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The TRIFLOW study: a randomised, cross-over study evaluating the effects of extrafine beclometasone/formoterol/glycopyrronium on gas trapping in COPD

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Abstract

Background: The effects of triple therapy on gas trapping in COPD are not fully understood. We evaluated the effects of the long acting bronchodilator components of the extrafine single inhaler triple therapy beclometasone dipropionate/formoterol/glycopyrronium (BDP/F/G) pMDI on gas trapping.

Methods: This open-label, randomised, single centre, 2-way cross-over study recruited 23 COPD patients taking inhaled corticosteroid combination treatments and with residual volume (RV) > 120% predicted at screening. Inhaled BDP was taken during run-in and washout periods. Baseline lung function (spirometry, lung volumes, oscillometry) was measured over 12 h prior to randomisation to BDP/F/G or BDP/F for 5 days followed by washout and crossover. Lung function was measured prior to dosing on day 1 and for 12 h post-dose on day 5.

Results: Co-primary endpoint analysis: BDP/F/G had a greater effect than BDP/F on FEV₁ area under the curve over 12 h (AUC₀₋₁₂) (mean difference 104 ml, p = 0.0071) and RV AUC₀₋₁₂ (mean difference - 163 ml, p = 0.0028). Oscillometry measurements showed a greater effect of BDP/F/G on the difference between resistance at 5 and 20 Hz (R5-R20) AUC₀₋₁₂, which measures small airway resistance (mean difference - 0.045 kPa/L/s, p = 0.0002). Comparison of BDP/F with the baseline measurements (BDP alone) showed that F increased FEV₁ AUC₀₋₁₂ (mean difference 227 ml) and improved RV AUC₀₋₁₂ (mean difference - 558 ml) and R5-R20 AUC₀₋₁₂ (mean difference - 0.117 kPa/L/s), all p < 0.0001.

Conclusions: In COPD patients with hyperinflation, the G and F components of extrafine BDP/F/G improved FEV₁, RV and small airway function. These long acting bronchodilators target small airway function, thereby improving gas trapping and airflow.

Trial registration The study was retrospectively registered at ClinicalTrials.gov on 15th February 2019 (No.: NCT03842904, <https://clinicaltrials.gov/ct2/show/NCT03842904>).

Keywords: COPD, Triple therapy, Small airways, Oscillometry

Background

Chronic obstructive pulmonary disease (COPD) is characterised by persistent inflammation in the small airways, associated with remodelling and ultimately small airway destruction [1, 2]. These pathological changes reduce airflow and increase gas trapping [3]. Inhaled treatment with a long acting beta-agonist (LABA) and/or a long

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acting muscarinic antagonist (LAMA) can bronchodilate the small airways to improve airflow, reduce air trapping and thereby improve dyspnoea and exercise capacity [4–7]. Inhaled corticosteroid (ICS) treatment can target small airway inflammation to improve clinical outcomes including exacerbation rates [8].

The triple combination inhaler containing beclomethasone dipropionate/formoterol/glycopyrronium (BDP/F/G) was developed as an extrafine formulation to enable efficient delivery of an ICS combined with a LABA and a LAMA to the small airways [9]. Phase 3 clinical trials have shown that this single inhaler triple therapy reduces exacerbation rates, and improves quality of life and lung function compared to double combination inhalers containing ICS/LABA or LAMA/LABA, and compared to LAMA monotherapy [10–12].

In order to further understand the effects of the bronchodilator components of extrafine BDP/F/G on the small airways and gas trapping, we conducted a clinical trial focusing on lung volumes and small airway physiology. To measure effects on gas trapping, we recruited patients with increased residual volume (RV) at study entry. The TRIFLOW study was a randomised, cross-over study evaluating the effects of the F and G components of BDP/F/G on lung volumes and small airway physiology (using oscillometry).

Methods

Participants

This study recruited male and female COPD patients from 40 to 75 years of age, with a post-bronchodilator forced expired volume in 1 s (FEV₁) of 30–80% predicted, a FEV₁/forced vital capacity (FVC) ratio of <0.70, and a RV >120% predicted. Eligible patients were current or ex-smokers with a smoking history of ≥ 10 pack years. All patients were required to be currently taking ICS as part of treatment with ICS/LABA or ICS/LABA/LAMA (as separate inhalers or a single inhaler). Patients were excluded using the following criteria: known respiratory disorder other than COPD; COPD exacerbation within 8 weeks or hospitalisation within 12 months due to COPD; or abnormal clinically relevant findings on physical examination, laboratory or electrocardiogram (ECG)

evaluations that in the investigator’s opinion made it unsafe for the patient to participate. All patients provided written informed consent using a protocol approved by the Health & Social Care Research Ethics Committee A (18/NI/0194).

