Supplementary Material

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

Short title: Effects of fluticasone/vilanterol on arterial stiffness

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List of independent ethics committees (IECS)/institutional review boards (IRBS) that approved this study

Name of IEC/IRB Committee, Address	Committee Chair(s)
Ethik-Kommission der Landes Aerztekammer Schleswig-Holstein, Bismarckallee 8–12, Bad Segeberg, Schleswig-Holstein, 23795, Germany	Hintze, Gerhard Ziegler, Albrecht
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Chonnam National University Hospital, 67, Jebongno, Donggu, Gwangju, 501-757, Korea	Yang, Sung Yeul Won, Young Ho
Korea University Guro Hospital Institutional Review Board, 148,Guro-dong-ru, Guro-gu, Seoul, 152-703, Korea	Baik-Lin, Eun
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Name of IEC/IRB Committee, Address	Committee Chair(s)
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Regional Committees for Medical and Health Research Ethics, Gullhaugveien 1-3, 0484 Oslo, Norway	Engedal, Knut
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The Medical City – Institutional Review Board, The Medical City, Ortigas Avenue, Pasig City, Metro Manila, 1600, Philippines	Sumpaico, Carlo Emmanuel
University of the Philippines Manila – Research Ethics Board, University of the Philippines Manila, Ermita, Manila, 1000, Philippines	Mantaring, Jacinto Blas V
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Unified Bio-Medical Research Ethics Review Committee, West Visayas State University, La Paz, Iloilo City, 5000, Philippines	Guillergan, Fred P
The Khon Kaen University Ethics Committee for Human Research, Princess Mother Memorial Building, Faculty of Medicine, 17th Floor, Khon Kaen University, Khon Kaen, Thailand	Vaeteewootacharn, Kriangsak
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Name of IEC/IRB Committee, Address	Committee Chair(s)
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Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok, 10400, Thailand	Ongpbipbadbanakul, Boonsong
Ethics Committee of Nan hospital, 1 Worawichai Road, Nan Province, 55000, Thailand Institute for the Development of Human Research Protections (IHRP), Building 8, Floor 7, Room 702, Department of Medical Science, Ministry Public Health, Nonthaburi, Thailand, 11000	Waraporn, Techasena Vichai, Chokevivat
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Name of IEC/IRB Committee, Address	Committee Chair(s)
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Western Institutional Review Board (WIRB), 1019 39th Avenue South East, Puyallup, Washington, 98374, United States	Wilkins, R Bert
University of Florida Institutional Review Board-01, Gainesville Health Science Center, P.O. Box 100173, 1600 South West Archer Road, Gainesville, Florida, 32608, United States	Iafrate, Peter R

All centres participated in the study under the US IND

Concomitant medications

Supplementary Table 1 Details of medications excluded during the study and the time prior to screening that participants must not have taken these medications

Medications excluded during the course of the study	**Excluded medications must not have been used for the following time intervals prior to screening (clinic visit 1) and thereafter at any time during the study**
Depot corticosteroids	12 weeks
Cytochrome P450 3A4 strong inhibitors[a]	6 weeks
Systemic, oral, parenteral (intra-articular) corticosteroids	30 days
Antibiotics[b] (for lower respiratory tract infection)	6 weeks
Inhaled corticosteroids	2 weeks
Inhaled ICS/LABA combination products	2 weeks
Inhaled long-acting anticholinergics (e.g., tiotropium)	1 week
PDE-4 inhibitors (e.g., roflumilast)	1 week
Oral leukotriene inhibitors (e.g., zafirlukast, montelukast, zileuton)	48 hours
Inhaled long acting beta$_2$-agonists (LABA) (e.g., salmeterol)	48 hours
Oral beta-agonists	48 hours
Inhaled sodium cromoglycate or nedocromil sodium	24 hours
Inhaled short acting beta$_2$-agonists (SABA)	4 hours[c]
Theophylline preparations	48 hours
Short acting anti-cholinergics (e.g., ipratropium bromide)	4 hours[d]
Any other investigational drug	30 days[e]

[a]Including but not limited to antiretrovirals (protease inhibitors) (e.g., indinavir, nelfinavir, ritonavir, saquinavir, atazanavir); imidazole and triazole anti-fungals (e.g., ketaconazole, itraconazole, voriconazole); clarithromycin, telithromycin, troleandomycin, mibefradil, cyclosporin, nefazodone. Grapefruit was allowed up to clinic visit 1, then limited to no more than one glass of grapefruit juice (250 mL/8 ounces) or one grapefruit per day.

