of patients,** pre-dose (prior to study medication administration) and 5 minutes, 15 minutes, 1hour, 4 hours and 8 hours post-dose blood sample collections will be performed in order to perform the pharmacokinetic evaluations (see section 7.2.8).
- The proper use of pMDI will be confirmed by the investigator for patients participating to the PK subgroup.
- **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.** Drug administration will be done according to section 6.2.3. For the patient using a spacer, pMDI medication will be taken via the AeroChamber Plus™.
- The Investigator will access the IRT to register the status the patient

- Post-dose (10 min) vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.5).

Before discharge,

- **Electronic diary and study medication** (dispensed at V2) will be given back to the patient together with **instructions for use**. The investigator will remind the patient about the administration of the study medication as per section 6.2.3. Patient will be instructed to take salbutamol as rescue if necessary.

- An **appointment for Visit 4** will be made within 8 weeks from Visit 3 (at approximately the same time as previous visit, between 7:00 and 09:00 a.m.). **The time window should not exceed 12 weeks (±5 days) from Visit 2**.
  - ➔ To continue **completing and transmitting the EXACT-PRO** and **study medication/rescue** intake in the digital platform.
  - ➔ To continue using kits dispensed at V2
  - ➔ To **bring back the electronic diary digital platform and the study medication** (in their boxes) at the next visit.
  - ➔ For the patient using a spacer, to bring back the **AeroChamber Plus™**.
  - ➔ To **avoid taking salbutamol in the 6 hours** preceding the next visit, unless absolutely necessary.
  - ➔ **Not to take study medication the morning of the next clinic visit**.

Important Notes for the visit for the subset of patients selected to perform PK assessment:

- ✓ Patient will have to be at the clinical centre in the morning at least **1 hour before drug administration in fasting conditions** (fasting from at least 10 hours).
- ✓ Patient will remain fasted until 2 hour post-dose. Breakfast and lunch will be served approximately 2 and 4 hour post-dose.
- ✓ Fluid intake will be forbidden for 1 hour post-dose, then, in order to maintain an adequate hydration, patients should take at least 240 mL of mineral water every 2 hours for the following 6 hours.
- ✓ No alcohol or xanthine (coffee, tea, chocolate, cola, etc) containing beverages or food as well as xanthine derivatives, nor grapefruit containing beverages or food will be allowed starting from 48 hour before the drug administration on the day of blood sampling for PK assessments until the end of blood sampling.
- ✓ Time 0 is defined as the moment when the first inhalation of the drug from inhaler 1 takes place. Subjects will take the medication in an upright position. Additionally, the subjects will be instructed to hold their breath for 10 sec following each inhalation and to wait 30 sec before taking the next inhalation.
- ✓ Patient will not be allowed to lie down or sleep for 2 hours after administration, except when undergoing clinical assessments. They must remain seated as much as possible and avoid strenuous activities. Patient will be required to stay in the ward area until at least 2 hours after dosing, after which they will be permitted to use the Volunteer Recreation Room at the discretion of the clinical staff.
- ✓ In order to prevent any kind of blood samples contamination, the administration of the study drug will take place in a room well separated from the blood sampling station. Patients will remain in the room of administration only for the time strictly needed for the administration. Furthermore, during study drug inhalation, patient and investigator assistant will wear special protective coats and gloves, which will be removed before blood sampling. The assistant administering the inhalations will not be allowed to participate in the blood sampling procedures

7.1.5 Visit 4 (Week 12 of Treatment Period)

The Visit 4 will start between 7:00 and 09:00 a.m.

If rescue salbutamol has been inhaled in the previous 6 hours, or if study and allowed medications has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 1 or 2 days. Only one re-schedule is allowed. If wash-out periods are still not respected at this rescheduled

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 investigator will collect the previous medication kits in their boxes and check whether new rescue shall be provided to the patient. For patients using a spacer, the AeroChamber Plus™ dispensed at V1 must also be collected.
- Changes of smoking status will be recorded. Pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- Changes 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. In case of withdrawal, it will be recorded as discontinued in the IRT and eCRF.
- 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 it will be given again to the patient.** (see section 7.2.2.2)
- The occurrence of COPD exacerbations and other adverse events (if any) will be evaluated and data will be recorded in the e-CRF.
- A urine pregnancy test will be performed in women of childbearing potential.
- A full physical examination will be performed.
- Weight will be recorded.
- The EQ-5D-3L questionnaire will be completed at the visit by the patient (see section 7.2.2.3).
- The St George's Questionnaire (SGRQ) will be completed at the visit by the patient (see section 7.2.2.4).
- Investigator will collect Health economic information as per section 7.2.3
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.5).
- Pre-dose spirometry measurement will be performed; the patient will have to perform a SVC manoeuvre to assess pre-dose inspiratory capacity (IC) followed by a FVC manoeuvre for other pre-dose parameters (FEV_1, FVC). Spirometry consists in three acceptable manoeuvres (see section 7.2.4).
- The investigator will access the IRT in order to obtain the appropriate subsequent kit numbers for a 14-week treatment period plus one new HandiHaler inhaler according to centralised randomisation system.
- **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.** Drug administration will be done according to section 6.2.3. For the patient using a spacer, pMDI medication will be taken via a new AeroChamber Plus™ dispensed to the patient. The corresponding tear-off labels will be stuck in the dispensation tracking form and the kit numbers will be recorded in the corresponding e-CRF. For pMDI, the use-by-date must be filled-in on the labels.

- Post-dose (10 min) vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.4).

Before discharge,

- **Study medication** plus one new HandiHaler inhaler will be dispensed to the patient together with instructions for use. Drug administration instructions will be given according to section 6.2.2
- **Electronic diary** will be given back to patient.
- **An appointment for Visit 5** will be made within 14 weeks from Visit 4 (at approximately the same time as previous visit, between 7:00 and 09:00 a.m.). **The time window should not exceed 26 weeks (±5 days) from Visit 2**. The patient will be instructed:
  - ➔ To **fast overnight** for the next visit in order to perform blood sampling (only water is allowed)
  - ➔ To **continue completing and transmitting the EXACT-PRO and study medication/rescue** intake in the digital platform.
  - ➔ To **bring back the electronic diary digital platform and the study medication** plus the new HandiHaler inhaler (in their boxes) at the next visit.
  - ➔ For the patient using a spacer, to bring back the **AeroChamber Plus™**.
  - ➔ To **avoid taking salbutamol in the 6 hours** preceding the next visit, unless absolutely necessary.
  - ➔ **Not to take study medication the morning of the next clinic visit**.

7.1.6 Visit 5 (Week 26 of Treatment Period)

The Visit 5 will start between 7:00 and 09:00 a.m.

If rescue salbutamol has been inhaled in the previous 6 hours, or if study and allowed medications has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 1 or 2 days. Only one re-schedule is allowed. If wash-out periods are still not respected at this rescheduled 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 their boxes) provided at Visit 4 will be collected. For patients using a spacer, the AeroChamber Plus™ dispensed at V4 must also be collected.
- Changes of smoking status will be recorded. Pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- 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. In case of withdrawal, it will be recorded as discontinued in the IRT and eCRF.
- 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 it will be given again to the patient.** (see section 7.2.2.2).
- The occurrence of COPD exacerbations and other adverse events (if any) will be evaluated and data will be recorded in the e-CRF.

- The investigator will check whether new rescue shall be provided to the patient.

- A urine pregnancy test will be performed in women of childbearing potential.
- A full physical examination will be performed.
- Weight will be recorded.