Study design

The study was a randomised, open label, 2 way cross over design (ClinicalTrials.gov registration: NCT03842904). Eligible patients commenced a 10–28 day run-in period receiving BDP (Clenil Modulite) 200 µg twice daily in place of current ICS treatment. Long acting bronchodilator treatments were withdrawn, and replaced with short acting bronchodilators for use as needed. After ≥ 10 days of run-in, a baseline visit was completed, followed by two treatment periods of 5 days each, separated by a wash-out period of 7–21 days during which BDP and short acting bronchodilators were used (Fig. 1). Patients were randomised (with a 1:1 ratio), to receive triple therapy (Trimbow: BDP/F/G, 100/6/10 µg pMDI, 2 puffs, twice daily) followed by dual therapy (Fostair: BDP/F, 100/6 µg pMDI, 2 puffs, twice daily) or vice-versa. BDP/F/G or BDP/F treatment was commenced on the morning of day 1 and a final dose given on the morning of day 5 (total of 9 doses).

At the baseline visit, and on day 5 of each treatment period, impulse oscillometry (IOS), spirometry, and whole body plethysmography were performed (in that order) prior to the morning dose. IOS and spirometry were then repeated 30 min and 1, 2, 4, 6, 8, 10 and 12 h post-dose. Plethysmography was repeated at 1, 2, 4, 8 and 12 h post-dose. On day 1 of each treatment period, patients performed spirometry, IOS, and whole body plethysmography prior to the first administration of BDP/F/G or BDP/F.

Lung function

IOS was performed on the IOS Masterscreen system (Erich Jaeger, Hoechberg, Germany), to European Respiratory Society (ERS) standards [13]. Acceptable tests had a coherence index of ≥ 0.7 for both 5 and 20 Hz, and the average values reported from three tests where R5, R20 and Fres values were within 10% of their respective

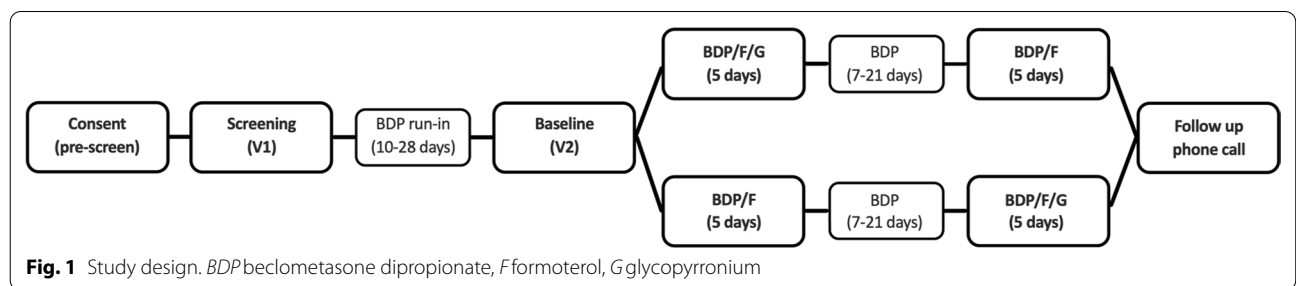


Fig. 1 Study design. BDP beclomethasone dipropionate, F formoterol, G glycopyrronium

mean values. Spirometry was performed on the NDD Easy On-PC system (NDD medical technologies, Zurich, Switzerland), to American Thoracic Society (ATS)/ERS standards [14]. Predicted values were calculated using the global lung function initiative (GLI) 2012 equations [15]. Whole body plethysmography was performed on the Vmax Encore system (CareFusion, Hoechberg, Germany), to ATS/ERS standards [16]. Thoracic gas volume (TGV) was quantified for three acceptable tests, where the associated functional residual capacity (FRC) values were within 5% of the mean value. Vital capacity (VC) manoeuvres were then performed in triplicate to ascertain residual volume (RV) and total lung capacity (TLC), where the highest two VC values agreed within 150 mls. Predicted values were calculated using the ERS 1993 equations [17]. The following measurements were collected: FEV₁; forced vital capacity (FVC); mid-expiratory flow (FEF_{25–75%}); RV; TLC; FRC; inspiratory capacity (IC); specific airway conductance (sGaw); airway resistance (Raw); peripheral respiratory resistance (R5–R20); expiratory flow limitation (ΔX_5); total respiratory resistance (R5); reactance (X5); resonance frequency (*Fres*); reactance area (AX);

