

A randomized trial of once-daily fluticasone furoate/vilanterol or vilanterol versus placebo to determine effects on arterial stiffness in COPD

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Introduction: Chronic obstructive pulmonary disease (COPD) is associated with increased cardiovascular morbidity and mortality. Elevated arterial stiffness, measured by aortic pulse wave velocity (aPWV), is a cardiovascular risk surrogate and is potentially modifiable by inhaled corticosteroid/long-acting beta₂-agonist combinations in patients with COPD.

Materials and methods: The effects of once-daily inhaled fluticasone furoate/vilanterol (FF/VI) 100/25 µg, VI 25 µg, versus placebo on arterial stiffness in patients with COPD and baseline aPWV ≥11.0 m/s were investigated in a 24-week, multicenter, double-blind, randomized, stratified (by COPD exacerbation history), parallel-group, placebo-controlled trial. Eligible patients were ≥40 years old, with ≥10 pack-year smoking history, forced expiratory volume in 1 s (FEV₁)/forced vital capacity ≤0.70, and post-bronchodilator FEV₁ ≤70% of predicted. Patients with a major cardiovascular event in the previous 6 months/current severe heart failure/uncontrolled hypertension were excluded. Primary endpoint is change from baseline in aPWV after 24 weeks of treatment. Safety analyses included adverse events (AEs).

Results: The intent-to-treat population included 430 patients: FF/VI (n=135), VI (n=154), and placebo (n=141). Patients were predominantly male (79%) and Asian or White (each 48%), with a mean age of 68.5 years (standard deviation [SD] =7.9), percentage predicted post-bronchodilator FEV₁ 50.1% (SD =13.3), and aPWV 13.26 m/s (SD =2.22) at screening. At 24 weeks, mean (standard error [SE]) changes from baseline in aPWV were -1.75 m/s (SE=0.26, FF/VI), -1.95 m/s (SE=0.24, VI), and -1.97 m/s (SE=0.28, placebo). AEs occurred in 57% (FF/VI), 51% (VI), and 41% (placebo) of patients.

Conclusion: No differences were observed in aPWV-adjusted mean change from baseline for FF/VI 100/25 µg, compared with placebo.

Keywords: aortic pulse wave velocity, chronic obstructive pulmonary disease, fluticasone furoate, vilanterol

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with accelerated atherosclerosis, and the majority of mild-to-moderate COPD-related mortality is due to cardiovascular disease (CVD).^{1,2} Airflow obstruction is independently associated with CVD.³⁻⁷ Structural and functional elements of COPD (emphysema/airflow obstruction) are associated with increased arterial stiffness,⁸⁻¹¹ which is associated with atherosclerosis and CVD.¹²⁻¹⁴

Although the mechanisms underlying these associations are not well defined, pulmonary and systemic inflammation are potential contributors.^{1,15,16} Systemic endothelial dysfunction and vascular re-modeling (including proliferation of smooth

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muscle cells, elastin degradation, and collagen deposition, which may be followed by calcification and ultimately result in arterial stiffening),¹⁸ are also evident at all severities of COPD and further contribute to arterial stiffening.¹⁹ Additional impacts of COPD, such as reduced ability to exercise, may also contribute to arterial stiffening by altering vascular hemodynamics.¹⁶

As a potentially modifiable element, in addition to being a strong risk factor for CVD, arterial stiffness may serve as an intermediate endpoint for interventions aimed at reducing cardiovascular risk. In inflammatory conditions, such as polymyalgia rheumatica and peripheral arterial disease, improvements in aPWV have been detected following treatment with corticosteroids²⁰ (targeting inflammation)¹⁶ or long-acting beta₂-agonists²¹ (long-acting beta₂ agonist [LABA], inducing endothelial nitric oxide synthase-mediated vasodilation).²²

In recent years, few studies have attempted modulation of arterial stiffness in COPD, using exercise therapy, LABA, or inhaled corticosteroids (ICS).^{22–25} Given the associations between lung function, inflammation, and arterial stiffness noted above, medications modulating pulmonary function/inflammation might also be effective in reducing arterial stiffness for patients with COPD. In a 12-week study, fluticasone propionate/salmeterol had no effect on aortic pulse wave velocity (aPWV [carotid femoral PWV]), the gold standard measure of arterial stiffness, relative to placebo.²⁵ However, post hoc analysis suggested that individuals with aPWV >10.9 m/s had significantly reduced arterial stiffness with the treatment.²⁵ Another 12-week study comparing once-daily fluticasone furoate (FF)/vilanterol (VI) with tiotropium in patients with aPWV ≥11 m/s reported aPWV reduction from baseline in both the arms, but no significant difference between the arms.²⁶ No placebo comparator was included, limiting the conclusions.²⁶ The length of treatment may also be important to see significant effects. For example, although LABAs may lower aPWV initially, the additional anti-inflammatory benefit of ICS therapy in a LABA/ICS combination may only be seen after longer-term treatment. This study hypothesized that once-daily FF/VI 100/25 µg would reduce aPWV after 24-weeks of treatment, compared with placebo. This is the first respiratory medication-focused, placebo-controlled, interventional trial examining aPWV modulation as a primary outcome of interest.

Materials and methods

Study design

This multicenter, randomized, placebo-controlled, double-blind, parallel-group study (March 2011 to November 2014;

61 centers; Norway/Germany/the Republic of Korea/the Philippines/Thailand/USA; GSK HZC113108; [ClinicalTrials.gov](#) NCT01336608) was approved by applicable institutional review boards/independent ethics committees and conducted in accordance with the International Conference on Harmonisation: Guidance for Good Clinical Practice (GCP)²⁷ and the Declaration of Helsinki.²⁸ Details of the ethical review boards for this study are provided in the [Supplementary Materials](#). Patients provided prior written informed consent.

Patients aged ≥40 years with a history of COPD, current/prior smoking history (≥10 pack-years), a post-albuterol (salbutamol) forced expiratory volume in 1 s (FEV₁) ≤70% of the predicted normal value, a FEV₁/forced vital capacity ratio ≤0.70, and aPWV ≥11.0 m/s, measured by SphygmoCor CPVH according to the manufacturer's instructions (AtCor Medical Inc., Itasca, IL, USA)²⁵ were eligible. Patients were excluded if: the underlying cause of their COPD was α1-antitrypsin deficiency; they had other respiratory disorders (including active tuberculosis or lung cancer); they had current severe heart failure; they had had a recent cardiovascular event (such as acute coronary syndrome or stroke, within the previous 6 months); they had clinically significant uncontrolled hypertension; they had an abnormal/clinically significant 12-lead electrocardiogram finding; or they had started, discontinued, and/or were receiving medications (such as anti-hypertensives, lipid-lowering agents, hypoglycemic agents or nitrates) without reaching a stable dose in the last 3 months and/or were not anticipated to remain at a stable dose throughout the study period.

After a 2-week, single-blind, placebo run-in period, during which COPD stability and protocol compliance were evaluated, eligible patients were randomized (by center, 1:1:1; telephone-based Registration and Medication Ordering System; stratified according to COPD exacerbation in the previous 3 years [yes/no]) to receive FF/VI 100/25 µg, VI 25 µg, or placebo, administered once daily for 24 weeks via the ELLIPTA[®] inhaler (GSK, Brentford, UK). Participants' usual COPD medications were discontinued from 24 h to 12 weeks prior to the first clinic visit (screening) and thereafter at any time during the study, with the exception of ipratropium bromide (for patients receiving a stable dose throughout the study) and the study-provided albuterol (salbutamol, used as rescue medication), which were withheld for 4 h prior to study visits. Full details are given in [Supplementary Table 1](#).

