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Population pharmacokinetics of inhaled fluticasone furoate and vilanterol in adult and adolescent patients with asthma

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[†]The lead author of this manuscript, Ann Allen, sadly passed away after the paper was developed. We, the co-authors, accept responsibility for including Ann's name in the authorship without her formal written consent being obtained.

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Abstract. Objectives: Population pharmacokinetic (PK) methods were used to characterize the PK of fluticasone furoate (FF) and vilanterol (VI) in patients with asthma following once daily inhaled FF/VI and FF and to identify significant covariates that impact the PK. Materials and methods: Four of the five studies in the meta-analysis were conducted in patients with asthma (> 90%), the fifth in healthy subjects. FF data were described by a two-compartment model with first order absorption and elimination. VI data were described by a three-compartment model with zero-order absorption and first order elimination. Results: Race was a significant covariate on inhaled clearance (CL/F) of FF PK. AUC₍₀₋₂₄₎ for Asian patients was on average 33 – 53% higher than for non-Asians. Race was also a significant covariate on VI PK, with lower (81%) central volume of distribution (Vc/F) for Asian patients compared with non-Asians; VI C_{max} was 220 – 287% higher in Asian patients. Treatment (combination or monotherapy), predicted percentage FEV₁, and other demographic variables did not influence the PK of FF or VI. Conclusions: Combination of FF/VI does not appear to affect the PK of FF or VI. The effect of race on PK of FF or VI does not have impact on dosage adjustments for FF/VI in East Asian patients with asthma.

Introduction

Fluticasone furoate (FF), a novel glucocorticoid, and vilanterol (VI), a potent, long-acting, β_2 -receptor agonist (LABA), are being developed in combination as a once-daily (q.d.), inhaled treatment for asthma and chronic obstructive pulmonary

disease (COPD). FF/VI combination is approved maintenance treatment for COPD as BREO™ ELLIPTA™¹ in the USA and for COPD and asthma as RELVAR™ ELLIPTA™ in the EU. FF monotherapy (Arnuity™ ELLIPTA™) is approved for asthma in the USA. VI monotherapy is being developed and has been approved in combination with a novel, long-acting, muscarinic antagonist for COPD (ANORO™ ELLIPTA™). The pharmacokinetics (PK), pharmacodynamics, and safety profiles of FF/VI have been described in healthy subjects, asthma and COPD patients [1, 2]; q.d. administration of FF/VI is effective at improving lung function in patients with COPD [3, 4] or asthma [5, 6, 7, 8].

FF and VI PK after q.d. administration of FF/VI (doses ranging from 50/25 to 800/100 μ g) have been determined in phase I/II studies. These were limited by being generally conducted in relatively small populations and used non-compartmental PK methods. Despite the use of sensitive analytical methods (lower limit of quantification (LLQ): 10 pg/mL), a large proportion of data were censored. Integration of PK concentration-time data from phase III studies conducted in target patient populations, and using model-based population PK approaches, allows adequate characterization of the PK profile and the influence of potential covariates, for example demographics and baseline characteristics as sources of PK variability in asthma subjects. The population PK approach can take into account the non-quantifiable data [9]. Therefore, we present a meta-analysis using pooled concentration-time data from several clinical studies in adults and adolescents to characterize the FF and

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Table 1. Summary of studies included in population PK meta-analysis.

