Efficacy and safety of fluticasone furoate/vilanterol (50/25mcg; 100/25 mcg; 200/25 mcg) in Asian patients with chronic obstructive pulmonary disease

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SUPPLEMENTAL MATERIAL/APPENDICES

Supplementary Appendix 1 Methods: Exclusion criteria

Exclusion criteria at the screening visit were as follows: pregnancy; current diagnosis of asthma or any other respiratory disorder, including α1-antitrypsin deficiency, as the underlying cause of COPD; an exacerbation requiring treatment with corticosteroids, antibiotics or other treatment prescribed by a physician in the 6 weeks prior to screening, or hospitalisation in the previous 12 weeks; lower respiratory tract infections requiring treatment with antibiotics in the previous 4 weeks; lung reduction surgery within the previous 12 months; use of long-term oxygen therapy >12 hours per day; medically unable to withhold albuterol or ipratropium bromide for 4 hours, or theophylline for 12 hours, prior to lung function test; participating in the acute phase of pulmonary rehabilitation in the previous 4 weeks or planning to enter the acute phase during the study. Clinically significant disease or abnormalities, that in the opinion of the investigator, would put safety of the patient at risk or affect efficacy or safety analysis. A history of hypersensitivity to any of the study medications including their excipients; a history of alcohol or drug abuse within the past 2 years; at risk of non-compliance; questionable validity of consent; prior use of study medication or other investigational drugs within 30 days of study entry or 5 half-lives of the investigational drug, whichever was longer; affiliation with any investigator or study centre.

Exclusion criteria at randomisation were: occurrence of an exacerbation or lower respiratory tract infection during the run-in period requiring treatment with systemic/oral corticosteroids and/or emergency treatment or hospitalisation; abnormal, clinically significant findings from 12-lead ECG or laboratory tests

performed at screening and pre-dose on the randomisation visit; failure to demonstrate adequate compliance with study procedures including taking the run-in medication.

Supplementary Appendix 2 Other permitted and prohibited concomitant medications.

Permitted non-COPD medications included: cardioselective beta-blockers (stable dose) and ophthalmic beta-blockers; antihistamines and nasal decongestants; over-the-counter cough suppressants (for ≤7days); intranasal sodium cromoglycate or nedocromil sodium; intranasal corticosteroids (stable daily dose for ≥4 weeks prior to screening and throughout the study); topical (≤1% hydrocortisone in strength) or ophthalmic corticosteroids; antibiotics that are not strong inhibitors of cytochrome P450 3A4 for treatment (≤14 days) of acute non-respiratory tract infections; influenza and/or pneumonia vaccination; tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs); diuretics; treatment(s) for smoking cessation; and all medications for other disorders as long as the dose remained constant wherever possible and their use was not expected to affect lung function.

Prohibited concomitant medications are summarised in the table below.

Prohibited concomitant medication	Timeframe of prohibition, prior to screening
Depot corticosteroids	12 weeks
Any other investigational drug	30 days (or 5 half lives, whichever was longer)
Systemic, oral, parenteral corticosteroids or cytochrome P450 3A4 strong inhibitors	6 weeks
ICS, ICS/LABA or antibiotics (for lower respiratory tract infection	4 weeks
Long-acting anticholinergics	1 week
Oral or inhaled LABAs; oral leukotriene inhibitors	48 hours
Inhaled sodium cromoglycate or nedocromil sodium	24 hours
Oral short-acting $beta_2$-agonists	12 hours
Ipratropium/albuterol (salbutamol) combination	4 hours

product	
Traditional or herbal medicines used for the treatment of COPD, including those with a known effect of bronchodilation; those with known effects on the HPA axis, heart rate and blood pressure, blood glucose and potassium levels; strong inhibitors of cytochrome P450 3A4; those with known effects on platelets and that could increase tendency to bleed	Prior to Visit 1 and at any time during the study

COPD = chronic obstructive pulmonary disease; HPA = hypothalamic-pituitary-adrenal; ICS = inhaled corticosteroid; LABA = long-acting $beta_2$ agonist.