Further clinic visits were scheduled at treatment weeks 4, 12, 18, and 24 with a follow-up phone call 1 week after the final visit. The treatments in this study were double-blind.

Neither the investigator (nor study staff) nor the patient knew which treatment the patient was receiving. Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product was essential for the clinical management or welfare of the patient. The sponsor's (GSK) Global Clinical Safety and Pharmacovigilance staff could unblind treatment codes in the event of a serious adverse event (SAE).

The following non-COPD medications were allowed if the patient had been on a stable dose for at least 3 months prior to screening and was anticipated to remain on a stable dose throughout the 6-month treatment period: anti-hypertensives (angiotensin-converting enzyme inhibitors, diuretics, angiotensin2-receptor antagonists, beta-blockers, calcium-channel blockers, alpha-blockers, central alpha-agonists), lipid-lowering agents (eg statins, ezetimibes), hypoglycemic agents for the treatment of diabetes (sulfonylurea, glitizone, metformin, etc), and nitrates. In addition, the following non-COPD medications were permitted: cardioselective beta-blockers (stable dose) and ophthalmic beta-blockers; antihistamines and nasal decongestants; over-the-counter cough suppressants; intranasal cromolyns or nedocromil; intranasal corticosteroids (provided the patient was on a stable daily dose for at least 4 weeks prior to clinic visit 1 and remained on this dose throughout the study); topical ($\leq 1\%$ hydrocortisone in strength) or ophthalmic corticosteroids; antibiotics that were not strong inhibitors of cytochrome P450 3A4 for short-term treatment (≤ 14 days) of acute non-respiratory tract infections (eg erythromycin); influenza and/or pneumonia vaccines; tricyclic antidepressants and monamine oxidase inhibitors; diuretics; smoking cessation medications; all medications for other disorders as long as the dose remains constant wherever possible and their use would not be expected to affect lung function or aPWV.

Two amendments were made to the original protocol (dated December 15, 2010), which applied to all investigational sites. The first revised the inclusion criteria for baseline aortic pulse wave velocity (aPWV) from ≥ 12 m/s to ≥ 11 m/s due to low enrollment (effective from August 19, 2011). The second revised the sample size re-estimation for reasons discussed below (effective from February 01, 2013).²⁹

Efficacy and safety assessments

The primary endpoint was change from baseline in aPWV at 24 weeks (day 168) for the comparison of FF/VI 100/25 μ g versus placebo. aPWV was measured (as described)²⁶ at screening and on weeks 4, 12, 18, and 24.

Secondary endpoints included morning trough (pre-bronchodilator/pre-dose) FEV₁ (measured at every clinic visit) and the mean number of albuterol used during a 24-h period throughout treatment. Other endpoints included inspiratory capacity (IC), biomarkers (high sensitivity C-reactive protein [hsCRP], fibrinogen, interleukin 6 [IL-6], pulmonary and activation-regulated chemokine [PARC]), and quality of life (by the St George's Respiratory Questionnaire for COPD patients [SGRQ]). Exploratory endpoints were peripheral/central pulse pressures (PP), aortic augmentation index (AIx),^{26,30} and COPD Assessment Test (CAT).

Safety assessments were performed at each clinic visit, including incidence of adverse events (AEs), pneumonia, and oropharyngeal examination. Vital signs (pulse rate and blood pressure [BP]) were measured at each visit. COPD exacerbations were not recorded as AEs, but were recorded as SAEs if they met the definition of a SAE. A SAE was any AE that resulted in any of the following outcomes: death; immediate risk of death, in the view of the investigator; hospitalization (or prolonged an existing hospitalization); disability or incapacity; congenital anomaly in the patient's offspring; or jeopardized the patient, according to the medical judgment of the investigator.

Statistical methods

Analyses for study population, efficacy, health outcomes, and biomarker data used the intent-to-treat (ITT) population (all the patients randomized who received at least one dose of medication were randomized, excluding 14 patients from one center with GCP issues not associated with the current trial). The safety population was the ITT population plus the 14 patients noted. Further details are provided in the [Supplementary materials](#).

Sample size calculations were based on an estimate of the standard deviation (SD) of mean change from baseline in aPWV of 2.6 m/s.²⁶ Accordingly, 143 patients per arm were required to provide 80% power for the detection of a 1 m/s treatment difference on day 168, at a significance level of 0.05, based on a two-sample, two-sided *t*-test, allowing for a 25% withdrawal rate. More information is provided in the [Supplementary materials](#).

Change from baseline aPWV recorded on days 28, 84, 126, and 168 was analyzed using mixed models repeated measures with terms for visit, treatment, age, gender, smoking history, COPD exacerbation history, geographic region, baseline aPWV, and interaction terms of baseline aPWV by clinic visit and treatment by clinic visit. From this model, treatment effects and differences were obtained for each

visit. Change from baseline trough FEV₁ was analyzed using a similar model, with the covariate of baseline FEV₁ instead of baseline aPWV. The mean number of occasions of albuterol use for the entire 24-week treatment period was analyzed using analysis of covariance with covariates of baseline rescue medication use, geographic region, and COPD exacerbation history.

Multiplicity was controlled using a closed testing procedure. For the primary treatment comparison, secondary endpoints were nested under the primary endpoint in the following order: trough FEV₁, followed by the mean number of occasions of albuterol use, to make inferences for predefined secondary endpoints while controlling for the overall Type I error. In the absence of significance for the primary endpoint, then the tests for the secondary and other efficacy endpoints must be interpreted as descriptive only. The primary treatment comparison was fluticasone furoate/vilanterol 100/25 µg versus placebo. All other treatment comparisons were considered as supportive.

AEs were coded and grouped by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA; Version 17.1). AEs of special interest were defined a priori based on known pharmacologic effects of LABAs and/or ICSs.

Post hoc analyses

Post hoc logistic regression analyses compared the proportion of responders (patients with an aPWV reduction from baseline of ≥ 1 m/s on day 168) between arms, where 1) withdrawn patients were classified as nonresponders and 2) withdrawn patients (prior to day 168) were classified as missing. An investigation comparing change from baseline in aPWV with the baseline aPWV was also carried out post hoc.

Results

Patient disposition

The ITT population comprised 430 patients, of whom 332 (77%) completed the study (Figure 1). The most frequent reason for early withdrawal was lack of efficacy. Baseline characteristics and demographics were generally comparable between arms (Table 1). Most patients were Asian or White and in Global Initiative for Chronic Obstructive Lung Disease (GOLD) group B or D, with moderate or severe airflow limitation.¹⁹ Hypertension (65%) and hypercholesterolemia (41%) were the most common comorbid cardiovascular history/risk factors.

Efficacy

Numerical reductions from baseline in aPWV were seen in all treatment groups at all time points (Figure 2), but the comparison of FF/VI versus placebo on day 168 (Table 2) was not statistically significant. All secondary and other endpoints were therefore regarded as descriptive only.

Exploratory analyses revealed no significant interactions of treatment with each of geographic region, age, gender, or smoking status on aPWV on day 168. There were no significant correlations between change from baseline in aPWV and central and peripheral systolic and diastolic BP, central and peripheral PP, central and peripheral mean arterial pressure (MAP), or trough FEV₁. A significant correlation on day 168 was observed between aPWV and IC in the VI 25 µg arm ($P=0.033$); however, this was not observed with either the FF/VI 100/25 µg or placebo arm. No relationship was seen between aPWV and inflammatory biomarkers (hsCRP, fibrinogen, IL-6, PARC) (Figure S1).

Changes from baseline in AIX were minimal and similar in magnitude across the treatment groups (Table 3). There were no differences between groups in changes in central and peripheral PP. FF/VI 100/25 µg and VI 25 µg improved trough FEV₁ from baseline, versus placebo (Figure 3A), and a numerical increase in IC was also observed at all time points with FF/VI 100/25 µg versus placebo (Figure 3B).