- The EQ-5D-3L questionnaire will be completed at the visit by the patient (see section 7.2.2.3).
- The St George's Questionnaire (SGRQ) will be completed at the visit by the patient (see section 7.2.2.4).
- Investigator will collect Health economic information as per section 7.2.3
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.5).
- Pre-dose 12-lead ECG will be performed after 10 minutes of rest (see section 7.2.6).
- A blood sample will be collected at pre-dose and after an overnight fasting for the assessments of (see section 7.2.9):
  - standard haematology and blood chemistry;

  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. Laboratory results will be entered in the eCRF by the investigator.

- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose inspiratory capacity (IC) followed by a FVC manoeuvre for other pre-dose parameters (FEV_1, FVC). Spirometry consists in three acceptable manoeuvres (see section 7.2.4).
- The investigator will access the IRT in order to obtain the appropriate subsequent kit numbers for a 14-week treatment period plus one new HandiHaler inhaler according to centralised randomisation system.
- **The morning dose of study medication will be administered at the clinic under supervision of the Investigator from the kit dispensed.** Drug administration will be done according to section 6.2.3. For the patient using a spacer, pMDI medication will be taken via a new AeroChamber Plus™ dispensed to the patient. The corresponding tear-off labels will be stuck in the dispensation tracking form and the kit numbers will be recorded in the corresponding e-CRF. For pMDI, the use-by-date must be filled-in on the labels.

- Post-dose (10 min) vital signs (SBP and DBP) blood pressure] will be measured, after 10 minutes of rest (see section 7.2.5).
- Post-dose 12-lead ECG will be performed 10 minutes after study drug administration (ECG to be recorded after 10 minutes of rest) (see section 7.2.6).

Before discharge,

- **Study medication** plus one new HandiHaler inhaler will be dispensed to the patient together with instructions for use. Drug administration instructions will be given according to section 6.2.3.
- **Electronic diary** will be given back to patient.

- An **appointment for Visit 6** will be made within 14 weeks from Visit 5 (at approximately the same time as previous visit, between 7:00 and 09:00 a.m.). **The time window should not exceed 40 weeks (±5 days) from Visit 2**. The patient will be instructed:
  - ➔ To **continue completing and transmitting the EXACT-PRO and study medication/rescue** intake in the digital platform
  - ➔ To **bring back the electronic diary digital platform and the study medication** plus the HandiHaler inhaler (in their boxes) at the next visit.
  - ➔ For the patient using a spacer, to bring back the **AeroChamber Plus™**.
  - ➔ To **avoid taking salbutamol in the 6 hours** preceding the next visit, unless absolutely necessary.
  - ➔ **Not to take study medication the morning of the next clinic visit**.

7.1.7 Visit 6 (Week 40 of Treatment Period)

The Visit 6 will start between 7:00 and 09:00 a.m.

If rescue salbutamol has been inhaled in the previous 6 hours, or if study and allowed medications has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 1 or 2 days. Only one re-schedule is allowed. If wash-out periods are still not respected at this rescheduled 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 their boxes) provided at Visit 5 will be collected. For patients using a spacer, the AeroChamber Plus™ dispensed at V5 must also be collected.

- Changes of smoking status will be recorded. Pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- 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. In case of withdrawal, it will be recorded as discontinued in the IRT and eCRF.
- 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 it will be given again to the patient.** (see section 7.2.2.2)
- The occurrence of COPD exacerbations and other adverse events (if any) will be evaluated and data will be recorded in the e-CRF.
- The investigator will check whether new rescue shall be provided to the patient.

- A urine pregnancy test will be performed in women of childbearing potential.
- A full physical examination will be performed.
- Weight will be recorded.

- The EQ-5D-3L questionnaire will be completed at the visit by the patient (see section 7.2.2.3).

- The St George's Questionnaire (SGRQ) will be completed at the visit by the patient (see section 7.2.2.4).
- Investigator will collect Health economic information as per section 7.2.3
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.5).
- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose inspiratory capacity (IC) followed by a FVC manoeuvre for other pre-dose parameters (FEV_1, FVC). Spirometry consists in three acceptable manoeuvres (See section 7.2.4).
- The investigator will access the IRT in order to obtain the appropriate subsequent kit numbers for a 12-week treatment period plus one new HandiHaler inhaler according to centralised randomisation system.
- Study medication will be dispensed to the patient together with instructions for use.
- **The morning dose of study medication will be administered at the clinic under supervision of the Investigator from the kit dispensed.** Drug administration will be done according to section 6.2.3. For the patient using a spacer, pMDI medication will be taken via anew AeroChamber Plus™ dispensed to the patient. The corresponding tear-off labels will be stuck in the dispensation tracking form and the kit numbers will be recorded in the corresponding e-CRF. For pMDI, the use-by-date must be filled-in on the labels.

- Post-dose (10 min) vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.5).

Before discharge,

- **Study medication** plus one new HandiHaler inhaler will be dispensed to the patient together with instructions for use. Drug administration instructions will be given according to section 6.2.2.
- **Electronic diary** will be given back to patient.
- An **appointment for Visit 7** will be made within 12 weeks from Visit 6 (at approximately the same time as previous visit, between 7:00 and 09:00 a.m.). **The time window should not exceed 52 weeks (±5 days) from Visit 2**. Patient will be instructed:
  - ➔ To **fast overnight** for the next visit in order to perform blood sampling (only water is allowed);
  - ➔ To continue **completing and transmitting the EXACT-PRO and study medication/rescue** intake in the digital platform.
  - ➔ To **bring back the electronic diary digital platform and the study medication** plus the HandiHaler inhaler (in their boxes) at the next visit.
  - ➔ For the patient using a spacer, to bring back the **AeroChamber Plus™**.
  - ➔ To **avoid taking salbutamol in the 6 hours** preceding the next visit, unless absolutely necessary.
  - ➔ **Not to take study medication the morning of the next clinic visit**.

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

The Visit 7 will start between 7:00 and 09:00 a.m.

If rescue salbutamol has been inhaled in the previous 6 hours, or if study and allowed medications has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 1 or 2

days. Only one re-schedule is allowed. If wash-out periods are still not respected at this rescheduled 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 their boxes) provided at Visit 6 will be collected. For patients using a spacer, the AeroChamber Plus™ dispensed at V6 must also be collected.

- Changes of smoking status will be recorded. Pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, it must be recorded in the eCRF.
- 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 (if any) will be evaluated and data will be recorded in the e-CRF.
- The occurrence of adverse events since the previous visit will be evaluated and recorded (if any). **The status of any unresolved AEs recorded during the study must be checked and updated**.
- The investigator will collect the previous medication kits.

- A full physical examination will be performed.
- Weight will be recorded.

- The EQ-5D-3L questionnaire will be completed at the visit by the patient (see section 7.2.2.3).
- The St George's Questionnaire (SGRQ) will be completed at the visit by the patient (see section 7.2.2.4).
- Investigator will collect Health economic information as per section 7.2.3
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.5).
- Pre-dose 12-lead ECG will be performed after 10 minutes of rest (see section 7.2.6).
- A blood sample will be collected at pre-dose and after an overnight fasting for the assessments of (see section 7.2.9):
  - 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. Laboratory results will be entered in the eCRF by the investigator.

- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose inspiratory capacity (IC) followed by a FVC manoeuvre for other pre-dose parameters (FEV_1, FVC). Spirometry consists in three acceptable manoeuvres (see section 7.2.4).
- **The last morning dose of study medication will be administered at the clinic under supervision of the Investigator from the kit dispensed at Visit 6 (40 weeks).** For the

patient using a spacer, pMDI medication will be taken via the AeroChamber Plus™ dispensed at V6.