Statistical methods

The co-primary objectives were to compare the effects of BDP/F/G versus BDP/F on change in FEV₁ and RV on day 5 compared to day 1 pre-dose, by analysing area under the curve over 12 h (AUC_{0–12}). The secondary objectives were to compare the effect of BDP/F/G versus BDP/F on change in all other lung function measurements for AUC_{0–12} and peak, while treatment differences for FEV₁ and RV peak and trough (12 h post-dose) were also determined. Additionally, the differences between AUC_{0–12} for BDP/F/G and BDP/F at day 5 were compared to the AUC_{0–12} for BDP alone at baseline visit (relative to baseline visit pre-dose value). A sample size of 20 patients was required to detect a mean difference > 0.23 L (FEV₁ AUC_{0–12}) between treatments. This corresponds to a 2-sided t-test with 80% power conducted at the 5% significance level, assuming a standard deviation of 0.17 L for the paired differences between treatment groups. The primary analysis was conducted using a mixed model. The model included fixed effects for treatment and period and a random effect for patient within treatment sequence. For the primary endpoint, the AUC_{0–12} from the baseline visit was included as a covariate. The AUC_{0–12} (normalised by time), peak and trough (defined as the 12 h measurement post-dose on day 5) values were analysed as change from within-period day 1 pre-dose measurement. All were analysed without any procedures to account for multiple comparisons.

Results

Participants

Sixty-six patients were screened, with 23 randomised, as shown in Fig. 2. One patient was withdrawn due to lack of treatment compliance, leaving 22 patients analysed. Patient characteristics are shown in Table 1. The mean FEV₁% predicted (post-bronchodilator) was 49%, and RV was 152% predicted.

Primary endpoints

Both BDP/F/G and BDP/F caused improvements in FEV₁ and RV on day 5 compared to day 1 pre-dose (Figs. 3, 4). The FEV₁ AUC_{0–12} change with BDP/F/G was greater compared to BDP/F; mean difference 104 mls; 95% CI 37, 171 mls; $p=0.0071$. RV AUC_{0–12} change was greater with BDP/F/G compared to BDP/F; mean difference –163 mls; 95% CI –263, –64 mls; $p=0.0028$.