The mean number of albuterol uses in a 24-h period throughout treatment was reduced by FF/VI 100/25 µg and VI 25 µg versus placebo (Figure 3C). On day 168, SGRQ total score was reduced by 4.08 units with FF/VI 100/25 µg, versus placebo (Figure 3D). The adjusted mean change from baseline in CAT score was reduced for FF/VI 100/25 µg and VI 25 µg on day 168 (Figure 3E).

During the treatment period, 41 patients (10%) experienced a total of 42 moderate/severe COPD exacerbations (none were fatal); the incidence was the same in the placebo and VI 25 µg groups (11%) and lower in the FF/VI 100/25 µg group (6%).

Post hoc analyses

When withdrawn patients were classified as nonresponders, there was a higher proportion of responders in the FF/VI 100/25 µg (50%) and VI 25 µg (50%) groups, versus placebo (36%). The odds ratios (95% confidence interval [CI]) were 1.7 (1.0–2.8; nominal $P=0.036$) with FF/VI 100/25 µg and 1.8 (1.1–2.9; nominal $P=0.017$) with VI 25 µg, relative to placebo. When withdrawn patients were classified as missing, there remained more responders on FF/VI 100/25 µg (60%)

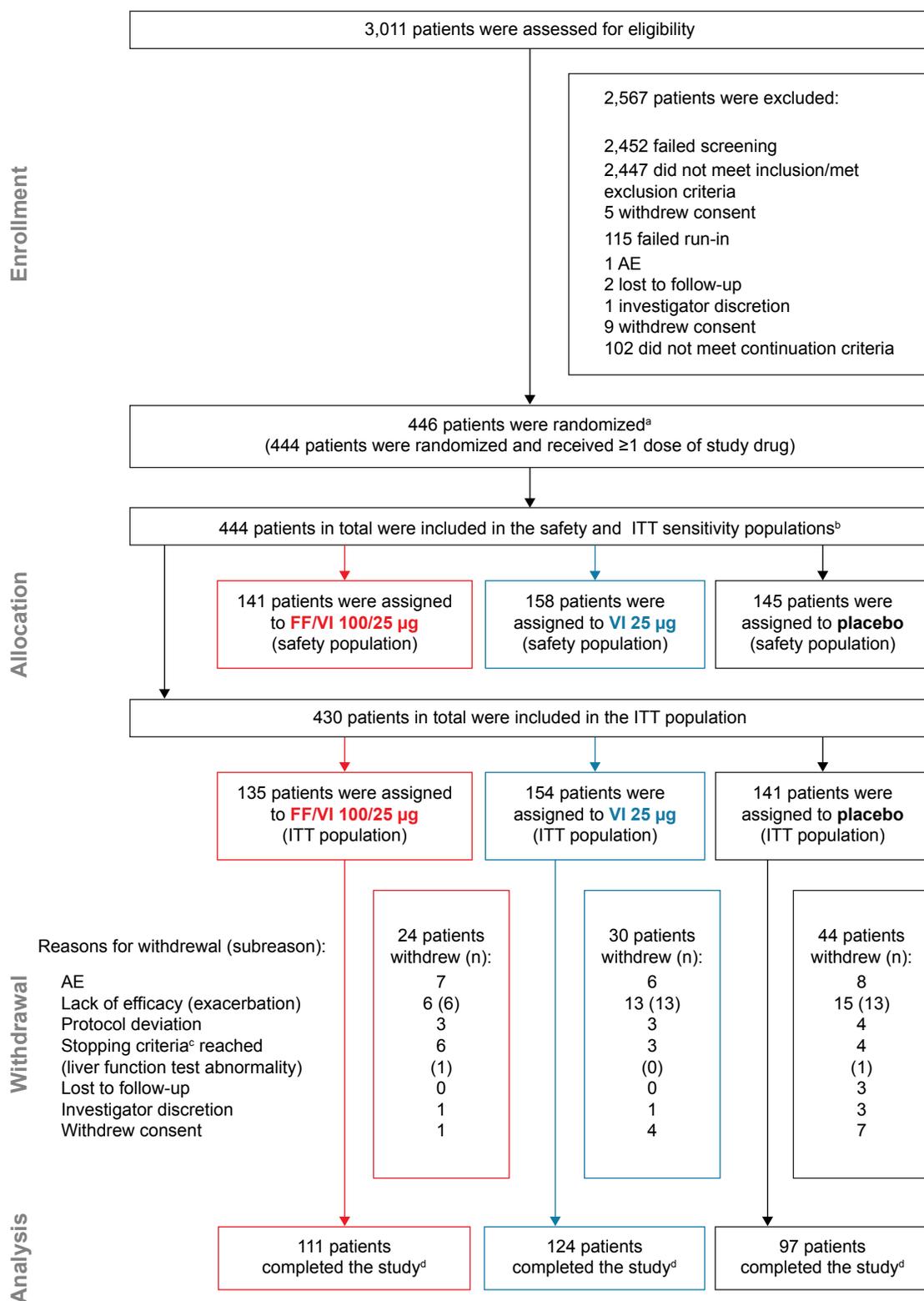


Figure 1 CONSORT diagram.

Notes: ^aTwo patients were randomized erroneously (did not receive study medication but were included in the ITT population); hence, these patients were counted in both the randomized population and the screen and run-in failure population; ^b14 patients were excluded from the ITT population (due to issues of good clinical practice not associated with this study, in one center); however, these patients were included in the safety population and the ITT sensitivity population; ^cstopping criteria = protocol-defined stopping criteria; ^dpatients were considered to have completed the study if they attended the last clinic visit (visit 6, day 168), had a follow-up contact, and did not withdraw.

Abbreviations: AE, adverse event; FF, fluticasone furoate; ITT, intent-to-treat; VI, vilanterol.