Supplementary Appendix 3 Details of the international review board committee names and approval numbers

Investigator	Sub-investigator	Investigator no./centre no.	Description of research facility, hospital/institution, and address	Name of IEC/IRB committee, address, committee chair
China				
Cai, Shaoxi. PhD	Meng, Ying Zhao, Haijin	228043/094637	Nanfang Hospital, No 1838 Guangzhou Da dao bei Avenue, Guangzhou, Guangdong, 510515, China	Nanfang Hospital, Guangzhou Da dao bei Avenue, Guangzhou, Guangdong, 510515, China Chairperson: Zhang, Xun
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Chen, Ping	Ji, Binbin Wang, Yan Zhao, Haitao	010641/082323	General Hospital of Shenyang Military Command, No 83 Wenhua Road, Shenhe District, Shenyang, Liaoning, 110015, China	General Hospital of Shenyang Military Command, No 83 Wenhua Road, Shenhe District, Shenyang, Liaoning, 110015, China Chairperson: Ni, Yanjun

He, Bei	Mei, Jingjing Wu, Rui Yang, Wei	209698/082616	Peking University Third Hospital, No. 49, Garden North Road, Haidian District, Beijing, 100191, China	Peking University Third Hospital, No. 49, Garden North Road, Haidian District, Beijing, 100191, China Chairperson: Fan, Dongsheng
Kang, Jian	Hou, Gang Wang, Qiuyue	218708/083884	The First Hospital of China Medical University, No.155 Nanjing North Street, Heping District, Shenyang, Liaoning, 110001, China	The First Hospital of China Medical University, No.155 Nanjing North Street, Heping District, Shenyang, Liaoning, 110001, China Chairperson: Yu, Xiaosong
Lin, Yingxiang. MD	Lin, Yingxiang MD An, Li Bu, Xiaoning Liang, Lirong Lu, Yong Zhang, Hong	243715/094465	Beijing Chao-Yang Hospital, 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing, 100020, China	Beijing Chao-Yang Hospital, 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing, 100020, China Chairperson: Shen, Yanying
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Sun, Shenghua. MD	Tang, Wenxiang Xie, Lihua Yang, Honghui Zhan, Juan	225652/086709	The 3rd Xiangya Hospital, Central South University, Respiratory, No.138 Tongzipo Road, Changsha, 410013, China	The 3rd Xiangya Hospital, Central South University, No.138 Tongzipo Road, Changsha, 410013, China Chairperson: Lu, Jiexiang

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Wen, Fuqiang. MD	Chen, Lei Ou, Xuemei Yang, Ting	209697/087957	West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, 610041, China	West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, 610041, China Chairperson: Zeng, Zhi
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Wang, Chin-Chou. MD, MPH	Chao, Tung-Ying Chen, Yung-Che Chin, Chien-Hung Fang, Wen-Feng Leung, Sum-Yee Liu, Shih-Feng Su, Mao-Chang Tseng, Chia-Cheng Wang, Yi-Hsi Wu, Chao-Chien	214397/081703	Chang Gung Memorial Hospital-Kaohsiung Medical Center, Division of Pulmonary & Critical Care Medicine, 123 Dapi Road, Niaosong District, Kaohsiung, 83301, Taiwan	Chang Gung Medical Foundation, 199 Tung Hwa North Road, Taipei, 10507, Taiwan Chairperson: Hsieh, Tsang-Tang

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All centres participated in the study under the US IND. [a]No patients randomised.

Supplementary Appendix 4 Statistical analysis used for 'other' efficacy endpoints and safety analyses

COPD symptoms were scored as follows: breathlessness on a scale of 0 (not breathless at rest or exertion) to 4 (breathless), cough scale 0 (none) to 3 (severe), and sputum production scale 0 (none) to 3 (severe). Total symptom-free 24 hour periods were defined as days on which cough, sputum and breathlessness were all scored as zero. The percentage of symptom-free 24 hour periods (cough, sputum, breathlessness, and combined total) during each month of treatment, over the 24-week treatment period and as change from baseline (percentage of symptom-free 24 hour periods during the run-in) were summarised. Mean symptom scores were summarised in the same way, and the percentage of night-time awakenings (requiring rescue use) free days were summarised. The mean symptom score averaged over the entire 24-week treatment period was analysed for cough, sputum and breathlessness separately, mean night-time awakenings requiring rescue use, percentage of rescue-free 24 hour periods, and mean rescue use were summarised and analysed using an analysis of covariance (ANCOVA) model with covariates of baseline symptom score, smoking status at screening and treatment. In addition, a sensitivity analysis was performed for those patients who had at least one night-time awakening during baseline.