[b]Antibiotics for non-respiratory tract infections were not excluded.

[c]Use of study-provided albuterol/salbutamol was permitted throughout the study, however, it was required to be withheld for 4 hours prior to and during each clinic visit.

[d]Ipratropium bromide alone was permitted, provided that the patient was on a stable dose from Screening (clinic visit 1) and remained on the stable dose throughout the study; however, it was required to be withheld for 4 hours prior to and during each clinic visit.

[e]Or five half-lives, whichever was longer.

Statistical analyses

Initial sample size calculations were performed based on an estimate of the standard deviation (SD) of mean change from baseline in aPWV of 2.2 m/s.[2] Accordingly, 102 patients per treatment group were estimated to provide 90% power for detection of a 1 m/s treatment difference in change from baseline aPWV on day 168, at a significance level of 0.05, based on a two-sample two-sided t-test. To allow for a withdrawal rate of 25%, an enrollment target of 136 randomized patients was planned per group. This was revised, in the protocol amendment mentioned above, due to data becoming available from a 12-week study indicating a model SD of mean change from baseline in aPWV of 2.68 m/s.[3] A blinded look at the raw SD of mean change from baseline aPWV at 24 weeks for study HZC113108 indicated an appropriate estimate of the SD to use for sample size calculations would be 2.6 m/s. Using this, 107 patients per treatment group would provide 80% power to detect a treatment difference of 1 m/s, at a significance level of 0.05 based on a two-sample two-sided t-test. Allowing for an approximate 25% withdrawal rate, a revised enrollment target of 143 randomized patients was planned per treatment group. During the conduct of the study, prior to unblinding, a decision was made to exclude data from 14 patients enrolled by one study center from the efficacy analyses, due to issues of good clinical practice not associated with this study. Consequently, an additional 14 patients were randomized to ensure at least 321 evaluable patients. As the planned sample size assessment was performed on blinded study data no adjustment for multiplicity was necessary.

Exploratory analyses – further information

Exploratory analyses were planned a priori and performed to determine whether baseline characteristics and COPD comorbidities influenced treatment response for aPWV. These were performed using a repeated measures model with terms for treatment, baseline aPWV, history of COPD exacerbation, smoking status at screening, geographic region, gender, age, day, the specified parameter, day by baseline aPWV interaction, day by treatment interaction, the specified parameter by treatment interaction, and the three-way interaction of the specified parameter by treatment by day.

Categorical parameters were as follows: FEV_1 reversibility at screening (reversible/not-reversible), medical history (of one of the following: hypertension, diabetes, cardiovascular diseases, or hypercholesterolemia), Global Initiative for Chronic Obstructive Lung Disease patient group, and COPD prior medication use (LABA or long-acting muscarinic antagonist [LAMA]; LABA and LAMA; LABA or LAMA in combination with ICS; LABA, LAMA, and ICS; or other). Continuous parameters were as follows: baseline aPWV, baseline central systolic BP, baseline central diastolic BP, baseline peripheral systolic BP, baseline peripheral diastolic BP, baseline central pulse pressure, baseline peripheral pulse pressure, baseline central mean arterial pressure, baseline peripheral mean arterial pressure, screening heart rate variability, screening percent predicted FEV_1, baseline FEV_1, and body mass index.

Populations – further information

The per-protocol population comprised all subjects in the ITT population not identified as having deviations considered to impact the primary efficacy analysis, and it was used for confirmatory analysis of the primary endpoint.

The ITT sensitivity population comprised all subjects in the ITT population with the inclusion of the additional randomized subjects from the site with Good Clinical Practice issues who received at least one dose of study medication, and it was used for sensitivity analysis for the primary endpoint.

The safety population comprised all subjects in the ITT sensitivity population, and it was used for the reporting of all safety data.