Table 1 Screening and baseline characteristics

	FF/VI 100/25 µg	VI 25 µg	Placebo	Total
ITT population, n	135	154	141	430
Demography				
Mean age (SD), years	68.5 (8.0)	68.7 (7.7)	68.2 (8.1)	68.5 (7.9)
Male, n (%)	104 (77)	118 (77)	119 (84)	341 (79)
Race				
African–American/African Heritage, n (%)	6 (4)	4 (3)	7 (5)	17 (4)
Asian, n (%)	65 (48)	74 (48)	68 (48)	207 (48)
White, n (%)	64 (47)	76 (49)	65 (46)	205 (48)
African–American/African Heritage and White, n (%)	0	0	1 (<1)	1 (<1)
Mean body mass index (SD), kg/m ²	24.3 (4.9)	24.7 (5.0)	24.6 (4.9)	24.5 (5.0)
Smoking history, n	135	154	141	430
Current smokers, n (%)	49 (36)	57 (37)	54 (38)	160 (37)
Former smokers, n (%)	86 (64)	97 (63)	87 (62)	270 (63)
Pack-years, mean (SD)	50.1 (28.7)	51.1 (29.1)	47.8 (28.6)	49.7 (28.8)
COPD type, ^a n	135	154	139	428
Chronic bronchitis, n (%)	84 (62)	84 (55)	83 (60)	251 (59)
Emphysema, n (%)	78 (58)	107 (69)	80 (58)	265 (62)
COPD severity				
GOLD stage, n	134	154	141	429
GOLD 1, n (%)	1 (<1) ^b	1 (<1) ^b	1 (<1) ^b	3 (<1) ^b
GOLD 2, n (%)	76 (57)	75 (49)	79 (56)	230 (54)
GOLD 3, n (%)	46 (34)	65 (42)	52 (37)	163 (38)
GOLD 4, n (%)	11 (8)	13 (8)	9 (6)	33 (8)
GOLD patient group, n	133	154	141	428
A, n (%)	13 (10)	11 (7)	18 (13)	42 (10)
B, n (%)	56 (42)	52 (34)	56 (40)	164 (38)
C, n (%)	8 (6)	17 (11)	10 (7)	35 (8)
D, n (%)	56 (42)	74 (48)	57 (40)	187 (44)
Pre-treatment COPD maintenance medications taken by >10% of patients, n (%)				
Short-acting beta ₂ agonist	80 (59)	101 (66)	89 (63)	270 (63)
LABA	34 (25)	59 (38)	45 (32)	138 (32)
ICS	31 (23)	51 (33)	45 (32)	127 (30)
Long-acting anticholinergic	42 (31)	47 (31)	37 (26)	126 (29)
Short-acting anticholinergic ^c	15 (11)	26 (17)	29 (21)	70 (16)
Methylxanthine	24 (18)	22 (14)	21 (15)	67 (16)
Rescue medication (albuterol) use, at baseline				
n	135	153	139	N/A
Mean occasions used/24 h ^d (SD)	1.75 (1.89)	2.07 (2.14)	1.76 (1.73)	
Health outcome scores, at baseline				
n	128	143	129	N/A
SGRQ total score (SD)	42.74 (17.04)	45.68 (17.03)	42.59 (16.54)	
n	135	154	141	N/A
CAT score (SD)	17.1 (7.3)	18.4 (8.3)	15.7 (7.5)	
Pulmonary function				
Screening post-BD FEV ₁ , L (SD)	1.29 (0.43) ^e	1.24 (0.42)	1.30 (0.44)	1.28 (0.43) ^f
Screening post-BD FEV ₁ /FVC ratio (SD)	49.0 (9.7) ^e	48.0 (11.1)	49.0 (10.7)	48.6 (10.5) ^f
Screening % FEV ₁ reversibility (SD)	12.7 (12.3) ^e	15.1 (13.4)	14.4 (14.9)	14.1 (13.6) ^f
n	135	153	141	429
Baseline pre-BD FEV ₁ , L (SD)	1.19 (0.45)	1.12 (0.42)	1.19 (0.47)	1.17 (0.45)
n	129	149	138	416
Baseline IC, L (SD)	1.80 (0.73)	1.75 (0.64)	1.77 (0.70)	1.77 (0.69)
Mean cardiovascular measurements, at screening				
n	131	153	141	425
aPWV, m/s (SD)	13.23 (2.09)	13.34 (2.43)	13.22 (2.12)	13.26 (2.22)
n	128	140	131	399

(Continued)

Table 1 (Continued)

	FF/VI 100/25 µg	VI 25 µg	Placebo	Total
Augmentation index, % (SD)	27.2 (9.9)	28.1 (10.9)	28.4 (9.5)	27.9 (10.1)
n	121	137	130	388
Heart rate variability index ^g (SD)	6.66 (2.92)	7.36 (3.20)	7.34 (3.55)	7.13 (3.25)
n	128	140	131	399
Central PP, mmHg (SD)	44.1 (11.9)	45.8 (11.8)	46.6 (13.1)	45.5 (12.3)
n	135	154	141	430
Peripheral PP, mmHg (SD)	56.9 (12.3)	58.7 (13.4)	59.3 (14.2)	58.3 (13.4)
Safety population, n	141	158	145	N/A
Mean cardiovascular measurements, at screening				
n	134	144	134	N/A
Central MAP, mmHg (SD)	96.81 (11.08)	97.74 (11.23)	97.24 (10.51)	
n	141	158	145	N/A
Peripheral MAP, mmHg (SD)	99.74 (10.69)	101.07 (10.84)	100.56 (10.34)	
n	141	158	145	N/A
Systolic BP, mmHg (SD)	137.7 (15.0)	140.2 (15.8)	140.3 (16.4)	

Notes: Screening = Week -1. Baseline values were assessed prior to dosing on day 1. ^aAssessed verbally by the investigator/study coordinator/other applicable site staff member, patients could select "chronic bronchitis," "emphysema," or both for COPD type; ^bthree patients with an FEV₁ >70% predicted at screening, or for whom this value was missing, were randomized (one to each treatment group); ^call listed participants were taking ipratropium bromide alone or in combination with salbutamol sulfate, fenoterol hydrobromide, salbutamol, or fenoterol; ^dmean number of occasions of use in a 24-h period; ^en=134; ^fn=429; ^ga continuous beat-by-beat measurement of interbeat intervals, measured by the SphygmoCor CPVH system (a non-invasive means of quantifying autonomic activity).

Abbreviations: aPWV, aortic pulse wave velocity; BD, bronchodilator; BMI, body mass index; BP, blood pressure; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IC, inspiratory capacity; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting beta₂ agonist; MAP, mean arterial pressure; N/A, not available; PP, pulse pressure; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire for COPD patients; VI, vilanterol.

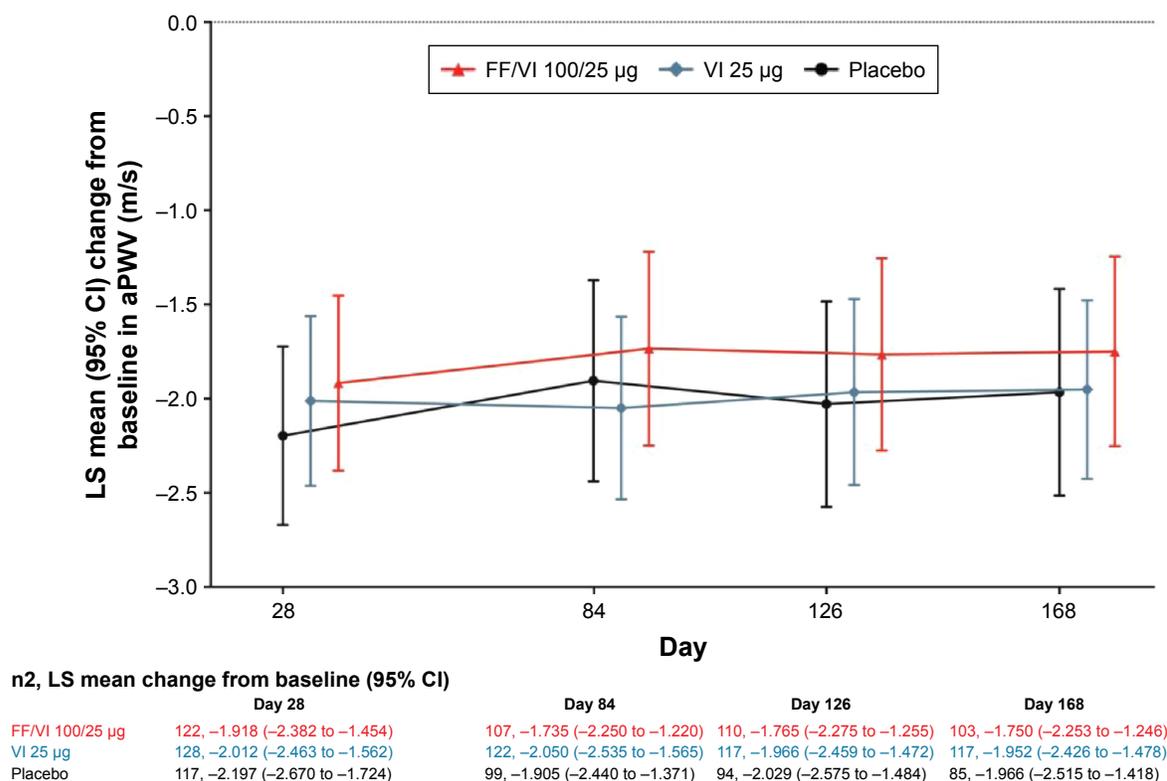


Figure 2 Adjusted mean change from baseline in aPWV (m/s).