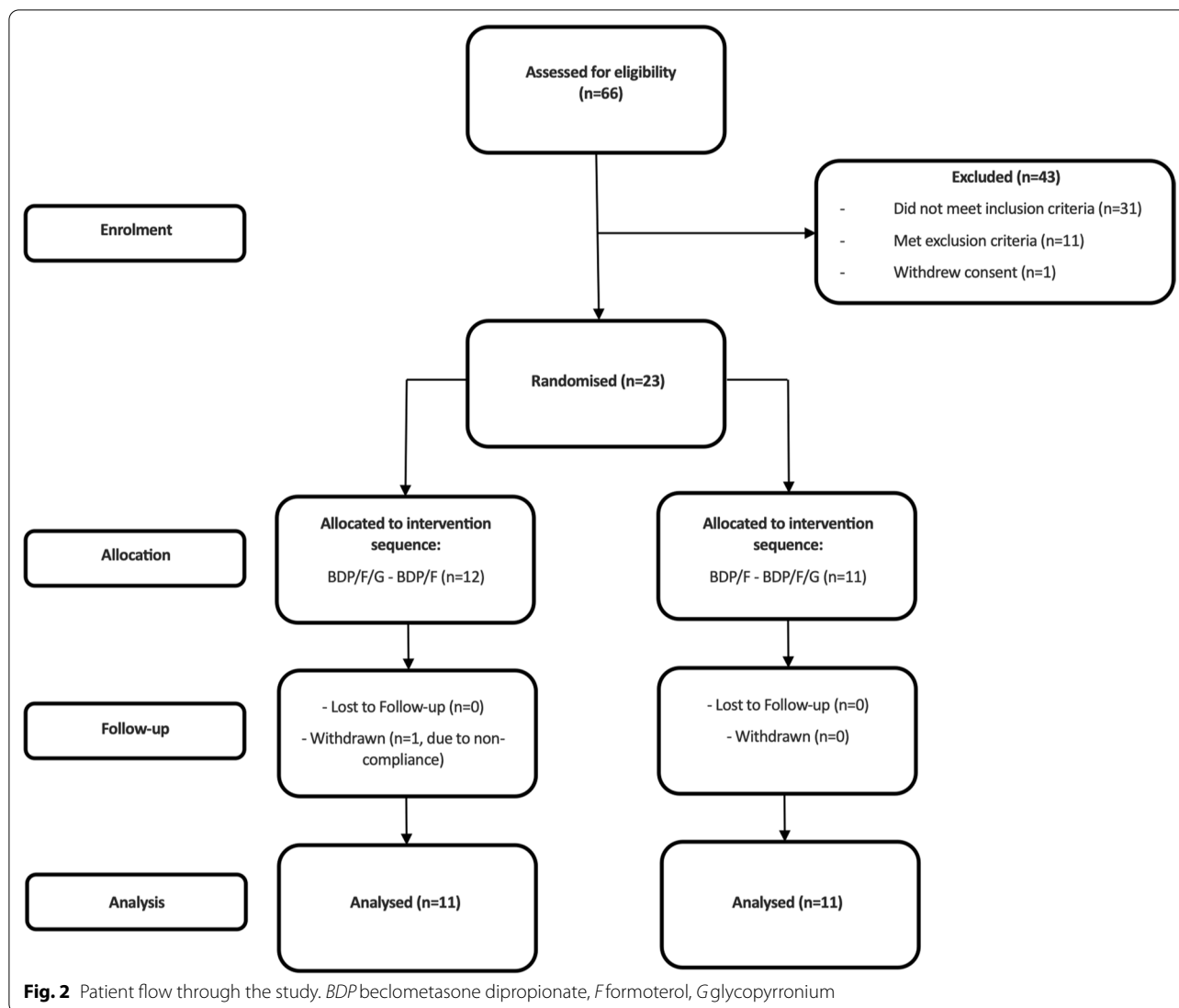
Secondary endpoints

BDP/F/G versus BDP/F

BDP/F/G caused larger improvements than BDP/F for most of the lung function AUC_{0–12} parameters (Table 2). Using IOS, the change in small airway resistance, measured by R5–R20 AUC_{0–12}, was greater with BDP/F/G compared to BDP/F (mean difference –0.045 kPa/L/s; $p=0.0002$). There were also significantly greater treatment differences in favour of BDP/F/G for *Fres*, AX and X5, while ΔX_5 failed to reach statistical significance ($p=0.06$). IC, TLC and FRC AUC_{0–12} measurements did not show statistically significant differences between treatments, although TLC and FRC showed numerical changes in favour of BDP/F/G. sGaw AUC_{0–12} change was greater with BDP/F/G ($p=0.01$).

Change in peak FEV₁ was greater for BDP/F/G versus BDP/F (mean difference 120 mls; $p=0.0016$), while for peak RV the difference was not significant (mean difference –79 mls; $p=0.11$). Other peak lung function results are shown in the Additional File 1; R5–R20 peak change with BDP/F/G was greater compared to BDP/F (mean difference –0.036 kPa/L/s; $p=0.0022$), while there were also significant differences for *Fres*, AX and X5, but not ΔX_5 . Lung volume peak measurements did not show statistically significant differences between treatments, while sGaw changes were in favour of BDP/F/G.

Trough RV improvement was greater for BDP/F/G compared with BDP/F (–179 mls; $p=0.0097$), while the treatment difference for trough FEV₁ (65 mls; $p=0.08$) did not reach statistical significance (see Additional File 1).



BDP/F/G and BDP/F change from baseline

The baseline AUC_{0-12} measurements were performed while patients were taking BDP alone. The differences between baseline measurements and BDP/F/G or BDP/F treatments (day 5) are shown in Table 3. The comparisons of BDP/F with the baseline measurements showed differences in $FEV_1 AUC_{0-12}$ (mean difference 227 mls), $RV AUC_{0-12}$ (mean difference - 558 mls) and $R5-R20 AUC_{0-12}$ (mean difference - 0.117 kPa/L/s), all $p < 0.0001$. The comparisons of BDP/F/G with the baseline measurements showed differences in $FEV_1 AUC_{0-12}$ (mean difference 320 mls), $RV AUC_{0-12}$ (mean difference - 678 mls) and $R5-R20 AUC_{0-12}$ (mean difference - 0.165 kPa/L/s), all $p < 0.0001$.