Analysis of aPWV using the per-protocol population

Data from the analysis of adjusted treatment difference in aPWV compared with placebo on day 168 (data not shown) using the per-protocol population were consistent with those using the ITT population. Further planned exploratory analyses of the primary endpoint are described below.

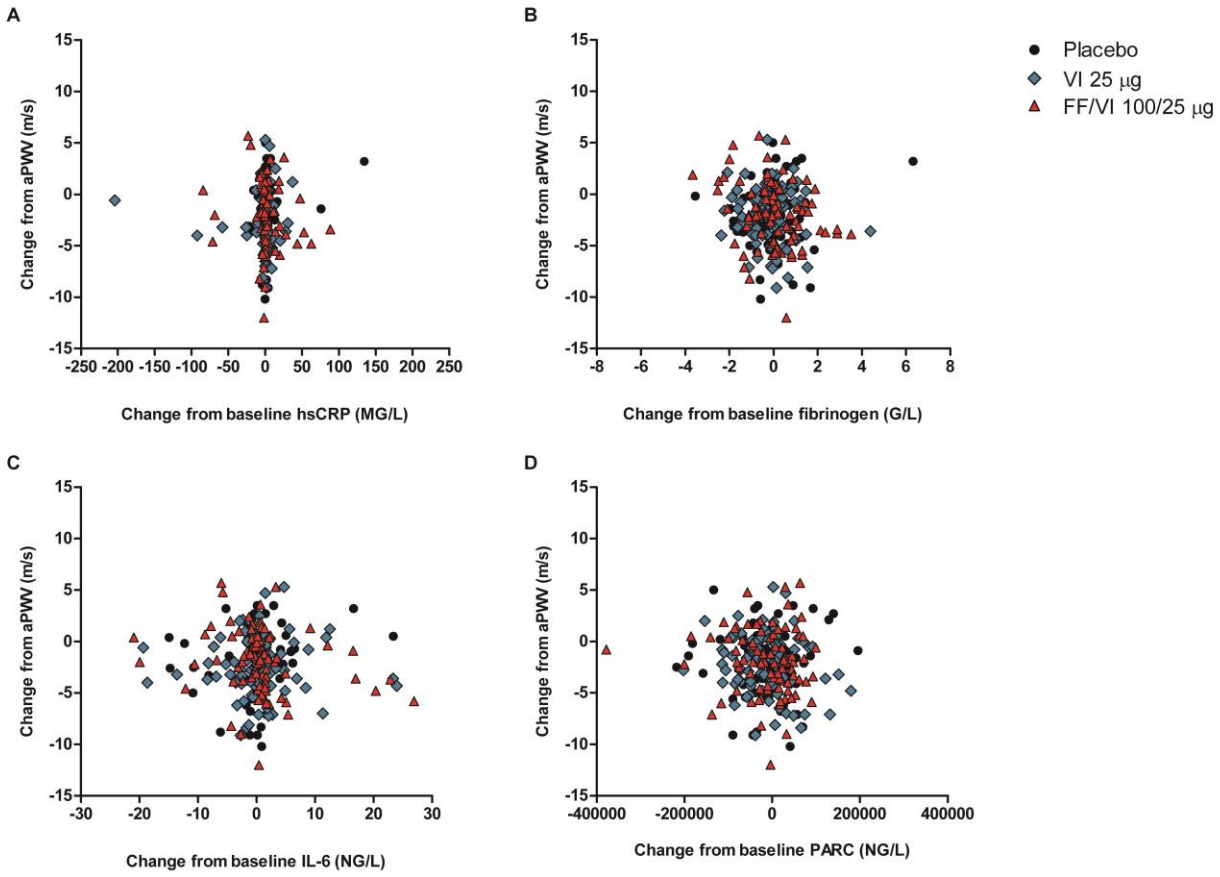
Exploratory analyses

Further planned analyses of the primary endpoint showed statistically significant treatment interactions on day 168 (at the 10% level of significance) for 7 of the 20 baseline characteristics analyzed, including aPWV (*P*=0.090), FEV_1 (L) (*P*=0.006), FEV_1 percentage predicted at screening (*P*=0.001), peripheral systolic BP (*P*=0.091), peripheral pulse pressure (*P*=0.097), Global Initiative for Chronic Obstructive Lung Disease patient group (*P*=0.019), and COPD maintenance treatment prior to the study (*P*=0.017).

