Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial

Gary T Ferguson, Klaus F Rabe, Fernando J Martinez, Leonardo M Fabbri, Chen Wang, Masakazu Ichinose, Eric Bourne, Shaila Ballal, Patrick Darken, Kiernan DeAngelis, Magnus Aurivillius, Paul Dorinsky, Colin Reisner

Summary

Background Inhaled corticosteroids have been used in patients with chronic obstructive pulmonary disease (COPD), but the potential benefits of their use in triple therapy are not well known. We aimed to compare the efficacy of a triple therapy with corresponding dual therapies in symptomatic patients with moderate to very severe COPD, without a requirement for a history of exacerbations.

Methods In this double-blind, parallel-group, multicentre phase 3 randomised controlled trial, we recruited patients from hospitals and care centres in Canada, China, Japan, and the USA. Eligible patients were 40–80 years of age, were current or former smokers (with a smoking history of ≥10 pack-years), had an established clinical history of COPD, and were symptomatic for COPD, despite receiving two or more inhaled maintenance therapies for at least 6 weeks before screening. We randomly assigned patients (2:2:1:1) using an interactive web response system to receive budesonide/glycopyrrolate/formoterol fumarate metered-dose inhaler 320/18/9·6 μg (BGF MDI), glycopyrrolate/formoterol fumarate metered-dose inhaler 18/9·6 μg (GFF MDI), budesonide/formoterol fumarate metered-dose inhaler 320/9·6 μg (BFF MDI), or open-label budesonide/formoterol fumarate dry-powder inhaler 400/12 μg (BUD/ FORM DPI). Primary endpoints for the Europe/Canada statistical analysis approach were FEV_1 area under the curve from 0–4 h ($AUC_{0–4}$) for BGF MDI versus BFF MDI and BGF MDI versus BUD/FORM DPI over 24 weeks; and change from baseline in morning pre-dose trough FEV_1 for BGF MDI versus GFF MDI and non-inferiority of BFF MDI versus BUD/FORM DPI (margin of –50 mL from lower bound of 95% CI) over 24 weeks. Comparisons with BUD/FORM DPI were made for the Europe/Canada statistical analysis approach only. This study is registered with ClinicalTrials.gov, number NCT02497001.

Findings Between Aug 20, 2015, and Jan 5, 2018, 3047 patients were screened from 215 sites, and 1902 were randomly assigned to receive BGF MDI (n=640), GFF MDI (n=627), BFF MDI (n=316), or BUD/FORM DPI (n=319). Over 24 weeks, BGF MDI significantly improved FEV_1 $AUC_{0–4}$ versus BFF MDI (least squares mean difference 104 mL, 95% CI 77 to 131; p<0·0001) and BUD/FORM DPI (91 mL, 64 to 117; p<0·0001). BGF MDI also significantly improved pre-dose trough FEV_1 versus GFF MDI (22 mL, 4 to 39; p=0·0139) and BFF MDI was non-inferior to BUD/FORM DPI (–10 mL, –36 to 16; p=0·4390). At week 24, patients in the BGF MDI group had a significantly improved FEV_1 $AUC_{0–4}$ compared with patients receiving BFF MDI (116 mL, 95% CI 80 to 152; p<0·0001); there was a non-significant improvement in the change from baseline in morning pre-dose trough FEV_1 at week 24 versus GFF MDI (13 mL, –9 to 36 mL; p=0·2375). The most common treatment-emergent adverse events were nasopharyngitis (n=49 [8%] in the BGF MDI group; n=41 [7%] in the GFF MDI group; n=26 [8%] in the BFF MDI group; and n=30 [9%] in the BUD/FORM DPI group) and upper respiratory tract infection (n=65 [10%]; n=38 [6%]; n=18 [6%]; and n=22 [7%]). Pneumonia incidence was low (<2%) and similar across treatments. There were two treatment-related deaths, both in the GFF MDI group.

Interpretation BGF MDI was efficacious, well tolerated, and could be a more appropriate treatment than the corresponding dual therapies for symptomatic patients with moderate to very severe COPD, irrespective of exacerbation history.

Funding Pearl—a member of the AstraZeneca Group.

Introduction

Long-acting bronchodilators, including long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), used alone or in combination, play an important part in the maintenance treatment of chronic obstructive pulmonary disease (COPD) at all

Lancet Respir Med 2018; 6: 747-58

Published Online September 16, 2018 http://dx.doi.org/10.1016/S2213-2600(18)30327-8

This online publication has been corrected. The corrected version first appeared at thelancet.com/respiratory on October 4, 2018

This online publication has been corrected. The corrected version first appeared at thelancet.com/respiratory on January 29, 2019

See Comment page 728

Pulmonary Research Institute of Southeast Michigan, Farmington Hills, MI, USA (Prof G T Ferguson MD); LungenClinic Grosshansdorf and Christian-Albrechts University Kiel, Airway Research Center North, Member of the German Center for Lung Research (DZL), Germany (Prof K F Rabe MD); Joan and Sanford I. Weill Department of Medicine, Weill Cornell Medicine, New York, NY, USA (Prof F J Martinez MD); Sahlgrenska University Hospital, Gothenburg, Sweden; Department of Medicine, University Hospital, Ferrara, Italy (Prof L M Fabbri MD); National Clinical Research Centre for Respiratory Diseases, China-Japan Friendship Hospital, Beijing, China (Prof C Wang MD); Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan (Prof M Ichinose MD); Pearl—a member of the AstraZeneca Group, Durham, NC, USA (E Bourne MS, K DeAngelis MD, P Dorinsky MD); Pearl—a member of the AstraZeneca Group,

Morristown, NJ, USA (S Ballal MS, P Darken PhD, C Reisner MD); **AstraZeneca Gothenburg, Mölndal, Sweden** (M Aurivillius MD); **and AstraZeneca, Gaithersburg, MD, USA** (C Reisner)

Correspondence to: Prof Gary T Ferguson, Pulmonary Research Institute of Southeast Michigan, Farmington Hills, MI 48336, USA
garytferguson@msn.com

Research in context

Evidence before this study

The benefits of therapies containing inhaled corticosteroids have been shown in patients with chronic obstructive pulmonary disease (COPD), but concern regarding the risk-to-benefit ratio of long-term administration of inhaled corticosteroids has led to their recommended use only as a treatment option in patients with a history of exacerbations who continue to experience disease symptoms or exacerbations. However, real-world evidence suggests that inhaled corticosteroids are prescribed to patients with COPD across the spectrum of symptom severity and exacerbation risk. Potential benefits of fixed-dose combination triple therapy (inhaled corticosteroid, long-acting muscarinic antagonist [LAMA], and long-acting β_2-agonist [LABA]), compared with fixed-dose combination dual therapies (LAMA and LABA or inhaled corticosteroid and LABA), are not well defined in symptomatic patients with COPD, particularly those with low exacerbation risk. Furthermore, the role of blood eosinophil counts as a predictor of patient response to inhaled corticosteroid therapy is unclear and largely based on retrospective analyses.

Added value of this study

To our knowledge, KRONOS is the first phase 3 study of a triple fixed-dose combination inhaled corticosteroid, LAMA, and LABA therapy in which the trial population was not enriched for patients who had COPD exacerbations in the year before study entry. The study population is representative of the majority of patients with moderate to very severe COPD who are seen in a clinical setting. More than 80% of the patients in KRONOS were symptomatic patients with moderate to very severe COPD who were not at high risk of exacerbations, a population that has not previously been the focus of phase 3 studies of triple therapies. We also did a prespecified subgroup analysis to investigate the relationship between blood eosinophil counts and treatment effects on lung function and exacerbation rates.

Implications of all the available evidence

Triple therapy improved lung function and symptoms, and reduced COPD exacerbations compared with dual fixed-dose combination therapies of inhaled corticosteroid and LABA, and LAMA and LABA, and was well tolerated in this patient population. The improvements in pre-dose trough FEV_1 for BGF MDI versus GFF MDI were mainly in patients with baseline eosinophil levels higher than approximately 250 cells/mm^3, whereas improvements in pre-dose trough FEV_1 for BGF MDI versus BFF MDI were evident over a broad range of eosinophil levels. There were reductions of approximately 20% in the rate of moderate or severe exacerbations in the BGF MDI group versus the GFF MDI group, associated with eosinophil concentrations that most patients exceeded. This finding suggests that triple therapy with BGF MDI could be more effective in improving lung function and reducing the exacerbation risk than LAMA/LABA dual therapy in most patients with COPD.

stages of disease severity.[1] Triple therapy containing dual bronchodilators and an inhaled corticosteroid is recommended only as a treatment option for patients with high exacerbation risk who continue to have symptoms or exacerbations while receiving treatment, particularly LAMA and LABA, or inhaled corticosteroid and LABA.[1] Despite guidance relating to which patients benefit from the addition of an inhaled corticosteroid to other treatments, real-world evidence suggests that inhaled corticosteroids are commonly prescribed to patients with high or low exacerbation risk,[2] often as an open triple therapy with a fixed-dose combination of inhaled corticosteroid with a LABA and a LAMA.[3]