- Post-dose (10 min) vital signs [systolic (SPB) and diastolic (DBP) blood pressure] will be measured, after 10 minutes of rest (see section 7.2.5).
- Post-dose 12-lead ECG will be performed 10 minutes after study drug administration (ECG to be recorded after 10 minutes of rest) (see section 7.2.6).
- The Investigator will access IRT to register the completion of the study for the patient.
- The patient will be discharged from the unit, providing that all her/his safety assessments are satisfactory.
- At investigator discretion, the pre-study patient's therapy will be resumed or changed if appropriate

7.1.9 Study Termination (for patients withdrawn before week 52)

If a patient is withdrawn before the end of the treatment period, a final evaluation will be performed. The Investigator must fill in the Study Termination visit in the CRF explaining the primary reason for withdrawal and including the assessments performed.

The following procedures will be performed:

- Changes of smoking status will be recorded. Pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- Changes of concomitant medications being taken by the patient will be recorded.
- 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 (if any) will be evaluated and data will be recorded in the e-CRF
- The occurrence of adverse events since the previous visit will be evaluated and recorded (if any). **The status of any unresolved AEs recorded during the study must be checked and updated**.
- The investigator will collect the medication kits, the dispensing devices (HandiHaler® and spacer) and the electronic diary.

- A full physical examination will be performed.
- Weight will be recorded.

- The EQ-5D-3L questionnaire will be completed by the patient (see section 7.2.2.3).
- The St George's Questionnaire (SGRQ) will be completed by the patient (see section 7.2.2.4).
- Investigator will collect Health economic information as per section 7.2.3
- Vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see section 7.2.5).
- A 12-lead ECG will be performed after 10 minutes of rest (see section 7.2.6).
- If possible, after an overnight fasting, a blood sample will be collected for the assessments of (see section 7.2.9):
  - 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.

- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose inspiratory capacity (IC) followed by a FVC manoeuvre for other pre-dose parameters (FEV_1, FVC). Spirometry consists in three acceptable manoeuvres (see section 7.2.4).
- The Investigator will access IRT to register the discontinuation of the patient.
- The patient will be discharged from the unit, providing that all her/his safety assessments are satisfactory.
- At investigator discretion, the pre-study patient's therapy will be resumed or changed if appropriate.

7.2 Investigations

7.2.1 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 [18]:

- **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 CRF 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 hospitalisation 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 utilisation.
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 section 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 β2-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 amoxycillin or amoxycillin/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.

7.2.2 Study Questionnaires

7.2.2.1 The COPD Assessment Test (CAT) questionnaire

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.**

Data collected by Investigator on paper will be entered by the Investigator in the eCRF.

7.2.2.2 The EXACT-PRO questionnaire

The EXACT-PRO (**EXA**cerbations of **C**hronic pulmonary disease **T**ool – **P**atient **R**eported **O**utcome) 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 and 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.

7.2.2.3 The EQ-5D-3L 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). It will be checked for completeness and collected before the patient leaves the centre.

Data collected by Investigator on paper will be entered by the Investigator in the eCRF.

7.2.2.4 The St. George's Respiratory Questionnaire

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 [14,15]. 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). It will be checked for completeness and collected before the patient leaves the centre.

7.2.2.5 Study treatment and rescue intake record

The patient will also receive, on the digital platform, together with the daily EXACT-PRO, customised questions in order to record daily rescue medication intake and study medication compliance (run-in and treatment) of the patient.

7.2.3 Health Economic information

Information on the total use of healthcare resources and absence from work associated with the patient's condition will be collected during the trial.
Whether the patient has a paid job will be recorded in the eCRF as well as the number of working days and hours per week.

Health Economic information will be collected by the Investigator based on medical records and patient interviews at each visit from randomisation visit (V2) until end of treatment (V7).

7.2.4 Spirometry

Pulmonary function tests (FEV_1, FVC and IC) 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 [16]. 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.

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 printed and kept with the source study document.

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

Inspiratory capacity (IC, L), which is the volume change recorded at the mouth when taking a slow full inspiration with no hesitation, from a position of passive end-tidal expiration, i.e. functional residual capacity (FRC), to a position of maximum inspiration, will be recorded at each clinic visit.
Patients should be relaxed (shoulders down and relaxed) and asked to breathe regularly for several breaths until the end expiratory lung volume is stable (this usually requires at least three tidal manoeuvres). They are then urged to take a deep breath to TLC with no hesitation.
The **average** of at least 3 acceptable slow vital capacity (SVC) manoeuvres will be recorded for **IC**. **These SVC manoeuvres must be performed before the forced vital capacity (FVC) manoeuvres used to assess other lung function parameters as described below.**

Forced Expiratory Volume in the 1st second (**FEV_1**, L), Forced Vital Capacity (**FVC**, L) will be recorded at each clinic visit from a forced vital capacity manoeuvre. At screening, the post-bronchodilator FEV_1 values (30 min after administration of salbutamol 4x100 mcg will be considered for eligibility.

The **highest value from three technically satisfactory attempts** will be recorded (irrespective of the curve they are derived from) for FEV_1 and FVC. 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 **FEV_1/FVC** will be derived from these **highest values** of each parameter [(14)].

Predicted values will be automatically calculated with the demographic data recorded in the centralised system.

Rescue medication (salbutamol) must be withheld for at least 6h prior to starting pre-dose lung function measurement at each visit.
Study medication (Run-in and Randomised treatments) wash-out shall also be respected prior to starting pre-dose lung function measurement as described in visit details (sections 7.1.2 to 7.1.9).
The wash-out for medications permitted for COPD exacerbations should be respected (see sections 5.1 and 5.2)**.**
If the wash-outs are not respected (even after rescheduling the visits once):
- at V1 and V2, the patient will be discontinued and recorded in IRT as screen failure
- from V3 to V7, the visit will be performed anyway and details of the intake (time and quantity) documented.

7.2.5 Vital signs and body weight

Systolic and diastolic blood pressure (SBP, DBP) will be measured after 10 min rest in resting position at pre-dose (pre-bronchodilator at Visit 1) and post-dose for all clinic visits.

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

7.2.6 *12-lead* ECG

ECG equipment will be provided to all sites. 12-lead ECG will be recorded in triplicate at screening and single measurements will be done at V5 and V7. Pre-bronchodilator 12-lead ECG measurement will be done at screening and pre-dose plus 10 minutes post-dose measurements will be done at Visit 5 and Visit 7, after 26 and 52 weeks of treatment respectively.

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 ECG.

At **Visit 1**, the ECG will be recorded in **triplicate** (meaning 3 ECG recordings in rapid succession (consecutively) and not more than 2 minutes apart) and the values reported will be the average of the 3 individual values recorded.

QTc value to be reported must be calculated using the Fridericia formula (Fridericia-corrected QTc=QT/$\sqrt[3]{RR}$). Heart rate (HR), PR and QRS values will be also evaluated from ECG.
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 are considered as normal if

- 40≤Heart rate≤110bpm,
- 120 ms ≤ PR ≤ 210 ms,
- QRS ≤ 120 ms,

These values are to be checked for ECG performed at screening visit for patient's eligibility.

In case of relevant ECG abnormalities, the inclusion of the patient will be judged by the investigator 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 ≤ 450 (males) and 470 ms (females) (as per Exclusion Criterion 11).