The incidence of AEs, COPD exacerbations and pneumonia, vital signs and ECG parameters, oropharyngeal examination data, urine cortisol and data for clinical laboratory parameters were summarised. All actual and change from baseline values for pulse rate, systolic and diastolic blood pressure were summarised by treatment using summary statistics together with maximum (pulse rate and systolic blood pressure) or minimum (diastolic blood pressure) post baseline values, including any recorded at scheduled, unscheduled and early withdrawal visits. From treatment day 2, pre-dose pulse rate, systolic and diastolic blood pressure were analysed using a repeated measures model, with a repeated effect of day within each patient and an associated unstructured covariance structure. For each endpoint, the model was fitted with a response variable of change from baseline value. The explanatory variables were treatment group, smoking status at screening, baseline (pulse rate, systolic or diastolic blood pressure) and day (as a categorical variable), in addition to day by baseline and day by treatment interaction terms. In addition, the 10 min post-dose assessment made on Day 1 was analysed using an ANCOVA model with treatment group, smoking status and baseline pulse rate, systolic blood pressure or diastolic blood pressure as the explanatory variables. Actual and change from baseline values for QTc(F), QTc(B) and heart rate were summarised by treatment using summary statistics together with maximum post baseline values, including any recorded at scheduled, unscheduled and early withdrawal visits.

Pre-dose QTc(F) and heart rate were analysed using a repeated measures model as described for the primary endpoint. In addition, the 10 minute post-dose assessment made on Day 1 was analysed using an ANCOVA, using the same model as described for vital signs. 24 hour UC excretion was log transformed, summarised and analysed for the UC population. Data were analysed using an ANCOVA model with covariates of log baseline, smoking status and treatment.

Total CAT scores and total CAT score change from baseline values at Weeks 12 and 24 were summarised.

Supplementary Table 1 Change from baseline and responder analysis for CRQ-SAS dyspnoea domain at Week 24 (Day 168) (ITT population).

	Placebo (*N* = 162)	FF/VI 50/25 (*N* = 160)	FF/VI 100/25 (*N* = 161)	FF/VI 200/25 (*N* = 160)
Mean CRQ-SAS Dyspnea score				
n[a]	151	144	154	151
b[b]	128	134	136	132
LS mean (SE)	5.55 (0.081)	5.77 (0.080)	5.89 (0.079)	5.83 (0.080)
LS mean change (SE)	0.09 (0.081)	0.30 (0.080)	0.43 (0.079)	0.37 (0.080)
Difference vs placebo (95% CI)		0.21 (–0.01, 0.43)	0.34 (0.12, 0.56)	0.27 (0.05, 0.50)
p value		0.064	0.003	0.016
Responder analysis				
n	162	157	160	159
Responder[c], *n* (%)	56 (35)	61 (39)	60 (38)[d]	64 (40)
Non-responder[c], *n* (%)	106 (65)	96 (61)	100 (63)[d]	95 (60)
Treatment vs placebo odds ratio, 95% CI		1.22 (0.73, 2.04)	1.43 (0.86, 2.39)	1.52 (0.91, 2.52)
p value		0.438	0.166	0.108

CI = confidence interval; CRQ-SAS = Chronic Respiratory Questionnaire - Self-Administered Standardized; FF = fluticasone furoate; ITT = intent-to-treat; LS = least squares; SE = standard error; VI = vilanterol.

[a]Number of patients with analysable data for one or more time points; [b]Number of patients with analysable data at the given time points; [c]Patients were classified as a responder if they had a change from baseline in CRQ-SAS Dyspnea domain ≥0.5; [d]Data does not add up to 100% due to rounding.

Supplementary Table 2 Mean change from baseline in CRQ-SAS other domains and total score at Week 24 (Day 168) (ITT population).