Although adding an inhaled corticosteroid to a LABA has repeatedly been shown to improve airflow limitation,[4,5] quality of life,[4,5] and exacerbation rates[4,6,7] compared with use of a LABA alone, questions remain relating to the long-term use of inhaled corticosteroids in COPD, especially given the pneumonia risk reported in some studies[8,9] and the apparent limited effect of an inhaled corticosteroid and LABA on reducing exacerbations compared with a dual LAMA and LABA combination, as reported in one large study.[10] It continues to be debated whether peripheral eosinophil counts can be used to predict exacerbation risk or to identify patients with COPD who might clinically respond to inhaled corticosteroids.[11,12]

Triple fixed-dose combinations of inhaled corticosteroid, LAMA, and LABA have been developed for COPD,[13–16] but the potential benefits of triple versus dual fixed-dose combination therapies (LAMA and LABA, or inhaled corticosteroid and LABA) are not well characterised across the spectrum of patients with COPD, with most studies to date focused on patients with a high frequency of exacerbations or severe or very severe airflow limitation, or both.[13–17] Budesonide/glycopyrrolate/formoterol fumarate metered-dose inhaler (BGF MDI), formulated with co-suspension delivery technology, is a triple fixed-dose combination of inhaled corticosteroid, LAMA, and LABA that is in development as a maintenance therapy for patients with COPD. Co-suspension delivery technology facilitates the formulation of multiple drugs into a single MDI device that provides consistent aerosol performance[18] and drug deposition throughout the lungs.[19]

In this study, we aimed to compare triple therapy (BGF MDI) with dual therapies (glycopyrrolate/formoterol fumarate [GFF] MDI and budesonide/formoterol fumarate [BFF] MDI), in symptomatic patients with moderate to very severe COPD, irrespective of exacerbation history, measuring lung function, exacerbations, symptoms, and quality of life, and analysing the potential effect of peripheral eosinophil counts on treatment outcomes.

Methods

Study design and participants

KRONOS was a randomised, double-blind, parallel-group, phase 3 randomised controlled trial done in 215 sites across four countries (Canada, China, Japan, and the USA). Study sites included hospitals (n=108) and other care centres (n=107; mainly primary care and specialty centres).

Eligible patients were aged 40–80 years; were current or former smokers (with a smoking history of ≥10 pack-years); had an established clinical history of COPD, as defined by the American Thoracic Society (ATS)/European Respiratory Society[20] or by locally applicable guidelines[21] and confirmed by the investigator; and had moderate to very severe COPD, as defined by a post-bronchodilator FEV_1 less than 80% and 25% or more, according to predicted normal values using National Health and Nutrition Examination Survey III reference equations,[22] or applicable reference norms for Japan[21,23] and China (adjustment factor of 0·88).[24] Patients were symptomatic (COPD Assessment Test score ≥10) despite receiving two or more inhaled maintenance therapies for at least 6 weeks before screening (appendix). Patients were not required to have had a COPD exacerbation within the preceding year.

Exclusion criteria included a current diagnosis of asthma or a diagnosis of any respiratory disease or condition other than COPD, which in the opinion of the investigator could influence the results. Patients were also excluded if they had acute worsening of COPD that required treatment with oral corticosteroids or antibiotics less than 6 weeks before screening, with less than a 4-week washout of corticosteroids or antibiotics before Visit 1, or during screening. Patients were excluded if they were hospitalised because of COPD within 3 months before or during screening, as were patients unable to show baseline FEV_1 stability or perform acceptable spirometry.[25] Patients had to show that they could use an MDI correctly, with training provided if needed. We excluded patients who required a spacer device because they were unable to use the MDI correctly. Other exclusion criteria included change in smoking status within 6 weeks of or during screening, and the need for long-term oxygen therapy (>15 h/day). Full details can be found in the study protocol.

The study was done in accordance with Good Clinical Practice, including the Declaration of Helsinki. The protocol and informed consent form were approved by appropriate institutional review boards or independent ethics committees (appendix). All patients provided written informed consent before screening. Protocol amendments pertaining to study endpoints or data analyses are shown in the appendix.

Randomisation and masking

Study site personnel randomly assigned patients (2:2:1:1) using an interactive web response system to treatment with BGF MDI, GFF MDI, BFF MDI, or budesonide/formoterol fumarate dry-powder inhaler (BUD/FORM DPI). Randomisation was stratified by reversibility to salbutamol sulphate (yes/no), country, and disease severity (post-bronchodilator percent predicted FEV_1 ≥50% or <50%). There was no enrichment for blood eosinophils as part of the study protocol. Patients, study site personnel, and the study sponsor were masked to treatment assignment for BGF MDI, GFF MDI, and BFF MDI, since all were administered from matching MDIs. BUD/FORM DPI (Symbicort Turbuhaler, AstraZeneca, AB, Södertälje, Sweden) was administered open-label. Since BFF MDI is not an approved therapy, BUD/FORM DPI was included in this study as an active comparator approved for COPD, to support BFF MDI use as an active comparator for BGF MDI.

Procedures

Eligible patients discontinued prohibited medications for COPD, which included LAMAs, LABAs, or both, for the study duration and had their COPD maintenance therapy adjusted for the screening period (appendix). Briefly, all patients received sponsor-provided, open-label ipratropium bromide (34 µg ex-actuator; Atrovent hydrofluoroalkane [Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, USA] or equivalent product) administered four times daily for maintenance of COPD, and were permitted to continue using inhaled corticosteroids during screening (providing they had been on a stable dose of inhaled corticosteroid for 4 weeks before screening). Ipratropium and inhaled corticosteroid were stopped before randomisation.

See Online for appendix

After randomisation, patients received BGF MDI 320/18/9·6 µg (equivalent to budesonide/glycopyrronium/formoterol fumarate dihydrate 320/14·4/10 µg; inhaled corticosteroid, LAMA, and LABA triple therapy), GFF MDI 18/9·6 µg (LAMA and LABA dual therapy), BFF MDI 320/9·6 µg (inhaled corticosteroid and LABA dual therapy), or open-label BUD/FORM DPI 400/12 µg (inhaled corticosteroid and LABA) as two inhalations twice-daily for 24 weeks (appendix). All patients received sponsor-provided salbutamol sulphate (90 µg salbutamol base ex-actuator; Ventolin hydrofluoroalkane [GlaxoSmithKline, Research Triangle Park, NC, USA]), for rescue use as needed throughout the study. Rescue medication had to be withheld for at least 6 h before the start of test day procedures. The last dose of study drug must have been taken as scheduled the evening before test day procedures.

For the **study protocol** see https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=25410

At each visit from randomisation onwards, spirometry was assessed by study personnel, the St George's Respiratory Questionnaire (SGRQ) was completed by the participant, and electronic diary review was completed by study personnel, and occurrences of COPD exacerbations, medication changes, and adverse events were recorded. The Baseline Dyspnoea Index (BDI) questionnaire was completed at screening and the Transition Dyspnoea Index (TDI) questionnaire was completed at the remaining visits. Spirometry was done in accordance with ATS

criteria,[25] and all sites were provided with identical systems that met or exceeded the ATS minimum performance recommendations. Patients recorded daily rescue medication use and Evaluating Respiratory Symptoms COPD (E-RS: COPD) scores in the electronic diary.

There were predefined criteria for identifying and reporting exacerbations, pneumonia, and major adverse cardiovascular events (appendix). An external data monitoring committee oversaw the safety assessment. An independent clinical endpoint committee reviewed all adverse events reported as pneumonia or that potentially met criteria for major adverse cardiovascular events.

Blood eosinophil counts were measured at screening Visit 1 (of three planned visits) and at randomisation; the mean of non-missing values was recorded as the baseline blood eosinophil count. A history of COPD exacerbations in the previous year was obtained to characterise the study population.

Outcomes

Primary and secondary endpoints and treatment comparisons of interest differed according to regulatory registration requirements (appendix). The primary endpoints for the Europe and Canada statistical analysis approach were FEV_1 area under the curve from 0 to 4 h (AUC_{0-4}) over 24 weeks (BGF MDI *vs* BFF MDI and BGF MDI *vs* BUD/FORM DPI) and change from baseline in morning pre-dose trough FEV_1 over 24 weeks (BGF MDI *vs* GFF MDI and BFF MDI *vs* BUD/FORM DPI [non-inferiority]).