7.2.7 Renal and hepatic impairment assessements

7.2.7.1 Renal impairment

The renal function of each patient will be assessed and classified accordingly to the table below (EMEA, CHMP/EWP/225.02).

Group	Description	GFR (ml/min/1.73 m^2)
1	Normal renal function	> 80
2	Mild renal impairment	50-80
3	Moderate renal impairment	30-<50
4	Severe renal impairment	<30
5	End stage renal disease (ESRD)	Requiring dialysis

The determination of glomerular filtration rate (GFR) is based on creatinine measurement accordingly to the following MDRD equation:

eGFR = α x (Serum creatinine) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) x (1.212 if African American)

where α can equal 175 or 186 depending on whether the method used for creatinine assessment is calibrated or not.

GFR is expressed in mL/min per 1.73 m^2, Serum creatinine in mg/dL and age in years.

7.2.7.2 Hepatic impairment

The hepatic impairment will be assessed using the Child-Pugh classification (EMEA, CPMP/EWP/2339/02) as follows:

Assessment	Degree of abnormality	Score
Encephalopathy	None Moderate Severe	1 2 3
Ascites	Absent Slight Moderate	1 2 3
Bilirubin (mg/dL)	<2 2.1-3 >3	1 2 3
Albumin (g/dL)	>3.5 2.8-3.5 <2.8	1 2 3
Prothrombin Time (seconds > control)	0-3.9 4-6 >6	1 2 3

The method for encephalopathy and ascites assessments is described in more details in the following paragraph.

a) Hepatic encephalopathy

HE may be defined as a disturbance in central nervous system function because of hepatic insufficiency. This broad definition reflects the existence of a spectrum of neuropsychiatric manifestations related to a range of pathophysiological mechanisms. HE can cause mental and physical symptoms. They can vary person to person, and may progress slowly or occur suddenly [18, 19].
The grading of hepatic encephalopathy will be done accordingly to the West Haven Criteria for Semi-quantitative Grading of Mental Status, as follows:

Grade 1
Trivial lack of awareness
Euphoria or anxiety
Shortened attention span
Impaired performance of addition
Grade 2
Lethargy or apathy
Minimal disorientation for time or place
Subtle personality change
Inappropriate behavior
Impaired performance of subtraction
Grade 3
Somnolence to semi-stupor, but responsive to verbal stimuli
Confusion
Gross disorientation
Grade 4
Coma (unresponsive to verbal or noxious stimuli)

b) Ascites

Ascites is an abnormal accumulation of fluid in the abdomen. The most common cause of ascites is elevated pressure in the liver circulation (portal hypertension) due to liver disease such as cirrhosis. [20].Ascites can be graded as follows:

Grade 1 (mild)
Ascites is only detectable by ultrasound examination.
Grade 2 (moderate)
Ascites causing moderate symmetrical distens
Grade 3 (large)
Ascites causing marked abdominal distension.

Based on the scores attributed to the patient by the investigator, the grade for hepatic impairment severity will be determined accordingly to the table below:

Total Score	Group	Severity
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe

7.2.8 Pharmacokinetic evaluations: FF, GB and BDP/B17MP analysis

The pharmacokinetic evaluation will be performed via a **central Laboratory** only in a subset of patients in specific selected centres. **Blood sampling will be performed for all the patients included in the selected subset, but only the samples from patients in the CHF 5993 pMDI group will be submitted to PK analysis by the analytical laboratory.**

The blood samples will be collected in a subset of patients in the morning after an overnight (at least 10 hours) fasting at Visit 3. No alcohol or xanthine (coffee, tea, chocolate, cola, etc) containing beverages or food as well as xanthine derivatives, nor grapefruit containing beverages or food will be allowed starting from **48 hour before the drug administration on the day of blood sampling for PK assessments** until the end of blood sampling.

At steady state, Visit 3 (4 weeks after randomisation visit), blood sample collection will be done in order to perform the analysis: 4 ml per time point for the FF analysis, 4 ml per time point for the GB analysis and 6 ml per time point for the BDP/B17MP analysis. Based on a previous population pharmacokinetic analysis performed on B17MP, formoterol and glycopyrrolate data, an optimal time sampling strategy was conducted in order to select the best combination of sampling times. PK analyses showed that for the 3 compounds, a 3-compartment model was necessary to best describe the data. Therefore, blood samples at six different time points have to be taken in the current study (2 samples per elimination phase).

- Pre-dose, within 30 minutes before the study drug administration (always before vital signs),
- 5 min post dose,
- 15 min post dose,
- 1 hour post dose,
- 4 hour post dose,
- 8 hours post dose.

In case of coinciding investigations, the time point for blood collection for PK evaluation takes priority over any other scheduled study activities, e.g., vital signs. Where other activities are scheduled together with blood collection, these will be performed in a sequence allowing for blood sampling exactly at the scheduled time point. The exact time of each activity will be recorded in the CRF.
The following time tolerances from theoretical post-dose times will **be allowed**:

5 min post dose:	± 1 min
15 min post dose:	± 2 min
1 and 4 hours post dose:	± 5 min
8 hours post dose:	± 10 min

The time of blood sample collection should be recorded in the CRF and also the times of administration the day before the PK visit in addition to the time of administration the day of the PK visit.

The blood collection will be performed for the assessment of pharmacokinetic. To minimise the discomfort during blood sampling the following procedures will be followed:
- Topical anaesthesia to place IV catheters/cannula (e.g. lidocain cream) may be used,
- Indwelling catheters/cannulas rather than repeated venipunctures for blood sampling where possible.

Pre-printed bar-coded labels (with identification of study number, drug name, patient's number, theoretical collection time, study period and sample number) will be provided by the bioanalysis laboratory SGS.

- **Determination of formoterol fumarate (FF) in human plasma**

At Visit 3, blood samples of 4 mL per timepoint for the determination of FF in plasma in the 0-8h interval post morning dose (pre-dose, 5min, 15 min, 1h, 4h and 8 hours post morning dose) will be collected.
Samples will be collected into tubes containing lithium heparin (Venoject green top or equivalent) and will be immediately chilled (ice bath). The blood will be centrifuged within 20 min after blood collection.
The plasma will be separated in a refrigerated centrifuge (about +4°C) at circa 2500 x g for 15 min and transferred into polypropylene tubes with exactly 500 µL of plasma per tube. For stabilizing the compound, polypropylene tubes will be pre-filled with 50 µL of citric acid 1M by the PK analysis lab before sending to the clinical centre. Those pre-filled tubes with 50 mL of citric acid need to be centrifuged before opening tubes in order to ensure that citric acid is at the bottom of the tube. After each blood collection, a volume of **500 µL** plasma will be dispensed in two tubes containing the citric acid buffer, and any remaining plasma (regardless which amount) will be dispensed in a third tube containing the citric acid buffer. The plasma samples will have appropriate labels and will be stored at, or below, -65°C in the clinical centre.
Thereafter the plasma samples will be transported in dry ice to the PK analysis laboratory, where they will be stored at, or below, -65°C until submitted for analysis with a validated method.

- **Determination of Glycopyrrolate Bromide (GB) in human plasma**

At Visit 3, blood samples of 4 mL for the determination of GB in plasma in the 0-8 h interval post morning dose (pre-dose, 5min, 15 min, 1h, 4h and 8 hours post morning dose) will be collected.
Samples will be collected into tubes containing lithium heparin (Venoject green top or equivalent) and will be immediately chilled (ice bath).