Notes: n2 = number of patients with analyzable data at the given time point (day 28, day 84, day 126, or day 168). Analyzed using a repeated measures model with terms for treatment, baseline aPWV, COPD exacerbation history, smoking status at screening, geographic region, gender, age, day, day by baseline aPWV interaction, and day by treatment interaction.

Abbreviations: aPWV, aortic pulse wave velocity; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; LS, least squares; SE, standard error; VI, vilanterol.

Table 2 aPWV measurements on day 168

	FF/VI 100/25 µg	VI 25 µg	Placebo
ITT population, n	135	154	141
n1	125	137	123
n2	103	117	85
LS mean (SE)	11.51 (0.26)	11.31 (0.24)	11.30 (0.28)
LS mean change from baseline (SE)	-1.75 (0.26)	-1.95 (0.24)	-1.97 (0.28)
Difference from placebo (95% CI)	0.22 (-0.5-1.0)	0.01 (-0.7-0.7)	
P-value	0.568	0.969	
Difference from VI (95% CI)	0.20 (-0.5-0.9)		
P-value	0.566		

Notes: n1 = number of patients with analyzable data for one or more time points; n2 = number of patients with analyzable data at the given time point (day 168). Analyzed using a repeated measures model with terms for treatment, baseline aPWV, COPD exacerbation history, smoking status at screening, geographic region, gender, age, day, day by baseline aPWV interaction, and day by treatment interaction.

Abbreviations: aPWV, aortic pulse wave velocity; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; ITT, intent-to-treat; LS, least squares; SE, standard error; VI, vilanterol.

and VI 25 µg (62%) compared with placebo (53%). The odds ratios (95% CI) were 1.3 (0.7–2.4) with FF/VI 100/25 µg and 1.5 (0.8–2.6) with VI 25 µg, relative to placebo.

There was no observed pattern between the effect of baseline aPWV on aPWV at day 168, and no trends by treatment arm (Figure S2).

Safety

The incidence of on-treatment AEs was higher in the FF/VI 100/25 µg (57%) and VI 25 µg (51%) groups compared with placebo (41%). The most frequently reported AE was nasopharyngitis (Table 4). Local steroid effects, primarily oral candidiasis, occurred predominantly with FF/VI 100/25 µg and were of mild or moderate intensity. Other AEs of special interest for ICS-/LABA-containing treatment were infrequent (incidences of pneumonia were ≤1% in all groups) (Table 4). Two fatal serious AEs were reported during the treatment period (Table 4); neither was considered by the investigator to be related to the study treatment.

There were no differences between groups for changes in central or peripheral MAP, or systolic BP (Table 3).

Discussion

In this 24-week study, neither FF/VI 100/25 µg nor VI 25 µg had significant effects on arterial stiffness versus placebo. By contrast, the active treatments improved lung function (FEV₁) and quality of life (SGRQ total score reached the minimally clinically important difference of 4 on day 168)³¹ versus placebo. Although lung function is known to be inversely correlated with the elevated arterial stiffness,³² this study did not find any associations, with the exception of one significant positive correlation between aPWV on day 168

and IC (VI 25 µg); however, this may be a chance finding as no similar correlation was observed with FF/VI 100/25 µg or placebo in this population with moderate airflow obstruction (across all treatment groups, the mean FEV₁ was 50.1% [SD =13.34] of predicted normal values).

Arterial stiffness (measured by aPWV) provides incremental risk information to traditionally measured cardiovascular risk factors. Thus, elevated arterial stiffness is an indicator of cardiovascular risk reduction. aPWV increases with age, and for every 1 m/s increase in aPWV, cardiovascular risk increases by 15% in the general population;³³ COPD may accelerate this. Various mechanisms are implicated in the pathogenesis of accelerated atherosclerosis in COPD (oxidative stress, renin angiotensin system overactivation, and heightened sympathetic activity), but the strongest evidence points to systemic inflammation, which has been associated with an increased risk of cardiac injury in patients with moderate-to-severe airflow obstruction.^{1,16}

A plausible connection between COPD and CVD lies in the vascular response to cigarette smoke (a risk factor for the development of COPD)¹⁹ and hypoxic pulmonary vasoconstriction.³⁴ Evidence of endothelial dysfunction and vascular re-modeling have been detected both in individuals with COPD and in “healthy” individuals who smoke.¹⁸ This could be due to shared risk factors such as cigarette smoking, which in addition to being a risk factor for airway obstruction,¹⁶ is also known to induce vascular endothelial dysfunction.¹⁸ Notably in this study, the smoking history (including years smoked, cigarettes per day, pack-years, and smoking status) was similar across the groups.

Anti-inflammatories and bronchodilators used in COPD can reduce arterial stiffness, which may modulate

Table 3 Aortic Alx and blood pressure measurements on day 168

	FF/VI 100/25 µg	VI 25 µg	Placebo
ITT population, n	135	154	141
Aortic Alx ^a			
n1	123	127	116
n2	100	107	87
LS mean (SE)	28.8 (0.76)	27.3 (0.74)	26.8 (0.81)
LS mean change from baseline (SE)	0.7 (0.76)	-0.7 (0.74)	-1.3 (0.81)
Difference from placebo (95% CI)	2.0 (-0.2-4.2)	0.6 (-1.6-2.7)	
P-value	0.076	0.607	
Central PP, mmHg ²			
n1	123	127	116
n2	100	107	87
LS mean (SE)	46.4 (1.10)	42.0 (1.07)	43.7 (1.18)
LS mean change from baseline (SE)	0.9 (1.10)	-3.5 (1.07)	-1.8 (1.18)
Difference from placebo (95% CI)	2.7 (-0.4-5.9)	-1.7 (-4.8-1.5)	
P-value	0.091	0.295	
Peripheral PP, mmHg ^b			
n1	131	141	131
n2	111	126	97
LS mean (SE)	57.9 (1.08)	53.6 (1.02)	55.8 (1.16)
LS mean change from baseline (SE)	3.2 (1.08)	-1.1 (1.02)	1.2 (1.16)
Difference from placebo (95% CI)	2.0 (-1.1-5.2)	-2.2 (-5.2-0.8)	
P-value	0.198	0.154	
Safety population, n	141	158	145
Central MAP, mmHg ^c			
n1	126	131	118
n2	100	107	87
LS mean (SE)	93.7 (0.87)	91.4 (0.84)	94.1 (0.93)
LS mean change from baseline (SE)	-3.5 (0.87)	-5.8 (0.84)	-3.0 (0.93)
Difference from placebo (95% CI)	-0.4 (-2.95-2.05)	-2.8 (-5.22 to 0.28)	
P-value	0.724	0.029	
Peripheral MAP, mmHg ^c			
n1	137	145	134
n2	111	126	97
LS mean (SE)	96.7 (0.82)	94.8 (0.78)	96.6 (0.88)
LS mean change from baseline (SE)	-0.8 (0.82)	-2.7 (0.78)	-0.9 (0.88)
Difference from placebo (95% CI)	0.07 (-2.30-2.43)	-1.82 (-4.13-0.49)	
P-value	0.957	0.123	
Systolic BP, mmHg			
n	111	126	97
Mean (SD)	135.5 (15.88)	130.2 (14.35)	134.3 (15.63)
Mean change from baseline (SD)	1.5 (17.47)	-2.9 (16.67)	-0.3 (14.39)

Notes: n1 = number of patients with analyzable data for one or more time points; n2 = number of patients with analyzable data at the given time point (day 168). ^aAnalyzed using a repeated measures model in terms of treatment, baseline aortic Alx, COPD exacerbation history, smoking status at screening, geographic region, gender, age, day, day by baseline aortic Alx interaction, and day by treatment interaction; ^banalyzed using a repeated measures model in terms of treatment, baseline central or peripheral PP, COPD exacerbation history, smoking status at screening, geographic region, gender, age, day, day by baseline central or peripheral PP interaction, and day by treatment interaction; ^canalyzed using a repeated measures model in terms of treatment, baseline central or peripheral mean arterial pressure, COPD exacerbation history, smoking status at screening, day, day by baseline central or peripheral mean arterial pressure interaction, and day by treatment interaction.