Secondary endpoints for the Europe and Canada statistical analysis approach were change from baseline in morning pre-dose trough FEV_1 (BGF MDI *vs* BFF MDI), peak change from baseline in FEV_1 within 4 h after dosing, rate of moderate or severe COPD exacerbations, TDI focal score (Europe statistical analysis approach only), change from baseline in daily rescue medication use, change from baseline in SGRQ total score, E-RS: COPD total score (RS-Total score), and time to clinically important deterioration (BGF MDI *vs* GFF MDI, *vs* BFF MDI, and *vs* BUD/FORM DPI), all over 24 weeks, and time to onset of action on Day 1 (the first post-dose timepoint at which the mean change from baseline in FEV_1 exceeded 100 mL). CID was defined as a decrease of 100 mL or more from baseline in trough FEV_1, an increase of 4 points or more from baseline in SGRQ total score, a TDI focal score of –1 point or less, or a treatment-emergent moderate or severe COPD exacerbation occurring up to week 24. Time to first moderate or severe exacerbation was an additional efficacy endpoint.

FEV_1 AUC_{0-4} at week 24 (BGF MDI *vs* BFF MDI) and change from baseline in morning pre-dose trough FEV_1 at week 24 (BGF MDI *vs* GFF MDI) were primary endpoints for the US approach. Secondary endpoints for the US approach are shown in the appendix.

Details of the endpoints for the China/Japan statistical analysis approach are provided in the protocol.

Additional prespecified analyses included examining the relationship of responses (morning pre-dose trough FEV_1 and rate of moderate or severe exacerbations) to baseline blood eosinophil counts. Safety endpoints included adverse events, 12-lead electrocardiograms (ECGs), clinical laboratory testing, and vital sign measurements.

Statistical analysis

Patients from all countries were included in all statistical analysis approaches. We did all analyses using SAS (version 9.4 or later). All efficacy assessments were relative to pre-dose baseline values obtained at randomisation (FEV_1, BDI, and SGRQ), or over the last 7 days of screening (rescue medication use and RS-Total score). Baseline FEV_1 was defined as the average of non-missing values obtained 60 min and 30 min before dosing on day 1 of treatment.

The primary estimand of interest for superiority testing was the efficacy estimand, which was defined as the hypothetical effect of the randomised treatment in all patients assuming continuation of randomised treatments for the duration of the study, regardless of actual compliance. We did the primary efficacy analysis for the efficacy estimand using the modified intention-to-treat population (all patients with post-randomisation data obtained before discontinuation from treatment). We analysed patients according to assigned treatment group. The second estimand of interest for superiority testing was the attributable estimand, which we also assessed in the modified intention-to-treat population, accounting for patients who discontinued treatment because of lack of efficacy or tolerability (unfavourable outcomes), and imputing missing data; patients without data after randomisation were not included in the attributable estimand (appendix). The per-protocol estimand was the primary estimand for the non-inferiority analyses of BFF MDI compared with BUD/FORM DPI, and used the per-protocol population (all patients who were randomly assigned to treatment, used any amount of study treatment, and had post-randomisation data obtained before any major protocol deviations).

For the primary efficacy analyses, all comparisons were for superiority except for the comparison of BFF MDI versus BUD/FORM DPI, which was for non-inferiority (margin of –50 mL from lower bound of 95% CI). We analysed the change from baseline in morning pre-dose trough FEV_1 using a linear model with repeated measures. The model included treatment, visit, treatment by visit interaction, and inhaled corticosteroid use at screening as categorical covariates, and baseline FEV_1, percent reversibility to salbutamol, and baseline eosinophil counts as continuous covariates. We used an unstructured covariance matrix to model correlation within a patient. We calculated two-sided p values and point estimates with 95% CIs for each treatment difference.

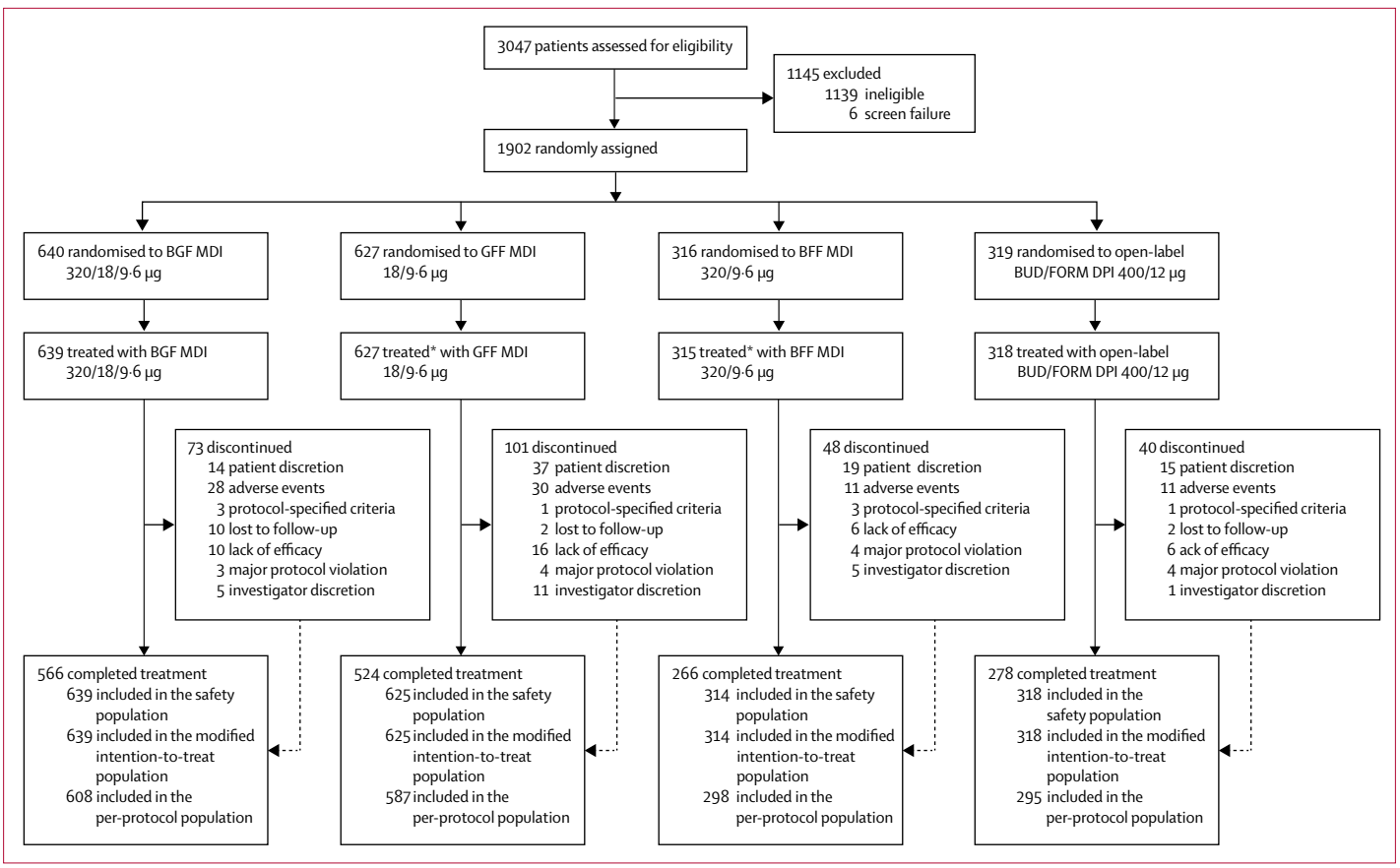

Figure 1: **Trial profile**
BGF=budesonide/glycopyrrolate/formoterol fumarate. MDI=metered-dose inhaler. GFF=glycopyrrolate/formoterol fumarate. BFF=budesonide/formoterol fumarate. BUD/FORM DPI=budesonide/formoterol fumarate dry-powder inhaler. *Two patients in the GFF MDI group and one patient in the BFF MDI group participated in multiple sponsor-led studies and were excluded from all analysis populations.

We analysed change from baseline in FEV_1 $AUC_{0–4}$ over 24 weeks and at week 24 using a similar approach to that used for morning pre-dose trough FEV_1. We calculated AUC using the trapezoidal rule and normalised it by dividing by the time (h) from dosing to the last measurement included. Details of the secondary endpoint statistical analyses, non-inferiority margins, type I error control, and sample size calculation are shown in the appendix. Treatment comparisons for which p values of 0·05 were reported wre considered as significant if they satisfied the type I error control strategy. Comparisons for which p was less than 0·05, which either failed or were not included in the type I error control strategy, are reported as nominally significant. This study is registered with ClinicalTrials.gov, number NCT02497001.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 20, 2015, and Jan 5, 2018, 3047 patients were screened, of whom 1902 were randomly assigned to receive BGF MDI (n=640), GFF MDI (n=627), BFF MDI (n=316), or BUD/FORM DPI (n=319; figure 1).

Overall, 1411 (74%) of 1896 patients in the modified intention-to-treat population had no exacerbations in the preceding 12 months, and 88% had no severe exacerbations and 1 or 0 moderate exacerbations in the preceding 12 months, 71·8% were receiving inhaled corticosteroids at screening, and 51·8% had baseline blood eosinophil counts ≥150 cells/mm³. There were no clinically relevant differences across treatment groups at baseline (table 1).