Study ID (Protocol no.; NCT no.)	Design (phase)	Disease	Number of patients, ITT (M/F)	Formulation(s) Device	Nominal doses (μg) ^a Frequency	Treatment duration PK sampling occasion	PK sampling schedule
Study 1 (HZA106827; NCT01165138)	Multicenter, randomized (1:1:1), double-blind, placebo-controlled, parallel-group (phase III)	Asthma	406 (164/242)	FF/VI FF Placebo DPI	100/25 μg 100 μg Placebo q.d. (PM)	12 weeks Weeks 8 and 12	Pre-dose and post-dose 5 – 15 minutes, 1 – 1.5 hours
Study 2 (HZA106829; NCT01134042)	Multicenter, randomized (1:1:1), double-blind, double-dummy, active-controlled, parallel-group (phase III)	Asthma	391 (162/229)	FF/VI FF FP DPI	200/25 μg 200 μg q.d. (PM)	24 weeks Weeks 12 and 24	Pre-dose and post-dose 5 – 15 minutes, 1 – 1.5 hours
Study 3 (HZA106839; NCT01018186)	Multicenter, randomized (2:2:1), double-blind, double-dummy, active-controlled, parallel-group (phase III)	Asthma	403 (149/254)	FF/VI FP DPI	100/25, 200/25 μg q.d. (PM)	52 weeks Weeks 2, 12, and 52	Pre-dose and post-dose 5 – 30 minutes on Week 2, pre-dose, and post-dose 5 – 30 minutes on Week 12 and post-dose 5 – 30 minutes and 45 minutes – 1.5 hours on Week 52
Study 4 (HZA106851; NCT01086410)	Multicenter, randomized (4:4:4:1), placebo-controlled, double-dummy and active-controlled, parallel-group (phase III)	Asthma	185 (98/87)	FF/VI Placebo Prednisolone DPI	100/25, 200/25 μg Placebo q.d. (PM)	6 weeks (prednisolone 1 week) Day 42	Pre-dose and post-dose 5, 10, 30 minutes, 1, 2, 4, 8, 12, 24 hours
Study 5 (HZA102936; NCT01209026)	Randomized (1:1:1:1:1), placebo-controlled, 4-way crossover (phase I)	Healthy subjects	85 (49/36)	FF/VI Placebo inhaled Moxifloxacin oral DPI	200/25, 800/100 μg Placebo inhaled 400 mg q.d. (AM)	1 week Day 7	Pre-dose and post-dose 5, 15, 30 minutes, 1, 2, 4, 9, 12, 16, 20, 24 hours

^aEmitted doses were 92/22 μg , 184/22 μg , and 736/88 μg for FF/VI treatments; 92 μg and 184 μg for FF treatments. Asthma patients had a pre-bronchodilator FEV₁ of 40 – 90% of the predicted normal value ($\geq 50\%$ for studies 3 and 4) and ≥ 200 mL reversibility of FEV₁ within 10 – 40 minutes following 2 – 4 inhalations of albuterol/salbutamol solution. Predicted FEV₁ was based upon NHANES III [16]. Caucasian equations were used unless a patient was recorded as having Hispanic Latino ethnicity or African/American heritage, in which case the Mexican/American or African/American equations were used, as appropriate. If patients were recorded as being of Asian race, then the Asian adjustment was used [17]. All asthma patients were using an ICS with or without a LABA for at least 4 weeks prior to the first study visit (with exception of study 4 where inhaled ICS and LABA were prohibited for the 4 weeks prior to visit 1). DPI = dry powder inhaler; FEV₁ = forced expiratory volume in the first second; FF = fluticasone propionate; FP = fluticasone furoate; ICS = inhaled corticosteroid; ITT = intent-to-treat; LABA = long-acting, β_2 -receptor agonist; M/F = male/female; NHANES = National Health and Nutrition Examination Survey; PK = pharmacokinetic; q.d. = once daily; VI = vilanterol.

VI PK profiles after q.d. inhaled FF/VI or FF administration and to identify significant covariates that impact PK in patients with asthma.

Methods

Study design

Four phase III multicenter, randomized, double-blind, placebo-controlled studies in patients with asthma were included in the meta-analyses (Table 1). Demographics, predicted FEV₁, and inclusion/exclusion criteria were generally similar, enabling the data to be combined. A further phase I randomized, placebo-controlled investigation (study 5) in healthy subjects with intense PK sampling, was included in both meta-analyses to support population PK modeling and stabilize parameter estimation (Table 1). This study included a supratherapeutic FF/VI dose (800/100 µg) providing robust definition of FF and VI PK profiles. All treatment doses and durations are detailed in Table 1. All blinded study medication was delivered using the ELLIPTA™ dry powder inhaler.

Studies 1–4 recruited patients (aged ≥ 12 years) with documented asthma clinical history at screening; study 5 included healthy male or female subjects (aged 18–65 years). All subjects gave written informed consent prior to any study-related procedures and the protocols were approved by the appropriate institutional review boards and conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki.

PK sample collection and bioanalysis

PK samples were collected at nominal times relative to the FF/VI, FF, or VI dosing time (Table 1). An intense sampling approach was used in two studies (4 and 5). The larger phase III studies (1, 2, and 3) had sparse PK samples collected pre-dose and within specific collection windows.