Abbreviations: Alx, augmentation index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CI, confidence interval; FF, fluticasone furoate; ITT, intent-to-treat; LS, least squares; MAP, mean arterial pressure; PP, pulse pressure; SD, standard deviation; SE, standard error; VI, vilanterol.

cardiovascular risk.^{25,26,35} Short-acting beta₂-agonists (and possibly LABAs) cause systemic vasodilation through the nitric oxide pathway.³⁶ A randomized study comparing fluticasone propionate/salmeterol with placebo reported no effect of active treatment on aPWV.²⁵ However, post hoc analysis

suggested that participants with baseline aPWV >10.9 m/s had substantial reductions in arterial stiffness with fluticasone propionate/salmeterol.²⁵ Pepin et al showed that both FF/VI and tiotropium reduced aPWV in patients with elevated baseline aPWV.²⁶ However, that study was not placebo controlled

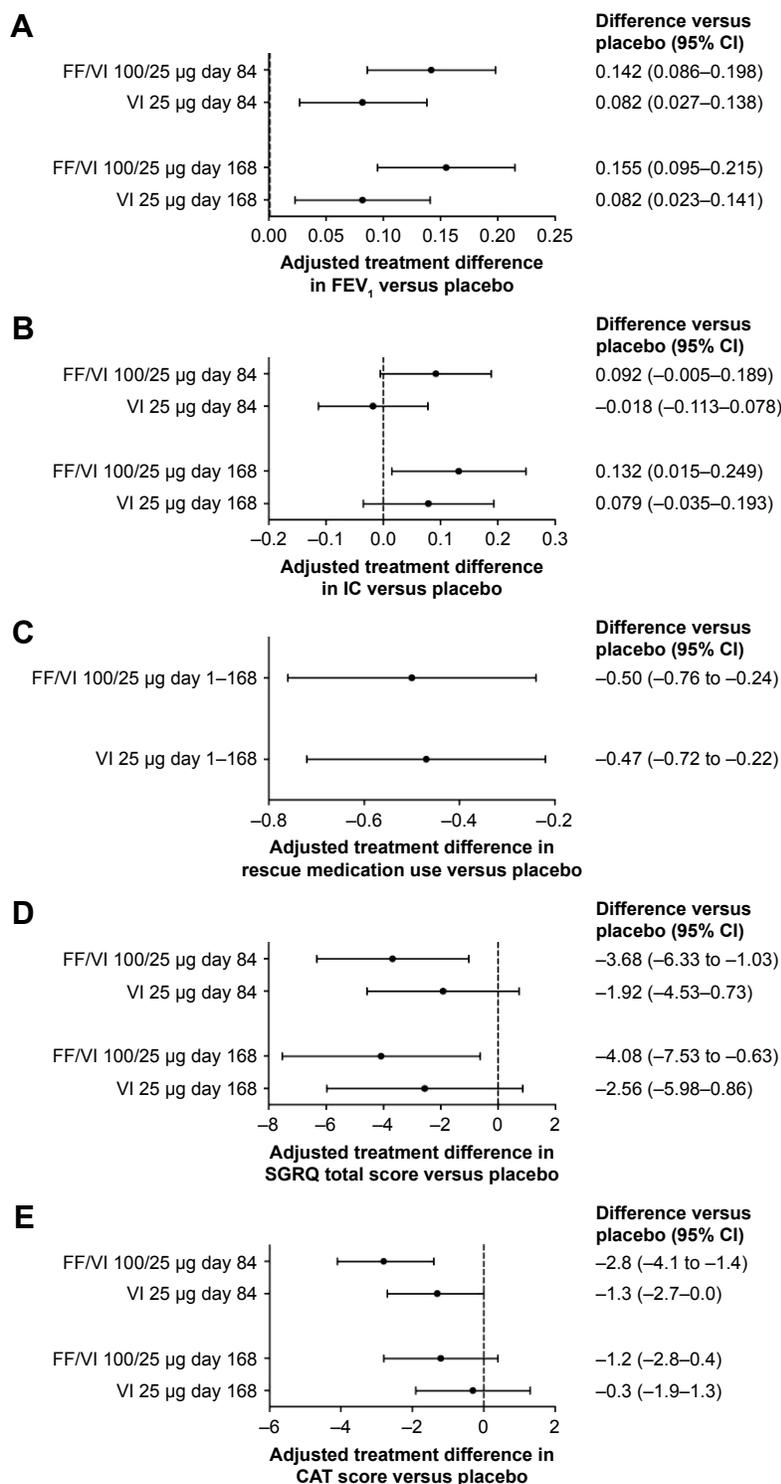


Figure 3 Adjusted treatment differences compared with placebo for lung function and health outcomes scores.

Notes: (A) Trough FEV₁ on days 84 and 168, analyzed using a repeated measures model with terms for treatment, baseline FEV₁, COPD exacerbation history, geographic region, day, day by baseline FEV₁ interaction, and day by treatment interaction. (B) IC on days 84 and 168, analyzed using a repeated measures model with terms for treatment, baseline IC, COPD exacerbation history, geographic region, day, day by baseline IC interaction, and day by treatment interaction. (C) Rescue medication use throughout the 168-day treatment period, analyzed using an analysis of covariance model with covariates of treatment, baseline mean number of occasions of rescue medication use, COPD exacerbation history, and geographic region. (D) SGRQ total score, analyzed using a repeated measures model with terms for treatment, baseline SGRQ total score, COPD exacerbation history, geographic region, day, day by baseline SGRQ total score interaction, and day by treatment interaction. (E) CAT, on days 84 and 168, analyzed using a repeated measures model in terms of treatment, baseline CAT score, COPD exacerbation history, geographic region, day, day by baseline CAT score interaction, and day by treatment interaction.

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; IC, inspiratory capacity; SGRQ, St George's Respiratory Questionnaire for COPD patients; VI, vilanterol.