Over 24 weeks, BGF MDI significantly improved FEV_1 $AUC_{0–4}$ versus BFF MDI (least squares mean [LSM] difference 104 mL, 95% CI 77 to 131; p<0·0001) and BUD/FORM DPI (91 mL, 64 to 117; p<0·0001; figure 2A; table 2). The change from baseline in morning pre-dose trough FEV_1 over 24 weeks was significantly improved by BGF MDI versus GFF MDI (22 mL, 4–39 mL; p=0·0139) and BFF MDI (74 mL, 52 to 95 mL; p<0·0001; figure 2B; table 2). BFF MDI was non-inferior to BUD/FORM DPI

	BGF MDI 320/18/9·6 µg (n=639)	GFF MDI 18/9·6 µg (n=625)	BFF MDI 320/9·6 µg (n=314)	Open-label BUD/FORM DPI 400/12 µg (n=318)
Mean age, years	64·9 (7·8)	65·1 (7·7)	65·2 (7·2)	65·9 (7·7)
Sex				
Male	460 (72·0%)	430 (68·8%)	224 (71·3%)	236 (74·2%)
Female	179 (28·0%)	195 (31·2%)	90 (28·7%)	82 (25·8%)
Ethnicity				
White	329 (51·5%)	301 (48·2%)	157 (50·0%)	163 (51·3%)
Black	23 (3·6%)	38 (6·1%)	15 (4·8%)	14 (4·4%)
Asian	284 (44·4%)	285 (45·6%)	142 (45·2%)	141 (44·3%)
Other	3 (0·5%)	1 (0·2%)	0	0
Mean body mass index, kg/m²	26·1 (6·7)	26·3 (6·4)	26·1 (5·8)	26·2 (6·3)
Current smoker	256 (40·1%)	257 (41·1%)	115 (36·6%)	122 (38·4%)
Median number of pack-years smoked*	45·0 (10·0–256·0)	45·0 (10·0–171·0)	45·0 (10·0–192·0)	45·0 (10·0–180·0)
COPD severity				
Mild	2 (0·3%)	0	1 (0·3%)	0
Moderate	310 (48·5%)	306 (49·0%)	154 (49·0%)	160 (50·3%)
Severe	275 (43·0%)	267 (42·7%)	133 (42·4%)	138 (43·4%)
Very severe	52 (8·1%)	52 (8·3%)	26 (8·3%)	20 (6·3%)
Mean COPD duration, years	7·1 (6·0)	6·5 (5·4)	7·3 (6·2)	6·7 (5·5)
Moderate or severe COPD exacerbations in the past 12 months				
0	469 (73·4%)	473 (75·7%)	235 (74·8%)	234 (73·6%)
1	125 (19·6%)	108 (17·3%)	61 (19·4%)	59 (18·6%)
≥2	45 (7·0%)	44 (7·0%)	18 (5·7%)	25 (7·9%)
Moderate or severe exacerbation rate				
Mean	0·4 (0·8)	0·3 (0·7)	0·3 (0·6)	0·4 (0·8)
Median	0·0 (0–8)	0·0 (0–5)	0·0 (0–4)	0·0 (0–8)
Eosinophils				
Median cells per mm³	150·0 (10·0–2815·0)	155·0 (15·0–2490·0)	152·5 (15·0–920·0)	150·0 (35·0–1100·0)
<150 cells/mm³	314 (49·1%)	291 (46·6%)	151 (48·1%)	157 (49·4%)
≥150 cells/mm³	325 (50·9%)	334 (53·4%)	163 (51·9%)	161 (50·6%)
Post-salbutamol FEV_1, % predicted				
Number	639	624	314	318
Mean	50·2 (14·3)	50·2 (13·8)	50·0 (14·0)	50·7 (13·8)
Reversibility to salbutamol				
Number	639	623	314	317
Mean difference in FEV_1 before and after salbutamol, mL	199·7 (144·5)	191·7 (154·2)	195·8 (162·1)	212·2 (152·7)
Reversible†	286 (44·8%)	266 (42·6%)	130 (41·4%)	140 (44·0%)
Use of inhaled corticosteroid at screening	464 (72·6%)	447 (71·5%)	225 (71·7%)	225 (70·8%)
BDI focal score				
Number	614	587	296	291
Mean	6·4 (2·1)	6·5 (2·1)	6·4 (2·2)	6·3 (2·2)
SGRQ total score				
Number	621	595	298	297
Mean	44·1 (17·0)	43·9 (16·4)	43·5 (17·0)	43·9 (17·5)

(Table 1 continues on next page)

for the change from baseline in morning pre-dose trough FEV_1 over 24 weeks (per-protocol estimand LSM difference –10 mL, 95% CI –36 to 16; p=0·4390). There were consistent results from the secondary analyses of these endpoints with the attributable estimand (table 2).

Treatment differences were generally consistent over time: patients in the BGF MDI group had a significantly improved FEV_1 $AUC_{0–4}$ at week 24 compared with patients receiving BFF MDI (LSM difference 116 mL, 95% CI 80 to 152; p<0·0001; figure 2A; appendix). Regarding the other primary endpoint for the US approach, there was a non-significant improvement in the change from baseline in morning pre-dose trough FEV_1 at week 24 versus GFF MDI (13 mL, –9 to 36 mL; p=0·2375; figure 2B; appendix); in the secondary analyses, there was a nominally significant improvement in this endpoint (24 mL, 1 to 46 mL; p=0·0370; appendix).

BGF MDI significantly increased peak change from baseline in FEV_1 over 24 weeks versus BFF MDI (LSM difference 105 mL, 95% CI 78–133; p<0·0001), but not versus GFF MDI (table 2). The time to onset of action on day 1 was within 5 min for all treatments (table 2).

The model-estimated rates of moderate or severe exacerbations were 0·46 per year for BGF MDI, 0·95 per year for GFF MDI, 0·56 per year for BFF MDI, and 0·55 per year for BUD/FORM DPI (table 3). The rate of moderate or severe exacerbations was significantly lower during treatment with BGF MDI versus GFF MDI (table 3). BGF MDI reduced the rate of moderate or severe exacerbations compared with BFF MDI and BUD/FORM DPI, but these reductions were not significant (table 3). For the additional endpoint of time to first moderate or severe exacerbation of COPD, the risk during treatment with BGF MDI was nominally significantly lower versus GFF MDI (hazard ratio [HR] 0·593; p<0·0001 [Cox regression] and p=0·0001 [log rank]) and numerically lower versus BFF MDI (HR 0·747; p=0·0635 [Cox regression] and p=0·0281 [log rank]; figure 3).

BGF MDI significantly improved TDI focal score versus BUD/FORM DPI, but not versus GFF MDI and BFF MDI, and provided nominally significant improvements in change from baseline in RS-Total score over 24 weeks versus GFF MDI but not BFF MDI or BUD/FORM DPI (table 3). BGF MDI also resulted in nominally significant improvements in SGRQ total score over 24 weeks versus GFF MDI but not BFF MDI or BUD/FORM DPI (table 3).

Time to clinically important deterioration was nominally significantly reduced by BGF MDI versus BFF MDI and BUD/FORM DPI, but there was no difference compared with GFF MDI (table 3). There was no significant difference between groups in the average puffs per day of daily rescue medication (table 3).

BFF MDI was non-inferior to BUD/FORM DPI over 24 weeks for most other applicable type I error controlled endpoints (FEV_1 $AUC_{0–4}$ [primary endpoint], TDI focal score, SGRQ total score, and RS-Total score; appendix).

Non-inferiority was not shown for average daily rescue medication use or risk of clinically important deterioration, although for the latter there was insufficient evidence to conclude that treatment effects differed and the former might have been influenced by the open-label nature of BUD/FORM DPI.

The prespecified subgroup analysis of treatment responses by blood eosinophil count showed that improvements in change from baseline in morning pre-dose trough FEV_1 for BGF MDI relative to GFF MDI were driven by patients with at least 150 cells/mm³ (appendix). Further analyses of response by continuous baseline eosinophil count with locally weighted scatter-plot smoothing (LOESS) showed that the differences in improvements in morning pre-dose trough FEV_1 between BGF MDI and GFF MDI over 24 weeks increased with blood eosinophil counts and occurred primarily at eosinophil counts above approximately 250 cells/mm³ (figure 4A). By contrast, improvements in morning pre-dose trough FEV_1 with BGF MDI versus BFF MDI occurred across a broad range of eosinophil counts (figure 4B; appendix). The LOESS curves for BGF MDI and BFF MDI converged from around 400 cells per mm³ but these results should be interpreted with caution because of the variability that resulted from only approximately 5% of patients having blood eosinophil levels of 400 cells per mm³ or more.

The rates of moderate or severe exacerbations with BGF MDI were lower than with GFF MDI for patients in both eosinophil subgroups (appendix), with locally weighted scatter-plot smoothing showing that treatment differences increased with baseline blood eosinophil concentrations; beginning at approximately 75–100 cells/mm³ (figure 4C), a level exceeded by more than 75% of patients (figure 4C; appendix). No apparent differences were seen between BGF MDI and GFF MDI below these concentration thresholds. Differences between BGF MDI and BFF MDI in the rate of moderate or severe exacerbations were similar across most eosinophil counts (figure 4D; appendix).