Safety

There were no serious AEs (adverse events) leading to withdrawal from the study or discontinuation of treatment. Further safety information is described in the Additional File 1.

Discussion

This study focused on COPD patients with evidence of gas trapping, measured by RV. For the primary endpoint analysis (AUC_{0-12}), BDP/F/G had greater effects compared to BDP/F on FEV_1 and RV (mean treatment differences; 104 mls and - 163 mls respectively). This demonstrates that the G component of extrafine BDP/F/G reduced gas trapping in COPD patients.

Table 1 Patient characteristics

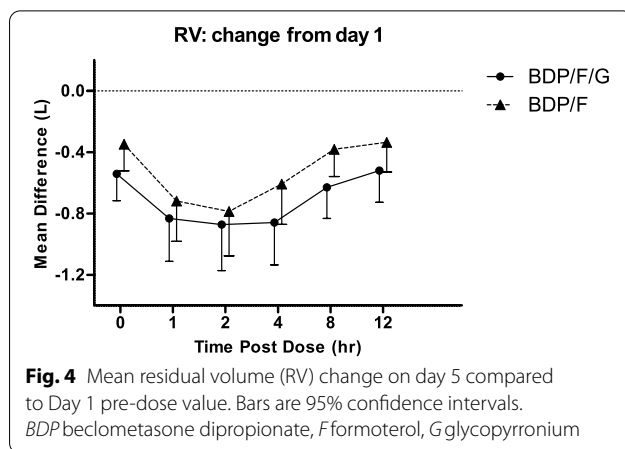
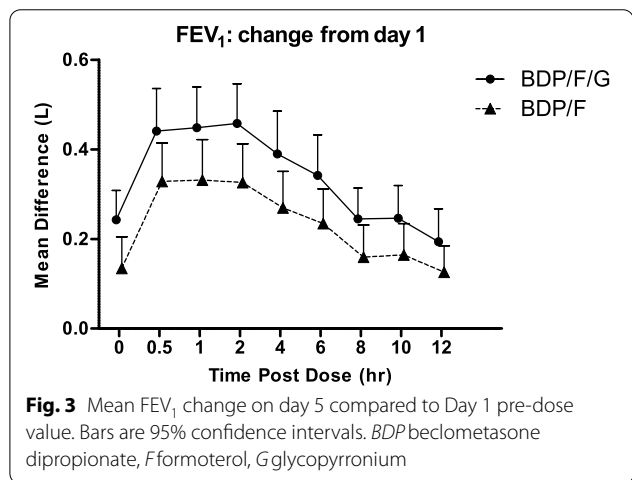
Characteristic	n=22 COPD
Gender, male/female	9/13
Age, years	64 (9)
Current/ex-smokers	9/13
Pack years	46 (25)
Prescribed dual ^a /triple ^b inhaler therapy (n/n)	2/20
Prescribed supplemental oxygen (n)	0
Exacerbation history (n, zero/one/two exacerbation(s) in the last year)	13/8/1
CAT score	19.6 (8.4)
mMRC Dyspnoea Scale (n, grade 0/1/2/3/4)	3/10/4/4/1
FEV1 reversibility (%)	19 (13)
FEV ₁ (L) ^c	1.27 (0.34)
FEV ₁ (%) ^c	49 (9)
FVC (%) ^c	90 (10)
FEV ₁ /FVC ratio (%) ^c	43 (11)
FEF _{25-75%} (%) ^c	18 (7)
sGaw (L/s/kPa/L)	0.469 (0.195)
Raw (kPa/L/s)	0.512 (0.140)
RV (L)	3.16 (0.91)
RV (% predicted)	152 (35)
IC (% predicted)	80 (15)
FRC (% predicted)	139 (27)
TLC (% predicted)	114 (13)
R5 (kPa/L/s) ^c	0.570 (0.172)
R20 (kPa/L/s) ^c	0.395 (0.103)
R5–R20 (kPa/L/s) ^c	0.176 (0.118)
X5 (kPa/L/s) ^c	−0.289 (0.150)
ΔX5 (kPa/L/s) ^c	0.215 (0.194)
F _{res} (1/s) ^c	23.40 (5.07)
AX (kPa/L) ^c	2.427 (1.739)