Table 4 AEs, SAEs, AESI, and AEs leading to withdrawal

Preferred term	FF/VI 100/25 µg	VI 25 µg	Placebo
n	141	158	145
On-treatment AEs reported by ≥3% of patients in any treatment group, n (%)			
Nasopharyngitis	9 (6)	12 (8)	5 (3)
Headache	8 (6)	9 (6)	5 (3)
Back pain	4 (3)	5 (3)	5 (3)
Oral candidiasis	9 (6)	2 (1)	1 (<1)
Upper respiratory tract infection	2 (1)	4 (3)	6 (4)
Arthralgia	5 (4)	1 (<1)	4 (3)
Oropharyngeal pain	6 (4)	2 (1)	1 (<1)
COPD	2 (1)	5 (3)	1 (<1)
Hypertension	2 (1)	2 (1)	4 (3)
Pyrexia	3 (2)	1 (<1)	4 (3)
Cough	1 (<1)	1 (<1)	4 (3)
Sinusitis	4 (3)	1 (<1)	1 (<1)
Angina pectoris	0	0	4 (3)
Influenza	0	4 (3)	0
On-treatment SAEs, n (%)			
Any on-treatment SAE	9 (6)	12 (8)	5 (3)
Fatal SAEs	1 (<1) ^a	1 (<1) ^b	0
Non-fatal SAEs	8 (6)	11 (7)	5 (3)
COPD	2 (1)	5 (3)	1 (<1)
Pneumonia	2 (1)	1 (<1)	2 (1)
Infective exacerbation of chronic obstructive airways disease	0	1 (<1)	0
Pulmonary tuberculosis	0	1 (<1)	0
Pyelonephritis	1 (<1)	0	0
Septic shock	0	1 (<1)	0
Facial bone fracture	0	1 (<1)	0
Fibula fracture	1 (<1)	0	0
Hip fracture	1 (<1)	0	0
Tibia fracture	1 (<1)	0	0
Angina pectoris	0	0	1 (<1)
Angina unstable	0	0	1 (<1)
Fecaloma	1 (<1)	0	0
Inguinal hernia	0	0	1 (<1)
Hypokalemia	0	1 (<1)	0
Type 2 diabetes mellitus	0	1 (<1)	0
Adenocarcinoma of colon	0	1 (<1)	0
Malignant lung neoplasm	0	0	1 (<1)
Increased hepatic enzymes	1 (<1)	0	0
Cerebrovascular accident	0	1 (<1)	0
Acute renal failure	0	1 (<1)	0
Benign prostatic hyperplasia	0	1 (<1)	0
Post-treatment SAEs, n (%)			
Acute respiratory failure	0	1 (<1)	0
AESI, n (%)			
Corticosteroid-associated eye disorder	0	2 (1)	0
Decreased bone mineral density and associated fracture	4 (3)	1 (<1)	2 (1)
Hypersensitivity	4 (3)	7 (4)	10 (7)
Pneumonia	2 (1)	3 (2)	2 (1)
Lower respiratory tract infection ^c	1 (<1)	2 (1)	1 (<1)
Local steroid effect	15 (11)	6 (4)	4 (3)
Effect on potassium	0	2 (1)	1 (<1)
Tremor	0	0	0

(Continued)

Table 4 (Continued)

Preferred term	FF/VI 100/25 µg	VI 25 µg	Placebo
Adrenal suppression	0	0	0
Cardiovascular effects ^d	5 (4)	5 (3)	13 (9)
Subgroups: cardiac arrhythmia	3 (2)	1 (<1)	2 (1)
Cardiac failure	0	2 (1)	1 (<1)
Stroke	1 (<1)	1 (<1)	0
Hypertension	3 (2)	2 (1)	4 (3)
Cardiac ischemia	0	1 (<1)	6 (4)
Effect on glucose ^d	0	3 (2)	3 (2)
System Organ Class: AEs leading to withdrawal, n (%)			
Any AE leading to withdrawal	8 (6)	9 (6)	8 (6)
Respiratory, thoracic, and mediastinal disorders	2 (1)	5 (3)	2 (1)
Infections and infestations	3 (2)	2 (1)	2 (1)
Cardiac disorders	0	1 (<1)	2 (1)
Neoplasms, including benign, malignant, and unspecified	1 (<1)	0	2 (1)
Investigations	2 (1)	0	0
Vascular disorders	0	1 (<1)	1 (<1)
Gastrointestinal disorders	0	0	1 (<1)
Injury, poisoning, and procedural complications	1 (<1)	0	0
Nervous system disorders	0	1 (<1)	0
Renal and urinary disorders, system organ classes	0	1 (<1)	0

Notes: ^aCardiorespiratory arrest secondary to COPD; ^bcolorectal and prostate cancer; ^cexcluding pneumonia; ^ddefined using Standardized MedDRA Queries.

Abbreviations: AE, adverse event; AESI, AEs of special interest (events related to the pharmacologic action of inhaled corticosteroids or long-acting beta₂-agonists); COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; SAE, serious AE; VI, vilanterol.

and the reduction in stiffness in both the arms could be due to regression to the mean, since patients were included with high baseline aPWV. The present study included a placebo arm; although FEV₁ was improved in the active treatment arms versus placebo, this study did not observe any significant change in aPWV between FF/VI 100/25 µg, VI 25 µg, and placebo. The mean reduction in aPWV across all arms attained the minimally clinically important difference of 1 m/s³⁷ and was likely due to regression to the mean as patients were recruited with elevated aPWV.

Systemic inflammation itself can also result in vascular remodeling and increased arterial stiffness;¹⁶ however, the evidence for this relationship in COPD is unclear, with one study suggesting a weak association,³⁸ and no association has been demonstrated in other studies.^{8,9,12,23,39} Approximately one-third of patients in the Evaluation of COPD to Longitudinally Identify Predictive Surrogate Endpoints (ECLIPSE) study had no baseline systemic inflammation, and only 16% showed persistent systemic inflammation.⁴⁰ This study did not observe reductions in inflammatory biomarkers with FF/VI 100/25 µg or VI 25 µg versus placebo, nor any correlation between systemic inflammation and elevated arterial stiffness.

Increased arterial stiffness is due to multiple factors, including senescence, elastin fiber breaks, collagen

deposition, fibrosis, inflammation, and calcification.¹⁶ Although the results suggest that ICS/LABA therapies do not reduce arterial stiffness, it is possible that the patients had arteries that were calcified and resistant to modulation. Patients with aPWV ≥ 11 m/s may have had heterogeneous causes of elevated stiffness that were less amenable to modulation; however, regardless of baseline aPWV, all patients had aPWV reductions during the study.

The uniform reduction of aPWV across all three arms cannot be easily explained. A systemic decrease in “white coat” effects over time may be hypothesized; however, data from a previous study²⁵ do not agree. The requirement of a stable use of concomitant medications shown to influence aPWV might have led to a good compliance of taking those medications across all arms, which subsequently reduced aPWV for all patients. However, again, it does not seem to be the case for the previous study²⁵ with the same requirement. This study has also noted a higher proportion of hypertensive patients in the placebo group compared with either active group in the present study, which may or may not have contributed to the reduction of aPWV with placebo; however, there were no significant changes between groups and anti-hypertensives were included in the list of concomitant medications for which a stable dose was required. The observation on aPWV

in the present study cannot be directly compared with that in the other previous study²⁶ that did not include placebo.

Safety findings were in line with established FF/VI 100/25 µg and VI 25 µg profiles. There were fewer COPD exacerbations in the FF/VI 100/25 µg group than in VI 25 µg or placebo. The incidence of pneumonia in the ICS-treated groups was not greater than that in the placebo group, which might be related to study duration,^{41–44} as the overall incidence of pneumonia was low in this study.

This study had some limitations. As mentioned previously, it was speculated that by selecting patients with a high baseline aPWV (decided a priori based on previous post hoc results⁴⁵), patients with calcified arteries and variable aPWV have been selected. Calcification was not measured directly in this study, but as the patients with higher baseline aPWV values had similar reductions in aPWV compared with patients with lower baseline aPWV, this did not seem to be the case. Additionally, the findings cannot be generalized to patients with COPD and low baseline aPWV. Furthermore, patients may have taken concomitant medications that could have impacted their aPWV during the study, but any such effects were unknown, and this was also the case in previous studies.^{25,26} Finally, as the sample size requirement was altered during the course of the study, an alpha adjustment may have been required if a significant difference in aPWV change had been detected with FF/VI 100/25 µg or VI 25 µg treatment, versus placebo.