The incidence of treatment-emergent adverse events, treatment-related adverse events, serious treatment-emergent adverse events, and treatment-emergent adverse events leading to discontinuation was similar across treatments (table 4). The most common treatment-emergent adverse events were nasopharyngitis (n=49 [8%] in the BGF MDI group; n=41 [7%] in the GFF MDI group; n=26 [8%] in the BFF MDI group; and n=30 [9%] in the BUD/FORM DPI group) and upper respiratory tract infection (n=65 [10%]; n=38 [6%]; n=18 [6%]; and n=22 [7%]). The incidence of severe treatment-emergent adverse events was similar across treatments (ranging from 18 [5·7%] of 314 patients in the BFF MDI group to 60 [9·6%] of 625 patients in the GFF MDI group).

The most frequently reported serious treatment-emergent adverse events were COPD (70 [3·7%] of 1896 patients) and pneumonia (15 [0·8%] patients; table 4; appendix). The rates of cases of major adverse cardiovascular events and pneumonia, confirmed by the clinical endpoint committee, were low and similar across treatments (table 4). Non-adjudicated major adverse

	BGF MDI 320/18/9·6 µg (n=639)	GFF MDI 18/9·6 µg (n=625)	BFF MDI 320/9·6 µg (n=314)	Open-label BUD/FORM DPI 400/12 µg (n=318)
(Continued from previous page)				
Mean CAT total score	18·7 (6·4)	18·1 (6·1)	18·4 (6·6)	18·0 (6·4)
Rescue medication use‡				
Number	293	269	141	155
Median puffs per day	3·6 (1·0–13·0)	3·7 (1·0–18·4)	3·9 (1·0–17·7)	3·9 (1·0–20·3)

Data are mean (SD), median (range), or n (%), unless otherwise indicated. BGF=budesonide/glycopyrrolate/formoterol fumarate. MDI=metered dose inhaler. GFF=glycopyrrolate/formoterol fumarate. BFF=budesonide/formoterol fumarate. BUD/FORM DPI=budesonide/formoterol fumarate dry powder inhaler. COPD=chronic obstructive pulmonary disease. BDI=Baseline Dyspnoea Index. SGRQ=St George's Respiratory Questionnaire. CAT=COPD Assessment Test. *Number of pack-years smoked=(number of cigarettes each day/20) × number of years smoked. †Reversible was defined as improvement in FEV_1 after salbutamol administration (compared with before salbutamol administration) of 12% or more and 200 mL or more. ‡Rescue medication user population.

***Table 1*: Demographic and baseline disease characteristics of the modified intention-to-treat population**

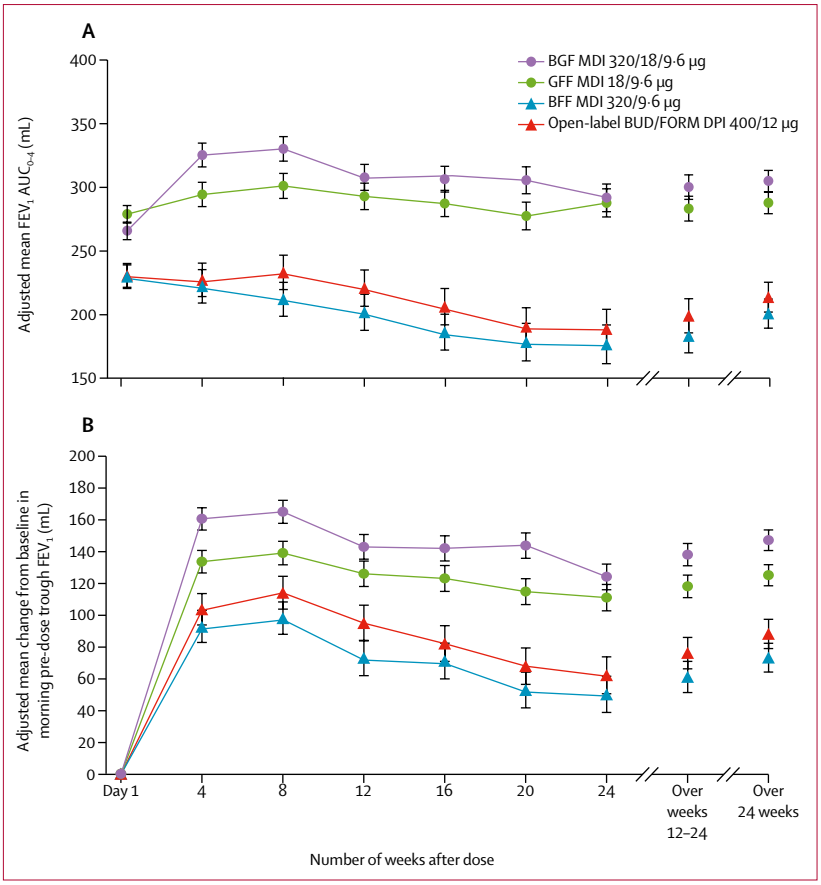

***Figure 2*: Primary lung function endpoints over time, in the modified intention-to-treat population**
(A) FEV_1 AUC_{0-4}. (B) Change from baseline in morning pre-dose trough FEV_1. Error bars represent SE. AUC_{0-4}=area under the curve 0–4 h. BGF=budesonide/glycopyrrolate/formoterol fumarate. MDI=metered-dose inhaler. GFF=glycopyrrolate/formoterol fumarate. BFF=budesonide/formoterol fumarate. BUD/FORM DPI=budesonide/formoterol fumarate dry-powder inhaler.

	BGF MDI 320/18/9·6 µg (n=639)	GFF MDI 18/9·6 µg (n=625)	BFF MDI 320/9·6 µg (n=314)	Open-label BUD/FORM DPI 400/12 µg (n=318)
Primary endpoints				
FEV_1 AUC_{0-4}, mL				
Number of patients	501	485	245	248
LSM	305	288	201	214
SE	8·4	8·5	11·7	11·5
LSM (95% CI); p value	NA	16 (–6 to 38); p=0·1448	104 (77 to 131); p<0·0001*	91 (64 to 117); p<0·0001*
Change from baseline in morning pre-dose trough FEV_1, mL				
Number of patients	622	601	300	301
LSM	147	125	73	88
SE	6·5	6·6	9·2	9·1
LSM (95% CI); p value	NA	22 (4 to 39); p=0·0139*	74† (52 to 95); p<0·0001*	59 (38 to 80); p<0·0001‡
Secondary endpoints				
FEV_1 AUC_{0-4}, mL§				
Number of patients	501	485	245	248
LSM	293	271	189	204
SE	8·4	8·4	11·6	11·4
LSM (95% CI); p value	NA	22 (0 to 43); p=0·0488‡	104 (77 to 130); p<0·0001*	89 (63 to 116); p<0·0001*
Change from baseline in morning pre-dose trough FEV_1, mL§				
Number of patients	622	601	300	301
LSM	137	110	63	80
SE	6·6	6·6	9·3	9·2
LSM (95% CI); p value	NA	27 (9 to 45); p=0·0027*	74 (52 to 96); p<0·0001	56 (35 to 78); p<0·0001‡
Peak change from baseline in FEV_1 <4 h after dose, mL				
Number of patients	501	485	245	248
LSM	381	364	275	291
SE	8·8	8·9	12·2	12·0
LSM (95% CI); p value	NA	17 (–6 to 40); p=0·1425	105 (78 to 133); p<0·0001	90 (62 to 118); p<0·0001
Time to onset of action on day 1 (change from baseline in FEV_1 at 5 min after dose, mL)				
Number of patients	429	417	220	210
Mean	175	180	160	164
SD	122	131	116	122

Least squares mean results are for the treatment difference for BGF MDI versus comparators. Results are for efficacy estimand, unless otherwise stated. BGF=budesonide/glycopyrrolate/formoterol fumarate. MDI=metered dose inhaler. GFF=glycopyrrolate/formoterol fumarate. BFF=budesonide/formoterol fumarate. BUD/FORM DPI=budesonide/formoterol fumarate dry powder inhaler. AUC_{0-4}=area under the curve from 0 to 4 h. LSM=least squares mean. NA=not applicable. *Prespecified comparison. †Prespecified secondary endpoint. ‡Nominally significant (ie, not significant after type I error control or not included in the type I error control strategy). §Attributable estimand.

***Table 2*: Primary endpoints and lung function secondary endpoints**

cardiovascular events and pneumonia rates are shown in the appendix.

12 deaths occurred during the study, caused by cancer (n=2 in the BGF MDI group, n=2 in the BFF MDI group), cardiovascular disease (n=2 in the BGF MDI group, n=1 in the GFF MDI group), worsening of COPD (n=2 in the GFF MDI group), pneumonia (n=1 in the BUD/FORM DPI group), or other causes (n=1 smoke inhalation and n=1 sepsis, both in the BGF MDI group). There were two deaths in the GFF MDI group, both caused by worsening of COPD, which were judged by the investigator to be related to study drug treatment.