Data is mean (SD) where appropriate

^a ICS/LABA

^b ICS/LABA/LAMA

^c Post-bronchodilator



Furthermore, the greater improvement in R5–R20 AUC_{0–12} for BDP/F/G compared to BDP/F demonstrates that G also reduced small airway resistance. Overall, these results indicate that G had a beneficial effect on small airway physiology leading to improvements in gas trapping.

A secondary analysis, comparing BDP/F versus BDP/F/G, showed that F improved FEV₁, RV and IOS measurements including R5–R20 AUC_{0–12}. This demonstrates benefits of F on small airway physiology which are associated with decreases in gas trapping. The effect sizes observed showed that F treatment for 5 days caused 558 mls improvement in RV AUC_{0–12} and a 227 mls improvement in FEV₁ AUC_{0–12}. This comparison to baseline analysis also showed the extra benefit of the addition of G for 5 days, as BDP/F/G versus BDP treatment differences were 678 mls for RV AUC_{0–12} and 320 mls for FEV₁ AUC_{0–12}. Overall, these results indicate a greater effect of the addition of the first bronchodilator (BDP/F versus BDP) than the addition of the second bronchodilator (BDP/F/G versus BDP/F). This smaller effect of the second bronchodilator has been observed in many previous studies [5, 18, 19], and may be due to reaching near to the maximum improvement that may be achieved with these bronchodilator drug classes.

The primary and secondary outcomes, describing improvements in different components of lung mechanics, provide insights into the physiological effects of the long acting bronchodilators within BDP/F/G. Gas trapping is associated with an increased burden of symptoms in COPD [20, 21], and pharmacological interventions to reduce gas trapping can improve exercise performance [22, 23]. The primary endpoint analysis showed that using BDP/F/G can reduce gas trapping to a greater degree compared to BDP/F. This physiological effect may be extremely useful in clinical practice, in order to optimise the reduction of gas trapping and hence associated symptoms. The short treatment duration, and

Table 2 AUC₀₋₁₂ change from day 1

Parameter	BDP/F/G	BDP/F	BDP/F/G – BDP/F	
			Mean difference	p value
FVC (mls)	545 (414, 676)	339 (208, 470)	206 (54, 359)	0.0116
FEF25–75% (L/s)	0.110 (0.077, 0.143)	0.083 (0.050, 0.117)	0.026 (0.001, 0.051)	0.0395
sGaw (L/s/kPa/L)	0.311 (0.242, 0.381)	0.213 (0.143, 0.282)	0.099 (0.031, 0.167)	0.0101
Raw (kPa/L/s)	– 0.279 (– 0.323, – 0.236)	– 0.222 (– 0.266, – 0.179)	– 0.057 (– 0.077, – 0.037)	< 0.0001
IC (mls)	257 (135, 379)	260 (138, 382)	3 (– 146, 139)	0.96
FRC (mls)	– 490 (– 632, – 348)	– 387 (– 529, – 245)	– 103 (– 217, 11)	0.07
TLC (mls)	– 218 (– 319, – 117)	– 137 (– 238, – 36)	– 81 (– 196, 34)	0.16
R5–R20 (kPa/L/s)	– 0.163 (– 0.195, – 0.131)	– 0.118 (– 0.150, – 0.086)	– 0.045 (– 0.065, – 0.025)	0.0002
X5 (kPa/L/s)	0.203 (0.155, 0.252)	0.156 (0.108, 0.205)	0.047 (0.025, 0.069)	0.0003
ΔX5 (kPa/L/s)	– 0.137 (– 0.219, – 0.056)	– 0.095 (– 0.177, – 0.014)	– 0.042 (– 0.086, 0.002)	0.06
Fres (1/s)	– 7.201 (– 9.091, – 5.310)	– 5.005 (– 6.896, – 3.115)	– 2.195 (– 3.451, – 0.940)	0.0016
AX (kPa/L)	– 2.911 (– 3.467, – 2.356)	– 2.205 (– 2.761, – 1.650)	– 0.706 (– 1.047, – 0.365)	0.0004

Data = mean (95% CI) change in day 5 AUC₀₋₁₂ from day 1. Treatment difference = BDP/F/G (AUC₀₋₁₂ change at day 5 from day 1) – BDP/F (AUC₀₋₁₂ change at day 5 from day 1)

limited sample size of the current study means that we could not properly assess changes in symptoms or exercise capacity. Nevertheless, the TRILOGY phase 3 study, conducted over one year, provided evidence of greater improvements at many of the time-points for symptoms and quality of life for treatment with BDP/F/G compared to BDP/F [10].