Plasma samples (150 µL aliquot) were analyzed for FF by solid phase extraction (using [¹³C ²H₃]-GW685698 as internal standard) followed by high performance liquid chromatography (HPLC) with tandem mass

spectrometry (MS) using an Applied Biosystems API-5000 (Foster City, CA, USA). A gradient system using 5 mM ammonium formate and methanol was run with column ACE 50 *2.1 mm, C18 3 µm, Hichrom Ltd. (Reading, UK) running at 45 °C. The ion transition for FF was m/z 539 to 313. The FF assay validation range was 10–1,000 pg/mL. Within-run precision, between-run precision, and bias were all ≤ 14.3% over the assay range; the FF LLQ was 10 pg/mL.

Plasma samples (200 µL aliquot) were analyzed for VI by solid phase extraction (using [²H₁₂]-GW642444 as internal standard) followed by HPLC with tandem MS using an Applied Biosystems API-5000. A gradient system using 10 mM ammonium formate containing 0.1% formic acid and acetonitrile containing 0.1% formic acid was run with column 50 × 2.1 mm i.d. Hyper-sil Gold, 3 µm, Thermo Scientific running at 50 °C. The ion transition for VI was m/z 486 to 159. The VI assay validation range was 10–10,000 pg/mL. Within-run precision, between-run precision and bias were all ≤ 14.4% over the assay range; the VI LLQ was 10 pg/mL.

Where reported concentrations were above the higher limit of quantification, plasma samples were diluted as appropriate, prior to re-analysis to provide concentrations within the validated range. Quality controls (QC) prepared at three different concentrations were analyzed with each sample batch against separately prepared calibration standards to assess the day-to-day assay performance. QC results met the accepted criteria of no more than 1/3 of the QC results deviating from the nominal concentration by > 15%, with at least one QC result acceptable at each concentration.

Population modeling

All data preparation and presentations were performed using R® [10]. The FF and VI concentration-time data were modeled separately. Nonlinear mixed effects modeling of the sparse and rich data was conducted using NONMEM v7.1.2 (ICON, Ellicott City, MA, USA). The method selected for minimization was Stochastic Approximation Expectation Maximization with interaction

for both analyses. Given the sparse nature of the sampling and the high proportion of records reporting FF and VI concentrations below the LLQ (10 pg/mL or 20 pg/mL), particularly at the lower FF doses in the phase III studies and beyond 2 hours post-dose following VI, addition of more extensive sampling over 24 hours post-dose from healthy subjects (study 5) at a higher FF/VI dose (800/100 µg) was required to achieve an appropriate structural model to describe the data. As a consequence of the large extent of non-quantifiable data in each dataset, it was necessary to use a methodology that maximized the likelihood for all the data, treating those data below the LLQ as non-missing. Data were analyzed using the M3 methodology with the F_FLAG option and PHI function available in NONMEM v7 [9].

Supporting application interfaces for data handling, exploratory diagnostics, and simulation included Xpose v4 [10], R® and WinNonlin 5.2 (Pharsight, Mountain View, CA, USA).

Covariate analysis

The covariates considered for evaluation included population (patients with asthma or healthy subjects), age, weight, height, sex, ethnicity (Hispanic or Latino/non-Hispanic or Latino), race, BMI, % predicted FEV₁, treatment (combination or monotherapy) and study. Due to limited numbers in some race categories, “RACE” was grouped as: RACE = 1 – White Caucasian; RACE = 2 – East Asian, Japanese, South East Asian; RACE = 3 – African American/African, White Arabic, American Indian/Native Alaskan and “Other”.

Plots of inter-subject variability (ETA) vs. each covariate were used to select potential covariates for evaluation in the FF and VI PK models. Potentially significant covariates identified from the plots were then individually included on the fixed effect parameters in the base models. If the updated model had a lower objective function (OFV; > 3.84 points for χ^2 -distribution with one degree of freedom), that covariate was included. Next, all significant covariates were added to the base model. Once the full model had been defined, the significance of each covariate was tested individually by removal one at a time from the full model.

For VI, each potentially significant covariate identified was individually included on the fixed effect parameters in the base model. The covariate with the highest correlation was added to the base model to build the first intermediate base model. Next, the remaining significant covariates were individually added to the first intermediate model. The covariate with the highest correlation was added to the first intermediate model to form the second intermediate model. This process continued until there were no further significant covariates to be added and a full model had been identified.