The blood will be centrifuged within 20 min after blood collection.
The plasma will be separated in a refrigerated centrifuge (about +4°C) at circa 2500 x g for 15 min and transferred into polypropylene tubes.
After each blood collection, a volume of circa **500 µL** plasma will be dispensed in the first tube; the remaining plasma will be dispensed in the second tube.
After appropriate labelling, the plasma samples will be stored at, or below, -65°C in the clinical centre.
Thereafter the plasma samples will be transported in dry ice to the PK analysis laboratory, where they will be stored at, or below, -65°C until submitted for analysis with a validated method.

- **Determination of BDP/B17MP in human plasma**

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B17MP), which has potent topical anti-inflammatory activity.

At visit 3, blood samples of 6 mL for the determination of BDP and its metabolite B17MP assay in the 0-8 hours interval after dosing (pre-dose, 5min, 15min, 1h, 4h and 8 hours post morning dose) will be collected.
Samples will be collected into vacuum tubes containing K_2EDTA.

The samples will be immediately chilled (ice bath) and plasma preparation will be done within 20 min after blood collection. The plasma will be separated in a **refrigerated centrifuge** (+4°C) at ca 2500 g for 15 min and two aliquots of **at least 1.2 ml** will be transferred into 2 polypropylene tubes (1.2 ml each). After appropriate labelling, the plasma samples will be immediately stored at, or below -20°C in the clinical centre. Thereafter the plasma samples will be transported in dry ice to the PK analysis laboratory, where they will be stored at, or below, -20°C until submitted for analysis with a validated method.

7.2.9 Standard haematology and blood chemistry (including pregnancy test)

Laboratory normal ranges will be collected prior to FPFV at each site and provided to data management via the CRO. Laboratory results collected at V1, V5 and V7 will be entered in the eCRF by the investigator.
The blood samples for standard haematology and blood chemistry will be collected in the morning after an overnight fasting (at least 10 hours) at Visits 1, 5 and 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 local laboratory**:

- *Blood Chemistry*: creatinine, BUN, fasting serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase (γ-GT), total bilirubin, albumin, alkaline phosphatase, sodium, potassium, calcium, and chloride electrolytes (Na, K, Ca, Cl).

- *Haematology*: red blood cells count (RBC), white blood cells count (WBC) and differential, total haemoglobin (Hb), hematocrit (Hct), platelets count (PLT) and protrombin time.
- *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 also be performed at all visits except visit 7. 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 local laboratory.**
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.

8. EFFICACY ASSESSMENTS

8.1 Primary efficacy variable

Moderate and severe COPD exacerbation rate over 52 weeks of treatment.

8.2 Key secondary efficacy variable

Change from baseline in pre-dose morning FEV_1 at Week 52.

8.3 Secondary efficacy variables

- Time to first moderate or severe COPD exacerbation.
- Rate of severe COPD exacerbations over 52 weeks of treatment.
- Time to first severe COPD exacerbation.
- Rate of moderate COPD exacerbations over 52 weeks of treatment.
- Change from baseline in pre-dose morning FEV_1 at all the other clinic visits.
- Change from baseline to the average over the treatment period in pre-dose morning FEV_1.
- FEV_1 response (change from baseline in pre-dose morning $FEV_1 \geq 100$ ml) at Week 26 and Week 52.
- Change from baseline in pre-dose morning IC at all clinic visits.
- Change from baseline in the SGRQ total score and domain scores at all clinic visits.
- SGRQ response (change from baseline in total score ≤ -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).

8.4 Exploratory efficacy variables

- Change from baseline in pre-dose morning 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.

8.5 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 of 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 AND PHARMACOKINETIC ASSESSMENTS

9.1 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
- Standard Haematology and Blood Chemistry

9.2 Pharmacokinetic variables

- Clearances and volumes of distribution will be estimated by population PK analysis starting from B17MP, FF and GB plasma levels measured in a subset of patients in the CHF 5993 pMDI group at steady state (Week 4). Other pharmacokinetic parameters of interest could also be reported like for example AUCtau (AUC during a dosing interval at steady state).

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 unfavourable 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 an 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 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 patient's study participation end.

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 listed below 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.

Name and Title	Telephone	Mobile	Fax	E-mail
Emma Beddie Chiltern Safety Contact	+441315507746		+441753511116	pvteam@chiltern.com
Chiara Bonardi Drug Safety Scientist Corporate Pharmacovigilance Chiesi Farmaceutici S.p.A.	+390521279773	-	+390521271992	c.bonardi@chiesi.com

- 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 fulfil 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 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 Adjudication Committee

An Adjudication Committee will be established, in order to have a particular scrutiny of some potentially relevant adverse events to perform a MACE (Major Adverse Cardiovascular Event) 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 Adjudication Committee will be composed by three cardiologists and will meet at the end of the study to adjudicate the MACE data in blinded condition.
Any additional available information will be promptly made available by the Sponsor upon request of the Adjudication Committee members, as well as any request for additional clinical/instrumental/ laboratory evaluations deemed appropriate by the Adjudication Committee 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 will be involved however without access to unblinded data and/or unblinded/coded comparisons as the other Adjudication Committee members.
All Adjudication Committee members will keep information and data as confidential.

10.13 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 (AE), 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 agreed timelines.

The DSMB will have access to the relevant modules of the 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

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.
Questionnaire patient's 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 (PK data, Spirometry, data from electronic diary) will be processed centrally and reconciled against data recorded in the eCRF as part of cleaning activities.
Laboratory normal ranges will be collected prior to FPFV at each site and provided to data management via the CRO. Laboratory results collected at V1, V5 and V7 will be entered in the eCRF by the investigator.

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 Tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment and change from baseline in pre-dose morning FEV_1 at Week 52, and the non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium in terms of change from baseline in pre-dose morning FEV_1 at Week 52.

A total of 2580 patients will be randomised according to a 2:2:1 ratio to the CHF 5993 pMDI (1032 patients), Tiotropium (1032 patients) and CHF 1535 pMDI + Tiotropium groups (516 patients). A log-normal distribution is assumed for drop-out times, with drop-out rates of approximately 13%,

16.5% and 20% at Week 12, Week 26 and Week 52, respectively. A percentage of completed and evaluable patients with major protocol deviations of 9% is assumed.

- This sample size will provide approximately 93.3% power to detect a rate ratio of 0.8 between CHF 5993 pMDI and Tiotropium at a two-sided significance level of 0.05, using a negative binomial model and assuming a rate of 0.9 exacerbations per patient per year in the Tiotropium group and an overdispersion parameter of the negative binomial distribution of 0.56.
- At Week 52, 825 evaluable patients per group in the CHF 5993 pMDI and Tiotropium arms will provide approximately 99.7% power to detect a mean difference of 60 ml in terms of change from baseline in FEV_1 at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 260 ml.
- At Week 52, 751 evaluable patients in the CHF 5993 pMDI group and 375 evaluable patients in the CHF 1535 pMDI + Tiotropium group with no major protocol deviations will provide approximately 86.0% power to demonstrate the non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium in terms of change from baseline in FEV_1 at a one-sided significance level of 0.025, with a non-inferiority margin of -50 ml and assuming no difference between treatments and a SD of 260 ml.

An overall study power of approximately 80% will therefore be ensured.

At least 20 % of patients with very severe airflow limitation (post-bronchodilator FEV_1 at screening < 30% of predicted normal value) will be randomised in the study.