The peak lung function changes on day 5 (for the comparison of BDP/F/G versus BDP/F) followed the same pattern of results as AUC₀₋₁₂, except RV showed a lower numerical difference (65 mls) that was not statistically significant (p=0.08). This might be due to the reduction in gas trapping by the first bronchodilator (F) being relatively large at peak, leaving little room for improvement by the addition of the second bronchodilator (G). For both the AUC₀₋₁₂ and peak measurements, RV had the greatest sensitivity out of all the lung volume measurements to measure differences between BDP/F/G versus BDP/F; this is likely related to the enrichment of the study population for individuals with RV > 120% predicted at screening.

Using IOS allowed measurements of airway resistance and reactance to be collected. R5–R20 is a well

accepted measurement of small airway resistance, and previous papers have shown that bronchodilators improve R5–R20 in COPD patients [4, 24]. In this study, the concurrent improvements in R5–R20 and RV imply that bronchodilator related improvements in small airway function enabled reduced gas trapping. IOS reactance measurements (X5, Fres, AX) reflect lung compliance and elasticity, and here we observed consistent improvements in these parameters for the G and F components of extrafine triple therapy.

Small airway closure can prevent low frequency oscillometric signals from reaching the distal lung [7]. Small airway closure can therefore operate as regional “choke points” during expiration but not inspiration, which has been called expiratory flow limitation (EFL). This can cause marked differences in reactance measurements during tidal breathing, and is measured by ΔX5, which is an oscillometry measurement of EFL. It has been reported that EFL measurements are associated with greater airflow limitation and gas trapping, greater symptoms, more exacerbations and increased mortality [21, 25, 26]. The comparisons of BDP/F/G or BDP/F versus BDP (baseline) both showed large improvements in ΔX5, and consequently the BDP/F/G versus BDP/F

Table 3 AUC₀₋₁₂ change from baseline

Parameter	BDP/F/G		BDP/F	
	AUC ₀₋₁₂ mean change	p value	AUC ₀₋₁₂ mean change	p value
FEV ₁ (mls)	320 (257, 384)	< 0.0001	227 (163, 290)	< 0.0001
FVC (mls)	524 (420, 627)	< 0.0001	351 (248, 455)	< 0.0001
FEF _{25-75%} (L/sec)	0.112 (0.080, 0.144)	< 0.0001	0.082 (0.050, 0.113)	< 0.0001
sGaw (L/s/kPa/L)	0.310 (0.259, 0.362)	< 0.0001	0.224 (0.172, 0.275)	< 0.0001
Raw (kPa/L/s)	- 0.298 (- 0.369, - 0.226)	< 0.0001	- 0.242 (- 0.313, - 0.170)	< 0.0001
RV (mls)	- 678 (- 847, - 509)	< 0.0001	- 558 (- 727, - 389)	< 0.0001
IC (mls)	328 (219, 438)	< 0.0001	289 (180, 399)	< 0.0001
FRC (mls)	- 468 (- 612, - 323)	< 0.0001	- 426 (- 571, - 282)	< 0.0001
TLC (mls)	- 136 (- 243, - 28)	0.0144	- 132 (- 239, - 24)	0.0174
R5-R20 (kPa/L/s)	- 0.165 (- 0.198, - 0.132)	< 0.0001	- 0.117 (- 0.150, - 0.084)	< 0.0001
X5 (kPa/L/s)	0.208 (0.169, 0.248)	< 0.0001	0.159 (0.120, 0.198)	< 0.0001
ΔX5 (kPa/L/s)	- 0.207 (- 0.262, - 0.152)	< 0.0001	- 0.140 (- 0.195, - 0.085)	< 0.0001
F _{res} (1/s)	- 8.235 (- 10.108, - 6.363)	< 0.0001	- 5.600 (- 7.472, - 3.727)	< 0.0001
AX (kPa/L)	- 2.991 (- 3.614, - 2.368)	< 0.0001	- 2.228 (- 2.851, - 1.604)	< 0.0001

Data = mean (95% CI) change in day 5 AUC₀₋₁₂ from pre-randomisation baseline visit AUC₀₋₁₂. All AUC₀₋₁₂ values (day 5 and baseline) are relative to the pre-dose value at baseline

comparison yielded a small treatment difference that was not statistically significant.