BGF MDI was not associated with clinically meaningful changes in haematology, clinical chemistry, kidney function, or urinalysis variables. Effects on vital signs (heart rate or blood pressure) and ECG parameters (QTcF, PR, or QRS interval prolongation) were small and similar across treatments (data not shown).

Discussion

BGF MDI provided clinically meaningful improvements in lung function versus BFF MDI and BUD/FORM DPI, with modest improvements reported for BGF MDI versus GFF MDI. However, the primary reason for inhaled corticosteroid use in COPD is to control exacerbations, and there were significant reductions in exacerbation rates for BGF MDI versus GFF MDI. BFF MDI was non-inferior to BUD/FORM DPI for the primary and most secondary endpoints.

Unlike previous phase 3 trials of triple therapies (fixed-dose combination inhaled corticosteroid, LAMA, and LABA), KRONOS was not restricted to patients with a history of COPD exacerbations.[13–17] Therefore, in addition to supporting the use of triple therapy in patients with high exacerbation risk, the results of this study are particularly important for patients with low exacerbation risk. Patients entering the study were required to be symptomatic despite being on two or more inhaled maintenance therapies. This requirement arguably represents a patient who, because of continued symptoms or exacerbation risk, would be considered for additional treatment options, such as triple fixed-dose combination therapy. KRONOS is the second study published that compares triple therapy with corresponding dual therapies delivered by the same platform. This study design ensures that improvements observed with the triple versus dual therapies were due to the combined effect of active compounds rather than differences in device, drug, or dosing strategy.

Somewhat surprisingly for this population, the addition of inhaled corticosteroid to LAMA and LABA dual therapy (BGF MDI *vs* GFF MDI) showed a marked reduction in exacerbation frequency. There was a similar trend in exacerbation rates for triple therapy versus dual therapies in the TRIBUTE[13] and IMPACT[16] studies, both done over 52 weeks in patients with a high risk of COPD exacerbation. The difference in exacerbation rates with BGF MDI versus BFF MDI and versus BUD/FORM DPI was not significant, probably because a larger sample size would have been required, but the magnitude of effect between triple therapy and dual therapies was similar to those seen in IMPACT[16] and the 52-week TRILOGY study.[14] Additionally, in our study, in which patients discontinued any previous inhaled corticosteroid at randomisation, the time to first moderate or severe exacerbation showed a cumulative

incidence of exacerbations for GFF MDI, BFF MDI, and BUD/FORM DPI that diverged over time, not just in the first 4 weeks, indicating that results were not driven solely by withdrawal of inhaled corticosteroid, as postulated previously for IMPACT.[26] Our finding, that adding a LAMA to inhaled corticoisteroid and LABA (BGF MDI *vs* BFF MDI) improved lung function, is consistent with previous triple fixed-dose combination therapy studies.[14,16]

There were notable changes from baseline for symptom-based endpoints for all treatments. However, in studies with only active treatment groups, the magnitude of differences between treatments can be small and thus these endpoints might not always act as sensitive differentiators between active treatments. Nonetheless, numerical improvements in symptoms and quality-of-life endpoints generally favoured BGF MDI relative to the comparators.

The exacerbation history captured from the year before study entry was lower than the model-estimated exacerbation rates observed during the study, especially with GFF MDI. This finding raises the point of whether asking patients standard questions about exacerbations and acute COPD treatments are an accurate measure of exacerbation risk, since they require patients to recall these details correctly. Alternatively, as noted in the ECLIPSE study,[27] exacerbation variability might simply be a function of time, with divergent exacerbation patterns in many patients on a year-by-year basis.[27] Notwithstanding the reason for the trend in exacerbation rates before and during this study, results support the importance of therapies containing inhaled corticosteroids for preventing exacerbations in symptomatic patients with COPD.

The role of peripheral blood eosinophils as a predictor of clinical response is uncertain, with findings both for and against their use as a biomarker in patients with COPD.[11,12] Our LOESS regression showed an association between blood eosinophil counts and improvements in lung function and COPD exacerbation rates with combinations containing inhaled corticosteroids (ie, BGF MDI and BFF MDI), consistent with findings from a post-hoc analysis.[28] The relationship between blood eosinophil levels and the rate of moderate or severe COPD exacerbations will be further characterised in the 52-week phase 3 ETHOS study (NCT02465567), which is investigating two doses of BGF MDI compared with BFF MDI and GFF MDI and aims to randomly assign more than 2000 patients per treatment group.

Overall, the safety profile of BGF MDI was comparable with the well established profiles of the approved products GFF MDI and BUD/FORM DPI, as well as BFF MDI. The incidence of major adverse cardiovascular events was low and similar across treatments, supporting previous studies of GFF MDI that showed that potential class effects of LAMAs and LABAs on cardiovascular safety were not observed in healthy participants or patients with COPD.[29] Notably, incidences of adjudicated pneumonia were low and comparable between BGF MDI (2%) and GFF MDI (2%), suggesting that the budesonide dose used in the triple therapy was not associated with an appreciably increased risk of pneumonia compared with

	BGF MDI 320/18/9·6 µg	GFF MDI 18/9·6 µg	BFF MDI 320/9·6 µg	Open-label BUD/FORM DPI 400/12 µg
Model-estimated rate of moderate or severe COPD exacerbations				
Number of patients	639	625	314	318
Rate, per year	0·46	0·95	0·56	0·55
Rate ratio (95% CI); p value*	NA	0·48 (0·37 to 0·64); p<0·0001	0·82 (0·58 to 1·17); p=0·2792	0·83 (0·59 to 1·18); p=0·3120
TDI focal score				
Number of patients	614	587	296	291
LSM	1·25	1·07	1·01	0·78
SE	0·09	0·09	0·13	0·13
LSM (95% CI); p value*	NA	0·18 (–0·07 to 0·43); p=0·1621	0·24 (–0·07 to 0·54); p=0·1283	0·46 (0·16 to 0·77); p=0·0031
Change from baseline in RS-Total score				
Number of patients	638	621	313	313
LSM	–1·1	–0·7	–1·0	–1·0
SE	0·13	0·14	0·19	0·19
LSM (95% CI); p value*	NA	–0·38 (–0·74 to –0·01); p=0·0430†	–0·16 (–0·61 to 0·28); p=0·4790	–0·16 (–0·60 to 0·29); p=0·4923
Change from baseline in SGRQ total score				
Number of patients	621	595	298	297
LSM	–7·5	–6·3	–7·1	–6·3
SE	0·47	0·47	0·61	0·62
LSM (95% CI); p value*	NA	–1·22 (–2·30 to –0·15); p=0·0259†	–0·45 (–1·78 to 0·87); p=0·5036	–1·26 (–2·58 to 0·06); p=0·0617
Time to CID‡				
Number of patients	639	625	314	318
Patients with CID, n (%)	411 (64·3%)	413 (66·1%)	216 (68·8%)	225 (70·8%)
Hazard ratio (95% CI); p value*	NA	0·88 (0·76 to 1·00); p=0·0593	0·83 (0·70 to 0·98); p=0·0276†	0·81 (0·69 to 0·96); p=0·0119†
Change from baseline in average daily rescue medication use, puffs per day§				
Number of patients	293	269	141	155
LSM	–1·3	–1·1	–1·1	–1·6
SE	0·13	0·13	0·18	0·17
LSM (95% CI); p value*	NA	–0·25 (–0·60 to 0·09); p=0·1446	–0·24 (–0·65 to 0·18); p=0·2661	0·23 (–0·17 to 0·63); p=0·2667

Results are for the efficacy estimand. CID=clinically important deterioration. BGF=budesonide/glycopyrrolate/formoterol fumarate. MDI=metered dose inhaler. GFF=glycopyrrolate/formoterol fumarate. BFF=budesonide/formoterol fumarate. BUD/FORM DPI=budesonide/formoterol fumarate dry powder inhaler. COPD=chronic obstructive pulmonary disease. NA=not applicable. TDI=Transition Dyspnoea Index. LSM=least squares mean. RS-Total score=Evaluating Respiratory Symptoms in COPD Total score. SGRQ=St George's Respiratory Questionnaire. *Treatment difference for BGF MDI versus comparators. †Nominally significant (ie, not significant after type I error control or not included in the type I error control strategy). ‡CID was defined as a decrease of 100 mL or more from baseline in trough FEV_1, an increase of 4 points or more from baseline in SGRQ total score, a TDI focal score of –1 point or less, or a treatment-emergent moderate or severe COPD exacerbation occurring up to week 24. §Rescue medication user population.