A total of 550 randomised patients (220 expected in each of the CHF 5993 pMDI and Tiotropium groups and 110 expected in the CHF 1535 pMDI + Tiotropium group) will be selected for the evaluation of PK in order to reach a total of 200 evaluable patients in the CHF 5993 pMDI group at Week 4, considering a non-evaluable rate of approximately 9% at this time point. This sample size is based on an evaluation of historical PK data and it is considered sufficient to properly conduct the planned population PK analysis.

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.
- **PK population:** all patients from the Safety population in the subset selected for PK analysis and treated with CHF 5993 pMDI, excluding patients without any valid PK measurement or with major protocol deviations significantly affecting PK, for example: incorrect inhalation, change in patient's condition (cold), failure in delivery of the device, use of non-permitted medications. Exact definition of major protocol deviations concerning PK will be discussed by the clinical team and described in a specific document before bioanalytical data are disclosed.

Since superiority will be tested, the comparisons between CHF 5993 pMDI and Tiotropium in terms of the primary and the key secondary efficacy variables will be based on the ITT population. These analyses will be also performed on the PP population for sensitivity purposes.

Since non-inferiority will be tested, in the comparison between CHF 5993 pMDI and CHF 1535 pMDI + Tiotropium in terms of the key secondary efficacy variable the ITT and the PP populations will have equal importance.

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

In case of deviation between randomised treatment and treatment actually received, the treatment actually received will be used in the PK and 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, while the percent coefficient of variation will be also presented for concentration data. 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

- The validity of the negative binomial model planned for the primary efficacy analysis relies on the Missing At Random (MAR) assumption [21]. Of note, only COPD exacerbations with onset during the randomised treatment period (i.e., before study completion or discontinuation) will be included in the analysis. For the key secondary efficacy variable, linear mixed models for repeated measures will be used to handle missing data. Under the 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 (EMA Guideline on Missing Data in Confirmatory clinical trials. 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 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, PP or PK 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 variable

- The comparisons between treatments will be conducted according to a hierarchical testing procedure. The primary and the key secondary efficacy comparisons will be considered in the following order:
  1. superiority testing of CHF 5993 pMDI vs. Tiotropium in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment (primary efficacy variable);
  2. superiority testing of CHF 5993 pMDI vs. Tiotropium in terms of change from baseline in pre-dose morning FEV_1 at Week 52 (key secondary efficacy variable, see section 12.3.5);
  3. non-inferiority testing of CHF 5993 pMDI vs. CHF 1535 pMDI + Tiotropium in terms of change from baseline in pre-dose morning FEV_1 at Week 52 (key secondary efficacy variable, see section 12.3.5).

  At each step of the procedure, no confirmatory claims will be made unless the objectives will be met in all the preceding steps.

- 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 (1 or >1), severity of airflow limitation (post-bronchodilator FEV_1 at screening < or ≥ 30% of predicted normal value) 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 ratios with their 95% confidence intervals (CIs) will be estimated by the model. Superiority of CHF 5993 pMDI over Tiotropium will be demonstrated by a statistically significant rate ratio (defined as $p<0.05$) favouring CHF 5993 pMDI. The comparison CHF 5993 pMDI vs. CHF 1535 pMDI + Tiotropium will be considered as a secondary efficacy analysis.

- Two COPD exacerbations will be considered as a single episode in the statistical analysis if the second exacerbation started less than 10 days after the end of the systemic corticosteroids and/or antibiotics intake for the previous exacerbation.

12.3.5 Key secondary efficacy variable

- Change from baseline (Visit 2) in pre-dose morning FEV_1 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, severity of airflow limitation 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 differences between treatments and their 95% CIs at Week 52 will be estimated by the model. Superiority of CHF 5993 pMDI over Tiotropium will be demonstrated by a statistically significant difference between treatments at Week 52 favouring CHF 5993 pMDI. Non-inferiority of CHF 5993 pMDI relative to CHF 1535 pMDI + Tiotropium will be demonstrated if the 95% CI of the adjusted mean difference between treatments at Week 52 will lie entirely to the right of the pre-defined non-inferiority margin of -50 ml.

12.3.6 Secondary efficacy variables

- 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.
- The same analyses above defined for all moderate and severe COPD exacerbations will be performed separately on the number of severe and moderate COPD exacerbations during the treatment period and on the time to first severe COPD exacerbation.
- For change from baseline in pre-dose morning FEV_1, 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 key secondary efficacy analysis. In the estimation of the averages over the treatment period equal weights will be assigned to the clinic visits.
- FEV_1 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
- Change from baseline in pre-dose morning IC at all clinic visits will be analysed using a similar model as for the key secondary efficacy variable.
- Change from baseline (Visit 2) in the SGRQ total score and domain scores at all clinic visits will be analysed using a similar model as for the key secondary efficacy variable.
- SGRQ response at Week 26 and Week 52 will be compared between treatment groups using a similar model as for FEV_1 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 key secondary efficacy variable. 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.

Exploratory efficacy variables

- Change from baseline in pre-dose morning FVC at all clinic visits will be analysed using a similar model as for the key secondary efficacy variable.
- 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.

12.3.7 Pharmacokinetic and Safety variables

Pharmacokinetic variables

- Individual plasma concentration data of BDP, B17MP, FF and GB will be tabulated vs. the scheduled sampling times. Concentrations will be summarized scheduled sampling time using descriptive statistics. Mean plasma concentration vs. time profiles will be presented in linear/linear and log/linear scales.
- The plasma concentration data of B17MP, FF and GB will be subjected to a population PK analysis. For this analysis the data may be combined with results from previous studies (or analysis). The aim of the population PK analysis is to develop a compartmental model of the plasma concentration vs. time profiles, which will provide a good understanding of the inter-subject and intra-subject (if possible) variability in the drug exposure. In addition the effects of selected covariates on PK parameters will be evaluated, e.g. age, sex, race, smoking status, BMI, concomitant medications, renal and hepatic impairment.
- Information regarding the population PK analysis will be described in the separate population PK Analysis Plan. The results and the model development will be described in detail in a separate PK Report.

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 screening in pre-dose 12-lead ECG parameters (HR, QTcF, PR and QRS) will be analysed using a similar model as for the key secondary efficacy variable. 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 screening in post-dose 12-lead ECG parameters (HR, QTcF, PR and QRS)
- At Week 26 and Week 52, the change from pre-dose to post-dose in the 12-lead ECG parameters 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 screening 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.

- 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.

12.3.8 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, e.g., 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 CRFs for accuracy and completeness;
- to validate the contents of the eCRFs 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 and names.. 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 principal Investigator 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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3- Cazzola M et al. Novel long-acting bronchodilators for COPD and asthma. Br J Pharmacol. 2008 Oct;155(3):291-9.
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APPENDIX I

MINIMUM LIST OF SOURCE DATA REQUIRED

Patients' demography file

Patients' medical file

Study number

Patient ID

Medical and surgery history

Previous and concomitant medications

Weight, height

Date of informed consent signature

Date of specific study visits

Labels of study drugs

Examination or assessments carried out during the study

Laboratory reports

Adverse events / serious adverse events

The reason of withdrawn subject

APPENDIX II

PATIENT LEAFLET: INSTRUCTIONS FOR USE

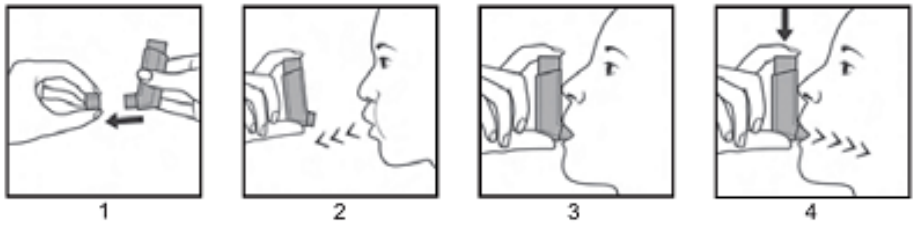
PRESSURISED METERED DOSE INHALER (pMDI)

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.