The design of the study, using the same inhaler device delivering extrafine formulations for all treatments, allowed the contributions of F and G on small airway function and gas trapping to be determined. We did not study a non-extrafine formulation with less peripheral lung deposition compared to BDP/F/G; this would be an interesting future study to compare changes in small airway function and gas trapping between treatments. While this was an open study, the objective nature of the endpoints (lung function measurements) restricted any bias that could be introduced by lack of treatment blinding. The main advantage of blinding is for patient reported outcomes which are more subjective. A potential limitation of the study was the relatively small sample size. However, the sample size was very similar to other crossover design studies investigating long acting bronchodilator effects on lung function [27, 28], and the enrichment for individuals with gas trapping (RV > 120% predicted) increased the homogeneity of the population

thereby decreasing the potential variability in lung function data.

The mean CAT score at screening was 19.6, suggesting this was a very symptomatic population. However, 13 out of the 22 patients had mMRC scores < 2 at study entry. The majority of patients (20 out of 22) were already receiving triple therapy in real life at study entry, which likely reduced the burden of dyspnoea. The differences between CAT and mMRC scores likely reflect the broader range of disease components assessed by the former, as previously reported [29]. All patients were using ICS at study entry; these drugs should be used in patients with a history of exacerbations [30], but often are inappropriately given to patients who do not have a history of exacerbations. While some of our study population had no exacerbations in the last year, this may reflect a positive treatment response to ICS initiation [31].

Late phase studies with large sample sizes often require statistical approaches to account for multiple testing. This smaller study was more exploratory in nature, providing information on the usefulness of a broad range of lung

function tests. This information can be used to select the most appropriate tests to be used in future studies comparing inhaled treatments. Multiple testing correction is often not performed in smaller clinical trials with a more exploratory nature [32]. Nevertheless, many of the p values reported were highly significant, arguing against the presence of false positives due to multiple testing.

In summary, this study focused on COPD patients with gas trapping, and demonstrated that the G and F components of extrafine BDP/F/G improved FEV₁, RV and small airway function. It can be concluded that these long acting bronchodilators target small airway function, thereby improving gas trapping and airflow.

Supplementary Information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12931-020-01589-5>.

Additional file 1. Triflow Supplement.

Abbreviations

BDP: Beclomethasone dipropionate; F: Formoterol; G: Glycopyrronium; COPD: Chronic obstructive pulmonary disease; ICS: Inhaled corticosteroid; LABA: Long acting beta-agonist; LAMA: Long acting muscarinic antagonist; ECG: Electrocardiogram; pMDI: Pressurised metered dose inhaler; IOS: Impulse oscillometry; CAT: COPD assessment test; mMRC: Modified medical research council; FEV₁: Forced expired volume in 1 s; AUC₀₋₁₂: Area under the curve over 12 h; FVC: Forced vital capacity; FEF_{25-75%}: Forced expiratory flow between 25 and 75% of FVC; sGaw: Specific airway conductance; Raw: Airway resistance; RV: Residual volume; IC: Inspiratory capacity; FRC: Functional residual capacity; TLC: Total lung capacity; R5: Total respiratory resistance; R20: Central respiratory resistance; R5–R20: Peripheral respiratory resistance; X5: Respiratory reactance; ΔX5: Expiratory flow limitation; F_{res}: Resonance frequency; AX: Reactance area; CI: Confidence interval; AEs: Adverse events; EFL: Expiratory flow limitation.

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Authors' contributions

DS and NK were major contributors to study design. All authors contributed to the collection and analysis of the patient data. DS interpreted the patient data. JD, CP and DS were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All patients provided written informed consent using a protocol approved by the Health & Social Care Research Ethics Committee A (18/NI/01194).

Consent for publication

Not applicable.

Competing interests

JD; The author declares that they have no competing interests. CP; The author declares that they have no competing interests. NK; The author declares that they have no competing interests. DS has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards

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