***Table 3*: Exacerbations, symptoms, quality of life, and CID endpoints, over 24 weeks**

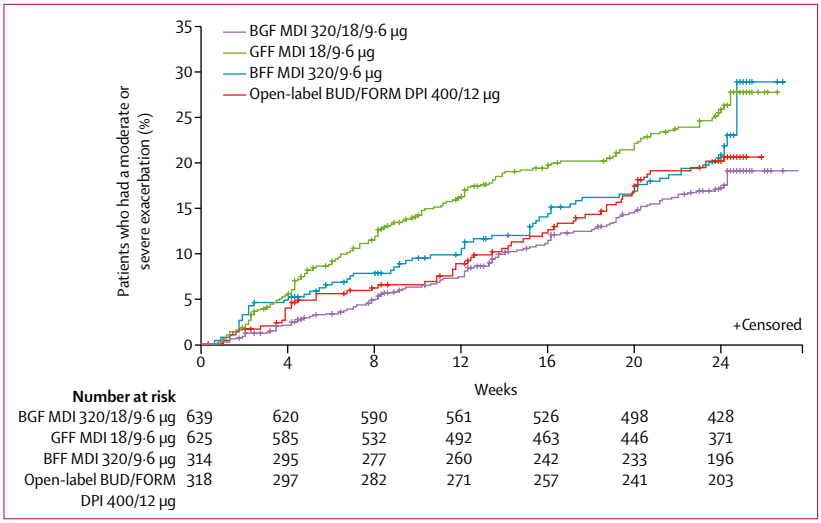

Figure 3: **Time to first exacerbation of chronic obstructive pulmonary disease**
BGF=budesonide/glycopyrrolate/formoterol fumarate. MDI=metered-dose inhaler. GFF=glycopyrrolate/formoterol fumarate. BFF=budesonide/formoterol fumarate. BUD/FORM DPI=budesonide/formoterol fumarate dry-powder inhaler.

dual bronchodilator therapy. This finding is consistent with pneumonia rates reported for budesonide/formoterol compared with formoterol monotherapy in studies over 6 and 12 months.[4,6] In IMPACT,[16] the incidence of pneumonia over 52 weeks in the fluticasone furoate-containing treatment arms (fluticasone furoate, umeclidinium, and vilanterol [inhaled corticosteroid, LAMA, and LABA] and fluticasone furoate and vilanterol [inhaled corticosteroid and LABA]) was higher than with umeclidinium and vilanterol (LAMA and LABA).[16]

Limitations included the shorter study duration of KRONOS (24 weeks) than other phase 3 studies of triple fixed-dose combination therapies for chronic obstructive pulmonary disease (52 weeks),[13–17] especially when considering exacerbations and long-term risks. However, the exacerbation rates observed in KRONOS were consistent with those from longer-term studies[13,16] and most patients (>70%) were taking an inhaled corticosteroid before study participation. Additionally, although we assessed the associations between lung function, exacerbations, and eosinophil levels using blood eosinophil levels at baseline, we did not use eosinophil levels to prospectively stratify therapy. Such studies,

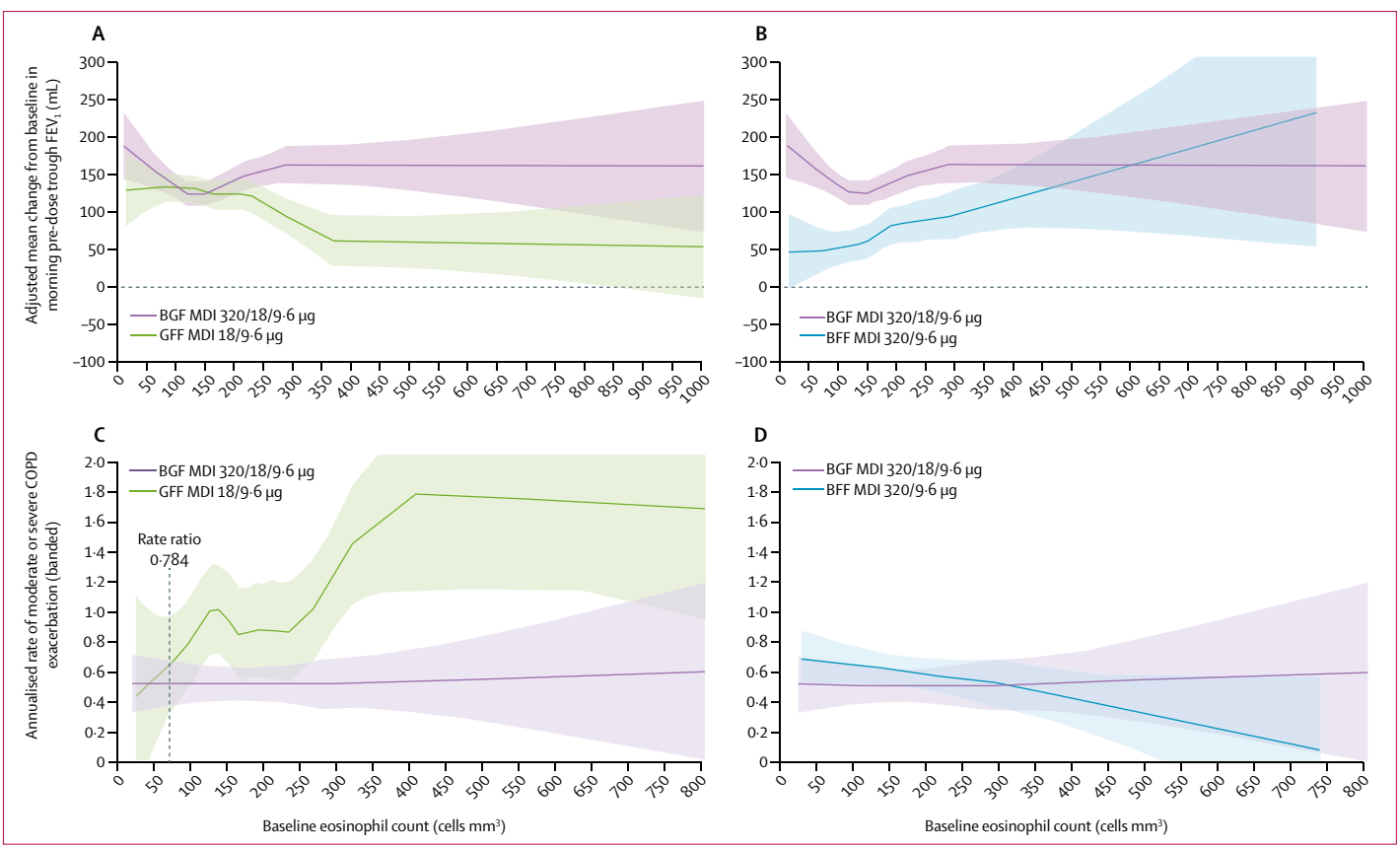

Figure 4: **Lung function and exacerbation responses by blood eosinophil counts, in the modified intention-to-treat population**
Change from baseline in morning pre-dose trough FEV_1 for BGF MDI versus GFF MDI (A) and BGF MDI versus BFF MDI (B), and rate of moderate or severe COPD exacerbations for BGF MDI versus GFF MDI (C) and BGF MDI versus BFF MDI (D). The banded areas represent 95% CIs. BGF=budesonide/glycopyrrolate/formoterol fumarate. MDI=metered-dose inhaler. GFF=glycopyrrolate/formoterol fumarate. BFF=budesonide/formoterol fumarate. COPD=chronic obstructive pulmonary disease.

	BGF MDI 320/18/9·6 µg (n=639)	GFF MDI 18/9·6 µg (n=625)	BFF MDI 320/9·6 µg (n=314)	Open-label BUD/FORM DPI 400/12 µg (n=318)
Treatment-emergent adverse events*				
Patients with ≥1 treatment-emergent adverse event	388 (61%)	384 (61%)	175 (56%)	183 (58%)
Patients with treatment-emergent adverse events related† to study treatment	112 (18%)	91 (15%)	48 (15%)	40 (13%)
Patients with serious treatment-emergent adverse events	55 (9%)	68 (11%)	21 (7%)	29 (9%)
Patients with serious treatment-emergent adverse events related† to study treatment	7 (1%)	12 (2%)	3 (1%)	6 (2%)
Patients with treatment-emergent adverse events that led to early discontinuation	30 (5%)	30 (5%)	11 (4%)	11 (3%)
Patients with confirmed major adverse cardiovascular event‡	2 (<1%)	3 (<1%)	2 (1%)	2 (1%)
Patients with confirmed pneumonia‡	12 (2%)	10 (2%)	6 (2%)	4 (1%)
Deaths (all causes)	6 (1%)	3 (<1%)	2 (1%)	1 (<1%)
Adverse events occurring in ≥2% of patients§				
Nasopharyngitis	49 (8%)	41 (7%)	26 (8%)	30 (9%)
Upper respiratory tract infection	65 (10%)	38 (6%)	18 (6%)	22 (7%)
Chronic obstructive pulmonary disease	17 (3%)	32 (5%)	8 (3%)	13 (4%)
Bronchitis	20 (3%)	15 (2%)	12 (4%)	9 (3%)
Muscle spasms	21 (3%)	8 (1%)	17 (5%)	6 (2%)
Dysphonia	20 (3%)	5 (1%)	15 (5%)	6 (2%)
Hypertension	13 (2%)	10 (2%)	8 (3%)	4 (1%)
Dyspnoea	9 (1%)	9 (1%)	8 (3%)	8 (3%)
Back pain	8 (1%)	12 (2%)	4 (1%)	8 (3%)
Nausea	7 (1%)	3 (<1%)	4 (1%)	7 (2%)

Data are n (%). BGF=budesonide/glycopyrrolate/formoterol fumarate. MDI=metered dose inhaler. GFF=glycopyrrolate/formoterol fumarate. BFF=budesonide/formoterol fumarate. BUD/FORM DPI=budesonide/formoterol fumarate dry powder inhaler. COPD=chronic obstructive pulmonary disease. *Numbers are number of patients. †Possibly, probably, or definitely related in the opinion of the investigator. ‡Confirmed by clinical endpoint committee. §By preferred term.