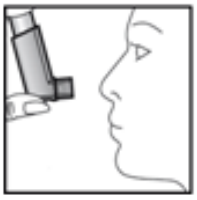
Whenever possible, stand or sit in an upright position when inhaling.

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.

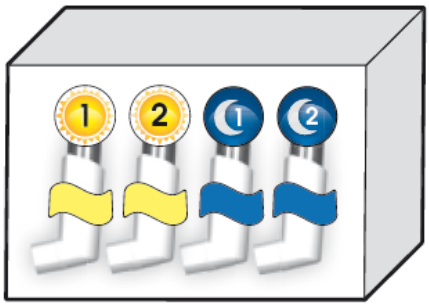
If you see 'mist' coming from the top of the inhaler or the sides of your mouth, this means that the drug will not be getting into your lungs as it should. Take another puff, carefully following the instructions from Step 2 onwards.

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

TREATMENT Periods



MORNING ADMINISTRATION
1 puff from **SUN 1** 1 puff from **SUN 2**
EVENING ADMINISTRATION
1 puff from **MOON 1** 1 puff from **MOON 2**

APPENDIX III

PATIENT LEAFLET: INSTRUCTIONS FOR USE

TIOTROPIUM 18 mcg HARD CAPSULE WITH HANDIHALER® INHALER

HANDIHALER - INSTRUCTIONS FOR USE

Important Information about using your study medication

Important Information about using your study medication
- **Do not swallow capsules.**
- **Capsules should only be used with the HandiHaler device and inhaled through your mouth (oral inhalation).**
- **Do not use your HandiHaler device to take any other medicine.**

Figure A

The parts of your HandiHaler device include:
1. dust cap (lid)
2. mouthpiece
3. mouthpiece ridge
4. base
5. green piercing button
6. centre chamber
7. air intake vents

Taking your full daily dose of medicine requires 4 main steps

STEP 1 - Opening your HandiHaler device:

Figure B

- Open the dust cap (lid) by pressing the green piercing button.

Figure C

- Pull the dust cap (lid) upwards away from the base to expose the mouthpiece.

Figure D

- Open the mouthpiece by pulling the mouthpiece ridge up and away from the base so the centre chamber is showing.

STEP 2 - Inserting the capsule into your HandiHaler device:

Figure E

- Each day, separate only 1 of the blisters from the blister card by tearing along the perforated line.

Figure F

Remove the capsule from the blister:
- **Do not** cut the foil or use sharp instruments to take out the capsule from the blister.
- Bend 1 of the blister corners and separate the aluminium foil layers.
- Peel back the foil until you see the whole capsule.
- If you have opened more than 1 blister to the air, the extra capsule should not be used and should be thrown away.

Figure G

- Place the capsule in the centre chamber of your HandiHaler device.

Figure H

- Close the mouthpiece firmly against the grey base until you hear a click. Leave the dust cap (lid) open.

STEP 3 - Piercing the capsule:

Figure I

- Hold your HandiHaler device with the mouthpiece pointed up.
- Press the green piercing button once until it is flat (flush) against the base, then release. This is how you make holes in the capsule so that you get your medicine when you breathe in.
- **Do not** press the green button more than one time.
- **Do not** shake your HandiHaler device.
- The piercing of the capsule may produce small gelatine pieces. Some of these small pieces may pass through the screen of your HandiHaler device into your mouth or throat when you breathe in your medicine. This is normal. The small pieces of gelatine should not harm you.

STEP 4 - Taking your full daily dose (2 inhalations from the same capsule):

Figure J

Breathe out completely in 1 breath, emptying your lungs of any air.
Important: Do not breathe into your HandiHaler device.

Figure K

With your next breath, take your medicine:

- **Hold your head in an upright position while you are looking straight ahead.**
- Raise your HandiHaler device to your mouth in a horizontal position.

Do not block the air intake vents.

- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the capsule vibrate** (rattle).
- Hold your breath for a few seconds and, at the same time, take your HandiHaler device out of your mouth.
- Breathe normally again.
- The rattle tells you that you breathed in correctly.
- **To get your full daily dose, you must again, breath out completely (See Figure J) and for a second time, breathe in (see Figure K) from the same capsule.**

Important: Do not press the green piercing button again.

Remember: To get your full medicine dose each day, you must breathe in 2 times from the same capsule. Make sure you breathe out completely each time before you breathe in from your HandiHaler device.

Caring for, storing and cleaning your HandiHaler

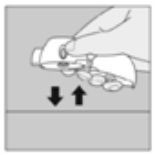


Figure L

- After taking your daily dose, open the mouthpiece and tip out the used capsule into your trash can, without touching it.
- Remove any capsule pieces or powder build-up by turning your HandiHaler device upside down and gently, but firmly, tapping it. Then, close the mouthpiece and dustcap for storage.
- **Do not** store your HandiHaler device and capsules (blisters) in a damp moist place.

Always store capsules in the sealed blisters.

Figure M

- **Clean the HandiHaler once a month.**
- Open the dust cap and mouthpiece.
- Then open the base by lifting the piercing button.
- Rinse the complete inhaler with warm water to remove any powder.
- Dry the HandiHaler thoroughly by tipping excess of water out on a paper towel and air-dry afterwards, leaving the dust cap, mouthpiece and base open.
- It takes 24 hours to air dry, so clean it right after you have used it and it will be ready for your next dose.
- If needed the outside of the mouthpiece may be cleaned with a moist but not wet tissue.
- **Do not** use a hair dryer to dry your HandiHaler device.
- **Do not** use your HandiHaler device when it is wet

APPENDIX IV

INSTRUCTIONS FOR USE OF AEROCHAMBER PLUS™ FLOW-VU ANTISTATIC 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.

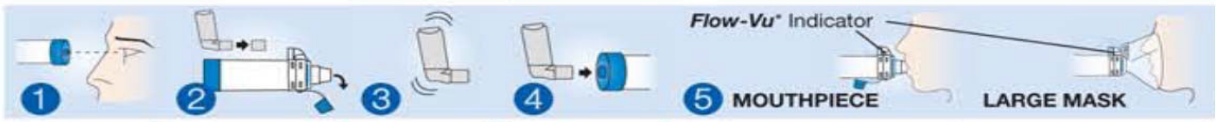
Trudell Medical International*
725 Third Street, London, Ontario, Canada N5V 5G4
customerservice@trudellmed.com
+1-519-455-7060
+1-519-455-6478
www.trudellmed.com

EC REP Trudell Medical International Europe Limited
BioCity Nottingham, Pennyfoot Street, Nottingham, United Kingdom NG1 1GF

CE

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. Before use carefully examine the chamber. Replace immediately if any defect is noticed.
2. Remove caps from inhaler and chamber.
3. Shake the inhaler immediately before use as per the instructions supplied with it.
4. Insert the inhaler into the Backpiece of the chamber.
5. 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.