To further investigate the interactions with each continuous covariate noted (except baseline aPWV), a treatment by covariate by day interaction was fitted with the covariate dichotomized at the median in order to evaluate whether there was an inconsistent treatment response for the primary endpoint (day 168). For baseline aPWV, separate analysis models were fitted to the subgroup with values above the median and to the subgroup with values below the median. The adjusted mean changes and treatment differences for each of the interactions and groupings did not show a consistent effect or clinically relevant trend, indicating the interactions were likely the result of random variation.

Biomarker Analyses

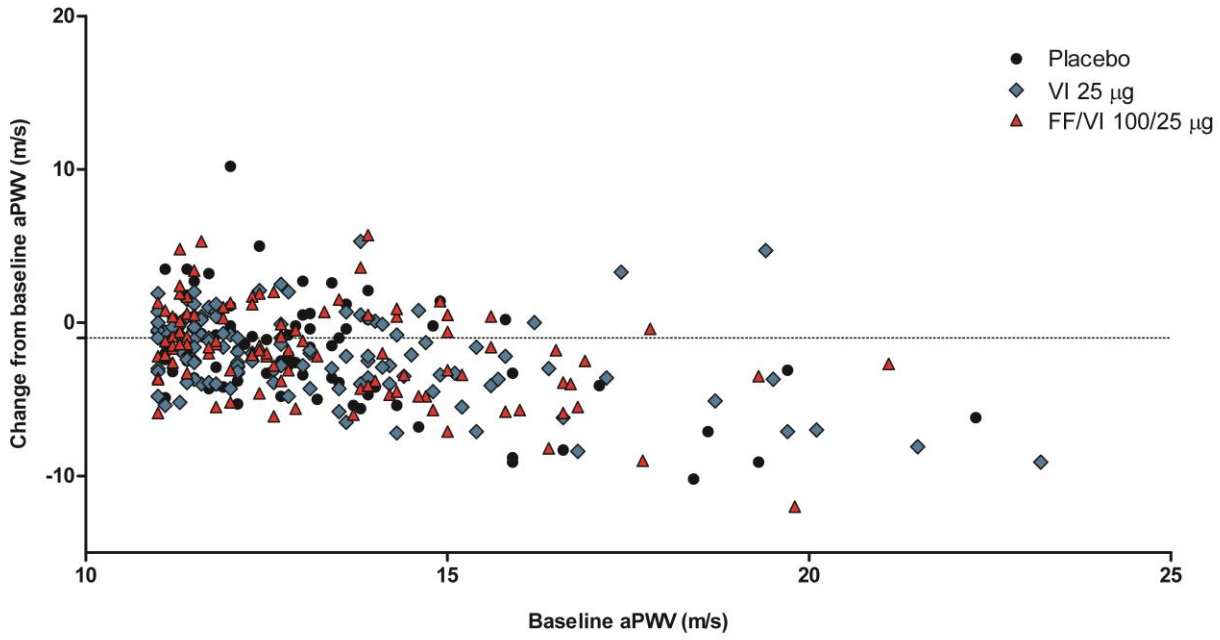
Supplementary Figure 1 Change from baseline on day 168 for biomarkers: A, hsCRP; B, Fibrinogen; C, IL-6; D, PARC; vs change from baseline in aPWV.



Abbreviations: aPWV, aortic pulse wave velocity; FF, fluticasone furoate; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin 6; PARC, pulmonary and activation-regulated chemokine; VI, vilanterol.

Post hoc analysis

Supplementary Figure 2 Change from baseline aPWV on day 168, versus baseline aPWV.



Abbreviations: aPWV, aortic pulse wave velocity; FF, fluticasone furoate; VI, vilanterol; response was defined as a reduction in aPWV of equal or more than 1m/s from baseline at day 168; non-response was defined as a reduction in aPWV less than 1m/s from baseline or an increase in aPWV from baseline at day 168, or a missing change from baseline in aPWV.