	Placebo (*N* = 162)	FF/VI 50/25 (*N* = 160)	FF/VI 100/25 (*N* = 161)	FF/VI 200/25 (*N* = 160)
Fatigue domain				
n[a]	151	147	155	151
n[b]	128	137	138	133
LS mean (SE)	4.69 (0.071)	4.88 (0.069)	5.06 (0.068)	5.02 (0.069)
LS mean change (SE)	–0.01 (0.071)	0.17 (0.069)	0.36 (0.068)	0.31 (0.069)
Difference vs placebo (95% CI)		0.18 (–0.01, 0.38)	0.37 (0.18, 0.56)	0.32 (0.13, 0.52)
p value		0.062	<0.001	0.001
Emotional function domain				
n[a]	151	147	155	151
n[b]	128	137	138	133
LS mean (SE)	5.01 (0.076)	5.34 (0.074)	5.47 (0.073)	5.39 (0.074)
LS mean change (SE)	–0.14 (0.076)	0.19 (0.074)	0.32 (0.073)	0.24 (0.074)
Difference vs placebo (95% CI)		0.33 (0.12, 0.54)	0.45 (0.25, 0.66)	0.37 (0.17, 0.58)
p value		0.002	<0.001	<0.001
Mastery domain				
n[a]	151	147	155	151
n[b]	128	137	138	133
LS mean (SE)	5.04 (0.080)	5.27 (0.078)	5.36 (0.078)	5.33 (0.079)
LS mean change (SE)	0.03 (0.080)	0.26 (0.078)	0.35 (0.078)	0.32 (0.079)
Difference vs placebo (95% CI)		0.23 (0.01, 0.45)	0.32 (0.10, 0.54)	0.29 (0.07, 0.51)
p value		0.038	0.004	0.010

Total score				
n[a]	151	147	155	151
n[b]	128	137	138	133
LS mean (SE)	5.08 (0.064)	5.34 (0.062)	5.46 (0.062)	5.40 (0.063)
LS mean change (SE)	–0.02 (0.064)	0.24 (0.062)	0.35 (0.062)	0.30 (0.063)
Difference vs placebo (95% CI)		0.26 (0.08, 0.43)	0.37 (0.20, 0.55)	0.32 (0.14, 0.49)
p value		0.004	<0.001	<0.001

CI = confidence interval; CRQ-SAS = Chronic Respiratory Questionnaire - Self-Administered Standardized; FF = fluticasone furoate; LS = least squares; ITT = intent-to-treat; SE = standard error; VI = vilanterol.

[a]Number of patients with analysable data for one or more time points; [b]Number of patients with analysable data at the given time points.

Supplementary Table 3 Summary of on-treatment adverse events leading to permanent discontinuation of study drug or withdrawal from the study (ITT population).

System Organ Class preferred term	Placebo (*N* = 162)	FF/VI 50/25 (*N* = 160)	FF/VI 100/25 (*N* = 161)	FF/VI 200/25 (*N* = 160)
Any event	15 (9)	6 (4)	8 (5)	18 (11)
Respiratory, thoracic and mediastinal disorders	9 (6)	2 (1)	3 (2)	9 (6)
Infections and infestations	4 (2)	2 (1)	2 (1)	5 (3)
Cardiac disorders	2 (1)	1 (<1)	0	2 (1)
Injury, poisoning and procedural complications	1 (<1)	0	1 (<1)	1 (<1)
Nervous system disorders	1 (<1)	0	0	2 (1)
Gastrointestinal disorders	2 (1)	0	0	0
General disorders and administration site conditions	2 (1)	0	0	0
Metabolism and nutrition disorders	1 (<1)	0	0	1 (<1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (<1)	1 (<1)
Skin and subcutaneous tissue disorders	1 (<1)	1 (<1)	0	0
Blood and lymphatic system disorders	0	0	0	1 (<1)
Renal and urinary disorders	0	0	1 (<1)	0
Reproductive system and breast disorders	0	0	1 (<1)	0
Vascular disorders	0	0	0	1 (<1)

Data are presented as n (%).

FF = fluticasone furoate; ITT = intent-to-treat; VI = vilanterol.

Supplementary Table 4 Summary of on-treatment exacerbations and pneumonia (ITT population)

	Placebo (*N* = 162)	FF/VI 50/25 (*N* = 160)	FF/VI 100/25 (*N* = 161)	FF/VI 200/25 (*N* = 160)
On-treatment exacerbations				
Patients with one or more exacerbation, *n* (%)	22 (14)	20 (13)	19 (12)	18 (11)
Severity of exacerbation, *n* (%)				
Moderate	12 (43)	10 (42)	12 (52)	8 (42)
Severe	7 (25)	2 (8)	3 (13)	8 (42)
Outcome				
Resolved[a]	26 (93)	24 (100)	21 (91)	18 (95)
Fatal	0	0	0	0
Not resolved	2 (7)	0	2 (9)	1 (5)[b]
On-treatment pneumonia				
Patients who had at least one:				
Pneumonia, *n* (%)	4 (2)	2 (1)	1 (<1)	5 (3)
Pneumonia recorded as SAE, *n* (%)	3 (75)	2 (100)	0	2 (40)
Fatal pneumonia, *n* (%)	1 (25)	0	0	1(20)

FF = fluticasone furoate; ITT = intent-to-treat; SAE = serious adverse event; VI = vilanterol.