***Table 4*: Summary of adverse events (safety population)**

including the ongoing ETHOS study (NCT02465567), will help to further elucidate the use of eosinophils as a biomarker in chronic obstructive pulmonary disease.

A history of exacerbations was not an entry requirement for KRONOS, which might have influenced exacerbation results compared with other studies. However, we believe that the patient population is a strength of the trial design, since it encompassed a broader range of disease severity compared with other triple fixed-dose combination studies.[13–16] The results suggest that previous treatment with inhaled corticosteroids might be indicative of an exacerbation risk that is not accurately captured by history alone.

The results of this study challenge recommendations that inhaled corticosteroids should be considered only as a treatment option for patients with high exacerbation risk. The findings show that a much broader patient population than currently recommended could benefit from triple fixed-dose combination therapy, and might identify the potential role for triple fixed-dose combination therapy in symptomatic patients whose condition is not adequately controlled by dual therapy, irrespective of exacerbation risk.

Contributors

GTF, KFR, LMF, CW, MI, EB, SB, PDa, CR, and PDo conceived and designed the study. GTF, CW, MI, EB, and KD acquired the data. GTF, FJM, EB, SB, KD, MA, PDa analysed the data. GTF, KFR, FJM, LMF, CW, EB, SB, KD, MA, PDa, PDo, and CR interpreted the data. GTF, LMF, KFR, FJM, KD, and PDo drafted the manuscript, and GTF, KFR, FJM, LMF, CW, MI, EB, SB, PDa, KD, MA, PDo, and CR critically revised it for important intellectual content and approved it for publication. GTF, KFR, FJM, LMF, CW, MI, EB, SB, PDa, KD, MA, PDo, and CR agree to be accountable for all aspects of the work.

Declaration of interests

GTF reports grants, personal fees, and non-financial support from AstraZeneca during the conduct of the study; grants, personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, Novartis, Pearl—a member of the AstraZeneca Group, and Sunovion; grants and personal fees from Theravance; and personal fees from Circassia, GlaxoSmithKline, Innoviva, Mylan, and Verona, outside of the submitted work. KFR reports personal fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi Pharmaceuticals, InterMune, Novartis, Sanofi, and Teva; and grants from Ministry of Education and Science, Germany, outside of the submitted work. FJM reports grants from AstraZeneca during the conduct of the study; personal fees and non-financial support from American College of Chest Physicians, AstraZeneca, Boehringer Ingelheim, Chiesi, Concert, Continuing Education, Genentech, GlaxoSmithKline, Inova Fairfax Health System, Miller Communications, National Association for Continuing Education, Novartis, Pearl—a member of the AstraZeneca Group, PeerView Communications, Prime Communications, Puerto Rican Respiratory Society, Roche, Sunovion, and Theravance; non-financial support from ProterixBio; personal fees from American Thoracic Society, Columbia University, Haymarket Communications, Integritas, inThought Research, MD Magazine, Methodist Hospital Brooklyn, New York University, Unity, UpToDate, WebMD/MedScape, and Western Connecticut Health Network; and grants from National

Institutes of Health, outside of the submitted work. LMF reports research or conference funding from AstraZeneca, Boehringer Ingelheim, Chiesi, Dompè, GlaxoSmithKline, Guidotti e Malesci, Menarini, Novartis, Pearl—a member of the AstraZeneca Group, Takeda, and Zambon; consulting or lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti e Malesci, Menarini, Novartis, Pearl—a member of the AstraZeneca Group, Takeda, and Zambon. MI reports personal fees from AstraZeneca, during the conduct of the study; and personal fees from Kyorin, Nippon Boehringer Ingelheim, and Novartis Pharma, outside of the submitted work. EB, SB, PDa, KD, PDo, and CR are employed by Pearl—a member of the AstraZeneca Group, the sponsor of the study. MA is employed by AstraZeneca. CW declares no competing interests.

Acknowledgments

We thank all the patients and their families and the team of investigators, research nurses, and operations staff involved in these studies. The KRONOS study was supported by Pearl–a member of the AstraZeneca Group. Medical writing support, under the direction of the authors, was provided by Thomas Owens, PhD, of CMC CONNECT, a division of Complete Medical Communications Ltd, Manchester, UK, funded by AstraZeneca, Cambridge, UK, in accordance with Good Publication Practice (GPP3) guidelines.[30]

References

1 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD, 2018. https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf (accessed July 5, 2018).

2 Ding B, Small M, Holmgren U. A cross-sectional survey of current treatment and symptom burden of patients with COPD consulting for routine care according to GOLD 2014 classifications. *Int J Chron Obstruct Pulmon Dis* 2017; **12:** 1527–37.

3 Brusselle G, Price D, Gruffydd-Jones K, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. *Int J Chron Obstruct Pulmon Dis* 2015; **10**: 2207–17.

4 Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs* 2009; **69:** 549–65.

5 Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; **356:** 775–89.

6 Ferguson GT, Tashkin DP, Skärby T, et al. Effect of budesonide/formoterol pressurized metered-dose inhaler on exacerbations versus formoterol in chronic obstructive pulmonary disease: the 6-month, randomized RISE (Revealing the Impact of Symbicort in reducing Exacerbations in COPD) study. *Respir Med* 2017; **132:** 31–41.

7 Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 µg) or salmeterol (50 µg) on COPD exacerbations. *Respir Med* 2008; **102:** 1099–108.

8 Crim C, Calverley PM, Anderson JA, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J* 2009; **34:** 641–47.

9 Ernst P, Gonzalez AV, Brassard P, Suissa S. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. *Am J Respir Crit Care Med* 2007; **176:** 162–66.

10 Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med* 2016; **374:** 2222–34.

11 Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? *Lancet Respir Med* 2017; **5:** 747–59.

12 Brusselle G, Pavord ID, Landis S, et al. Blood eosinophil levels as a biomarker in COPD. *Respir Med* 2018; **138:** 21–31.

13 Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; **391:** 1076–84.

14 Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; **388:** 963–73.

15 Vestbo J, Papi A, Corradi M, et al. 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. *Lancet* 2017; **389:** 1919–29.

16 Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018; **378:** 1671–80.

17 Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017; **196:** 438–46.

18 Doty A, Schroeder J, Vang K, et al. Drug delivery from an innovative LAMA/LABA co-suspension delivery technology fixed-dose combination MDI: evidence of consistency, robustness, and reliability. *AAPS PharmSciTech* 2018; **19:** 837–44.

19 Taylor G, Warren S, Dwivedi S, et al. Gamma scintigraphic pulmonary deposition study of glycopyrronium/formoterol metered dose inhaler formulated using co-suspension delivery technology. *Eur J Pharm Sci* 2018; **111:** 450–57.

20 Celli BR, MacNee W, and Committee members. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; **23:** 932–46.

21 The Japanese Respiratory Society. Guidelines for the diagnosis and treatment of COPD, 4th Edition, 2013. http://www.jrs.or.jp/uploads/uploads/files/guidelines/copd_summary_e.pdf (accessed July 5, 2018).

22 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; **159:** 179–87.

23 Sasaki H, Nakamura M, Kida K. Reference values for spirogram and blood gas analysis in Japanese adults. *J Jpn Respir Soc* 2001; **39:** S1–17.

24 Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. *Chest* 2010; **137:** 138–45.

25 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; **26:** 319–38.

26 Suissa S, Drazen JM. Making sense of triple inhaled therapy for COPD. *N Engl J Med* 2018; **378:** 1723–24.

27 Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; **363:** 1128–38.

28 Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med* 2018; **6:** 117–26.

29 Ferguson GT, Reisner C, Pearle J, DePetrillo P, Maes A, Martin UJ. Cardiovascular safety profile of a fixed-dose combination of glycopyrrolate and formoterol fumarate delivered via metered dose inhaler using co-suspension delivery technology. *Pulm Pharmacol Ther* 2018; **49**: 67–74.

30 Battisti WP, Wager E, Baltzer L, et al. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med* 2015; **163:** 461–64.