The main strength of this study was that this was a prospective, randomized, blinded study with a placebo arm and active comparator arms. The VI 25 µg arm was included to elucidate the impact of ICS (FF) and LABA (VI). aPWV is the gold standard to measure arterial stiffness and the SphygmoCor CPVH system that has been used can accurately assess this parameter, which is predictive of CV outcomes.^{46,47} However, the measurement of endothelial function may provide valuable supportive information in future studies. Furthermore, dose regimens of permitted concomitant medications known to affect aPWV were maintained during the study, and to avoid impact on aPWV from patients' previous medications, such as other ICS and LABAs, all these medications were excluded for an appropriate time period prior to the study.^{48,49}

Conclusion

No differences were observed in aPWV-adjusted mean change from baseline for FF/VI 100/25 µg compared with placebo. More research is needed to identify responders to ICS/LABA therapy, who may derive CVD benefits from the treatment in addition to lung function improvements.

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Disclosure

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References

1. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. *Transl Res*. 2013;162(4):237–251.
2. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J*. 2006;28(6):1245–1257.
3. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc*. 2005;2(1):8–11.
4. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *Bmj*. 1996;313(7059):711–715; discussion 715–716.
5. Curkendall SM, DeLuise C, Jones JK, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol*. 2006;16(1):63–70.
6. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3(8):631–639.
7. Tabara Y, Muro S, Takahashi Y, et al. Airflow limitation in smokers is associated with arterial stiffness: the Nagahama Study. *Atherosclerosis*. 2014;232(1):59–64.
8. McAllister DA, Maclay JD, Mills NL, et al. Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;176(12):1208–1214.
9. Sabit R, Bolton CE, Edwards PH, et al. Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;175(12):1259–1265.
10. Oda M, Omori H, Onoue A, et al. Association between airflow limitation severity and arterial stiffness as determined by the brachial-ankle pulse wave velocity: a cross-sectional study. *Intern Med*. 2015;54(20):2569–2575.

11. Chen R, He W, Zhang K, et al. Airflow obstruction was associated with elevation of brachial-ankle pulse wave velocity but not ankle-brachial index in aged patients with chronic obstructive pulmonary disease. *Atherosclerosis*. 2015;242(1):135–140.
12. Bhatt SP, Cole AG, Wells JM, et al. Determinants of arterial stiffness in COPD. *BMC Pulm Med*. 2014;14:1.
13. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol*. 2014;63(7):636–646.
14. Laurent S, Alivon M, Beaussier H, Boutouyrie P. Aortic stiffness as a tissue biomarker for predicting future cardiovascular events in asymptomatic hypertensive subjects [abstract]. *Ann Med*. 2012;44(Suppl):S93–S97.
15. Agusti A, Faner R. Systemic inflammation and comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2012;9(2):43–46.
16. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation*. 2003;107(11):1514–1519.
17. Cecelja M, Chowieniczky P. Molecular mechanisms of arterial stiffening. *Pulse (Basel)*. 2016;4(1):43–48.
18. Weir-McCall JR, Struthers AD, Lipworth BJ, Houston JG. The role of pulmonary arterial stiffness in COPD. *Respir Med*. 2015;109(11):1381–1390.
19. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013;187(4):347–365.
20. Pieringer H, Stuby U, Hargassner S, Biesenbach G. Treatment with corticosteroids reduces arterial stiffness in patients with polymyalgia rheumatica as measured with pulse wave analysis. *Ann Rheum Dis*. 2008;67:279.
21. Kals J, Kampus P, Kals M, Pulges A, Teesalu R, Zilmer M. Effects of stimulation of nitric oxide synthesis on large artery stiffness in patients with peripheral arterial disease. *Atherosclerosis*. 2006;185(2):368–374.
22. Dawes M, Chowieniczky PJ, Ritter JM. Effects of inhibition of the L-arginine/nitric oxide pathway on vasodilation caused by beta-adrenergic agonists in human forearm. *Circulation*. 1997;95(9):2293–2297.
23. Gale NS, Duckers JM, Enright S, Cockcroft JR, Shale DJ, Bolton CE. Does pulmonary rehabilitation address cardiovascular risk factors in patients with COPD? *BMC Pulm Med*. 2011;11:20.
24. Vivodtzev I, Minet C, Wuyam B, et al. Significant improvement in arterial stiffness after endurance training in patients with COPD. *Chest*. 2010;137(3):585–592.
25. Dransfield MT, Cockcroft JR, Townsend RR, et al. Effect of fluticasone propionate/salmeterol on arterial stiffness in patients with COPD. *Respir Med*. 2011;105(9):1322–1330.
26. Pepin JL, Cockcroft JR, Midwinter D, Sharma S, Rubin DB, Andreas S. Long-acting bronchodilators and arterial stiffness in patients with COPD: a comparison of fluticasone furoate/vilanterol with tiotropium. *Chest*. 2014;146(6):1521–1530.
27. Baber N. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). *Br J Clin Pharmacol*. 1994;37(5):401–404.
28. Rickham PP. Human experimentation. Code of ethics of the world medical association. Declaration of Helsinki. *Br Med J*. 1964;2(5402):177.
29. GSK [Clinical Study Register – Study 113108]. UK: GlaxoSmithKline plc [updated April 2, 2015]. Available at http://www.gsk-clinical-studyregister.com/study/113108?study_ids=hzc113108#ps. Accessed April 14, 2016.
30. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment Test. *Eur Respir J*. 2009;34(3):648–654.
31. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J*. 2002;19(3):398–404.
32. Brunner EJ, Shipley MJ, Witte DR, et al. Arterial stiffness, physical function, and functional limitation: the Whitehall II Study. *Hypertension*. 2011;57(5):1003–1009.
33. Qvist L, Nilsson U, Johansson V, et al. Central arterial stiffness is increased among subjects with severe and very severe COPD: report from a population-based cohort study. *Eur Clin Respir J*. 2015;16:2.
34. Wu C-F, Liu P-Y, Wu T-J, Hung Y, Yang S-P, Lin G-M. Therapeutic modification of arterial stiffness: An update and comprehensive review. *World J Cardiol*. 2015;7(11):742–753.
35. Sabit R, Bolton CE, Allanby C, Cockcroft JR, Shale DJ. Arterial stiffness is reduced by combination inhaled corticosteroid/long acting beta-2 agonist therapy in patients with COPD [abstract]. *Thorax*. 2007;62(Suppl):A142.
36. Dawes M, Chowieniczky PJ, Ritter JM. Effects of inhibition of the L-arginine/nitric oxide pathway on vasodilation caused by beta-adrenergic agonists in human forearm. *Circulation*. 1997;95(9):2293–2297.
37. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. *Hypertension*. 2002;39(5):1083–1087.
38. Mills NL, Miller JJ, Anand A, et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. *Thorax*. 2008;63(4):306–311.
39. Vanfleteren LE, Spruit MA, Groenen MT, et al. Arterial stiffness in patients with COPD: the role of systemic inflammation and the effects of pulmonary rehabilitation. *Eur Respir J*. 2014;43(5):1306–1315.
40. Agusti A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One*. 2012;7(5):e37483.
41. 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(3):641–647.
42. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;3:CD010115.
43. Liapikou A, Toumbis M, Torres A. Managing the safety of inhaled corticosteroids in COPD and the risk of pneumonia. *Expert Opin Drug Saf*. 2015;14(8):1237–1247.
44. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA; INSPIRE Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med*. 2008;177(1):19–26.
45. Vivodtzev I, Minet C, Tamisier R, et al. Arterial stiffness by pulse wave velocity in COPD: reliability and reproducibility. *Eur Respir J*. 2014;42(4):1140–1142.
46. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27(21):2588–2605.
47. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318–1327.
48. Weir DC, Robertson AS, Gove RL, Burge PS. Time course of response to oral and inhaled corticosteroids in non-asthmatic chronic airflow obstruction. *Thorax*. 1990;45(2):118–121.
49. Twentyman OP, Finnerty JP, Harris A, Palmer J, Holgate ST. Protection against allergen-induced asthma by salmeterol. *Lancet*. 1990;336:1338–1342.

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