[a]All exacerbations that were recorded as SAEs had an outcome of 'resolved' at the end of the study except for one in the FF/VI 200/25 mcg treatment group (see footnote b). [b]The patient had an exacerbation recorded as a SAE with an outcome recorded as 'recovering/resolving' at the end of the study, which has been summarised as 'not resolved'.

Supplementary Table 5 Pre-dose vital signs assessments and ECG heart rate at Week 24 (Day 168) (ITT population).

	Placebo (*N* = 162)	FF/VI 50/25 (*N* = 160)	FF/VI 100/25 (*N* = 161)	FF/VI 200/25 (*N* = 160)
Statistical analysis of pre-dose pulse rate (bpm)				
n[a]	162	158	160	159
n[b]	130	137	138	134
LS mean (SE)	76.2 (0.82)	76.2 (0.80)	76.3 (0.80)	76.6 (0.81)
LS mean change (SE)	–0.4 (0.82)	–0.4 (0.80)	–0.3 (0.80)	0.0 (0.81)
Difference vs placebo	–	0.1	0.2	0.4
95% CI	–	(–2.2, 2.3)	(–2.1, 2.4)	(–1.9, 2.7)
p value	–	0.962	0.895	0.719
Statistical analysis of pre-dose systolic blood pressure (mmHg)				
n[a]	162	158	160	159
n[b]	130	137	138	134
LS mean (SE)	128.5 (0.95)	128.1 (0.93)	128.3 (0.92)	128.9 (0.94)
LS mean change (SE)	–0.6 (0.95)	–0.9 (0.93)	–0.8 (0.92)	–0.1 (0.94)
Difference vs placebo	–	–0.4	–0.2	0.4
95% CI	–	(–3.0, 2.2)	(–2.8, 2.4)	(–2.2, 3.1)
p value	–	0.771	0.877	0.739
Statistical analysis of pre-dose diastolic blood pressure (mmHg)				
n[a]	162	158	160	159
n[b]	130	137	138	134
LS mean (SE)	76.8 (0.65)	76.6 (0.63)	76.2 (0.63)	77.1 (0.64)
LS mean change (SE)	–1.1 (0.65)	–1.3 (0.63)	–1.7 (0.63)	–0.8 (6.4)
Difference vs placebo	–	–0.2	–0.6	0.3
95% CI	–	(–2.0, 1.6)	(–2.4, 1.2)	(–1.5, 2.1)
p value	–	0.832	0.492	0.716

Statistical analysis of pre-dose QTc(F) (msec)				
n[a]	138	142	146	147
n[b]	130	137	138	134
LS mean (SE)	409.0 (1.45)	410.5 (1.41)	409.7 (1.41)	408.8 (1.43)
LS mean change (SE)	0.4 (1.45)	1.9 (1.41)	1.1 (1.41)	0.3 (1.43)
Difference vs placebo	–	1.5	0.7	–0.2
95% CI	–	(–2.5, 5.4)	(–3.3, 4.7)	(–4.2, 3.8)
p value	–	0.475	0.725	0.933
Statistical analysis of pre-dose ECG heart rate (bpm)				
n[a]	138	142	146	147
n[b]	130	137	138	134
LS mean (SE)	72.5 (0.87)	72.5 (0.85)	73.4 (0.84)	72.4 (0.85)
LS mean change (SE)	–1.5 (0.87)	–1.5 (0.85)	–0.6 (0.84)	–1.6 (0.85)
Difference vs placebo	–	0.0	0.9	–0.1
95% CI	–	(–2.4, 2.3)	(–1.5, 3.2)	(–2.5, 2.2)
p value	–	0.969	0.482	0.906

CI = confidence interval; ECG = electrocardiogram; bpm = beats per minute; FF = fluticasone furoate; ITT = intent-to-treat; LS = least-squares; QTc(F) = QT corrected using Fridericia's formula; SE = standard error; VI = vilanterol.

[a]Number of subjects with analysable data for one or more time points. [b]Number of subjects with analysable data at the given time points.