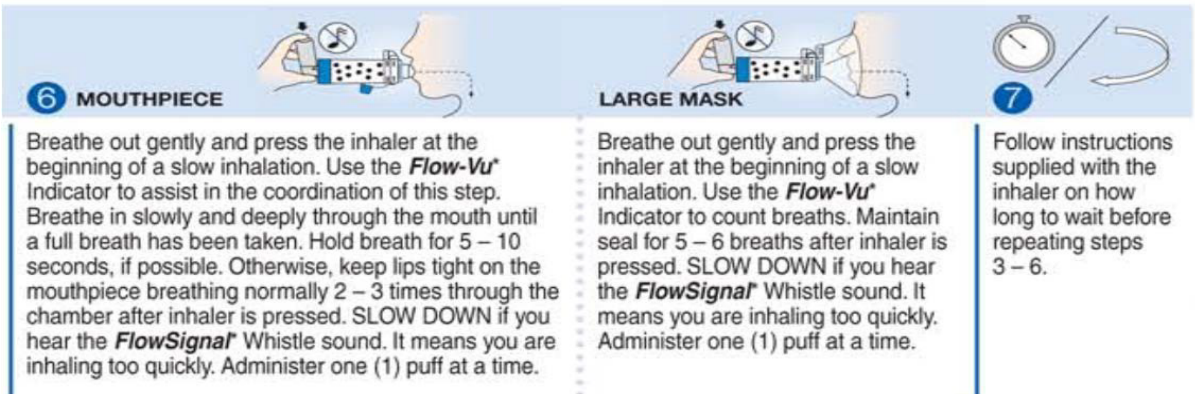
6 **MOUTHPIECE**

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.

LARGE MASK

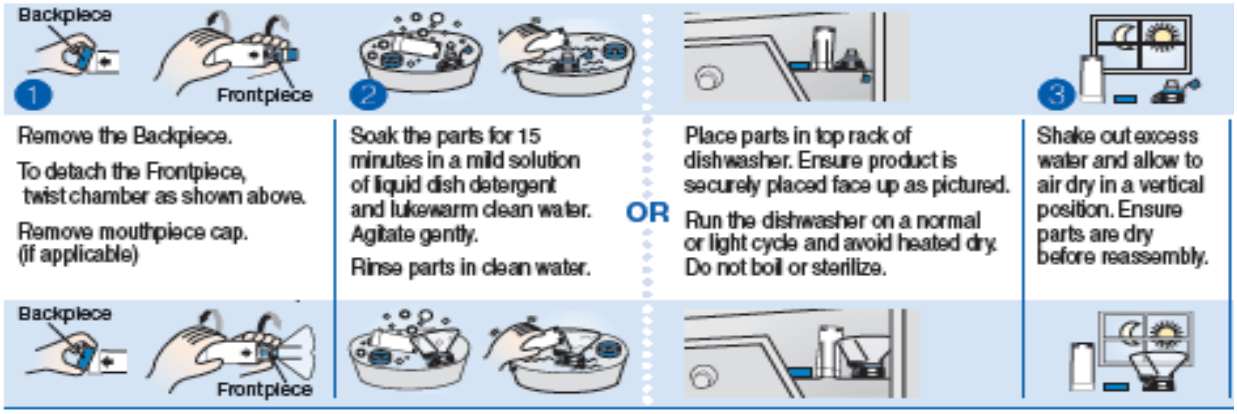
Breathe out gently and press the inhaler at the beginning of a slow inhalation. Use the ***Flow-Vu**** Indicator to count breaths. Maintain seal for 5 – 6 breaths after inhaler is pressed. SLOW DOWN if you hear the ***FlowSignal**** Whistle sound. It means you are inhaling too quickly. Administer one (1) puff at a time.

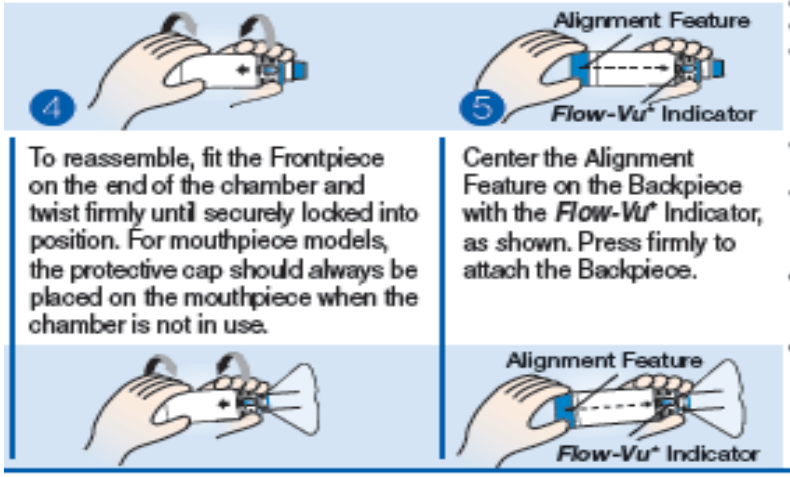
7 Follow instructions supplied with the inhaler on how long to wait before repeating steps 3 – 6.



CLEANING INSTRUCTIONS

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





Notes:

- 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.

⚠ **Cautions:**

- **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.**

APPENDIX V

SAMPLE OF PATIENT CARD

In case of emergency please contact:

Study Doctor's name : Dr ……..…

Name of the Hospital (if applicable) **:**
……..……..

Phone number : .....…….....…….....

If your study Doctor is not available
please contact your family Doctor

.....

Investigational substances:
- *CHF 5993 100/6/12.5µg extrafine HFA pMDI* (beclometasone dipropionate/formoterol fumarate/glycopyrrolate bromide 100/6/12.5 µg per metered dose)
(total daily dose 400/24/50 µg)

or
- *Tiotropium bromide 18 µg hard capsule DPI*
(administered with HandiHaler® inhaler)
(total daily dose 18 µg)

or
- *CHF 1535 100/6 µg extrafine HFA pMDI* (beclometasone dipropionate/formoterol fumarate 100/6 µg per metered dose) active
(total daily dose 400/24 µg)
+
Tiotropium bromide 18 µg hard capsule DPI
(administered with HandiHaler® İnhaler)
(total daily dose 18 µg)

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- Chiesi
- *Please keep this Card with You*

Mr/Mrs ……..……..…….. is actually involved in the clinical trial CCD-1208-PR-0090 concerning COPD treatment:

Patient's No: |___|___|___|___|___|___|-|___|___|___|

Planned visits after V0 (pre-screening visit):

V1 : |__|__| |__|__| |__|__| at |__|__| hour |__|__|
V2 : |__|__| |__|__| |__|__| at |__|__| hour |__|__|
V3 : |__|__| |__|__| |__|__| at |__|__| hour |__|__|
V4 : |__|__| |__|__| |__|__| at |__|__| hour |__|__|
V5 : |__|__| |__|__| |__|__| at |__|__| hour |__|__|
V6 : |__|__| |__|__| |__|__| at |__|__| hour |__|__|
V7 : |__|__| |__|__| |__|__| at |__|__| hour |__|__|

Run-in medication: Tiotropium bromide 18 µg hard capsule DPI (administered with HandiHaler® inhaler) for 2 weeks.

Treatment start date = V2 (52-week treatment).

Please remember:

- **No inhalation of the run-in medication the morning of the visit V2.**
- **No inhalation of the study medication the evening before the visits V3-4-5-6-7.**
- **No rescue (salbutamol or other SABA) inhalation 6 hours before the visit (except in the case of an emergency).**

Local CRO information (only if requested by the local law)

English version