The model improvement was evaluated based on goodness-of-fit criteria such as reduction in the OFV, agreement between observed and predicted concentration values, and reduction in the pattern of conditional weighted residuals (see Online Supplement for further detail).

Model evaluation

A visual predictive check (VPC) procedure [11] was used to assess the adequacy of the final models as follows: at least 200 replicates for the original dataset were simulated, based on the parameter estimates of the final models; 95% prediction intervals on the simulated datasets were computed. The observed plasma concentration-time data were plotted on the prediction interval to visually assess concordance between simulated and observed data. In addition, the observed proportion of the data below LLQ (BLQ) was plotted with the model predicted proportion of the BLQ data to visually assess the concordance between simulated and observed BLQ data.

Model predicted systemic exposure

Individual AUC_(0–24) was derived as the ratio of nominal dose and individual post-hoc estimate of inhaled clearance (CL/F) from the final population PK model. Concentration-time profiles were simulated using parameter estimates from the final models to provide estimates for C_{max} for each subject.

Table 2. Demographic characteristics.

Demographics	FF dataset n = 1,295	VI dataset n = 932
Population, n (%)		
Patients with asthma	1,213 (94)	856 (92)
Healthy subjects	82 (6)	76 (8)
Median age, years (range)	42.0 (12 – 84)	41.0 (12 – 82)
Sex, n (%)		
Female	747 (58)	532 (57)
Male	548 (42)	400 (43)
Body mass index (kg/m ²), mean (range)	26.86 (15.40 – 55.30)	26.59 (15.4 – 51.6)
Mean height, cm (range)	168 (132 – 198)	168 (132 – 196)
Mean weight, kg (range)	75.9 (27.0 – 150.5)	75.0 (27.0 – 149.1)
Ethnicity, n (%)		
Hispanic, Latino	52 (4)	42 (5)
Not Hispanic, Latino	1,243 (96)	890 (95)
Race, n (%)		
White – White/Caucasian/European heritage	1,021 (79)	714 (77)
African American/African heritage	94 (7)	67 (7)
Asian – East Asian heritage	1 (< 1)	1 (< 1)
Asian – Central/South Asian heritage	9 (1)	8 (< 1)
Asian – Japanese heritage	50 (4)	27 (3)
Asian – South East Asian heritage	104 (8)	104 (11)
American Indian/Native Alaskan	2 (< 1)	1 (< 1)
White – Arabic/North African	6 (< 1)	4 (< 1)
Other	8 (1)	6 (1)
Mean predicted FEV ₁ (asthma population), % (range)	80.1 (49.0 – 129.0)	78.5 (49.0 – 129.0)

FEV₁ = forced expiratory volume in one second; FF = fluticasone furoate; VI = vilanterol.

Results

Demographics and characteristics

Demographic and baseline characteristics are summarized in Table 2. Most subjects had asthma (94% for FF, 92% for VI). The FF dataset comprised 9,247 observations from 1,295 subjects and the VI dataset comprised 6,934 observations from 932 subjects. There were ~30% and 56% of samples reported as BLQ for FF (LLQ 10 pg/mL) and VI (LLQ 10 pg/mL), respectively. Pre-dose (trough; C_τ) FF concentrations were quantifiable ($\geq$ LLQ 10 pg/mL) in $\leq$ 34% of samples from patients with asthma following FF 100 µg or FF/VI 100/25 µg. At the higher FF dose (FF 200 µg or FF 200/25 µg) there were more quantifiable data at C_τ, with at least 47% of samples being greater than the LLQ. FF was quantifiable in most healthy subjects at all timepoints after FF/VI 200/25 µg and 800/100 µg. Following FF/VI 100/25 or 200/25, $\leq$ 21% of VI samples were quantifiable at pre-dose.

FF PK model development

Based on the observed concentration-time profiles (Figure 1) and initial model building, a two-compartment linear model with first order absorption and first order elimination was evaluated. An additive residual error model was selected. Although the model converged with a proportional residual error model, the covariance matrix could not be obtained. A two-compartment linear model with first order absorption and first order elimination (ADVAN4, TRANS4) was found to describe the FF concentration-time data significantly better than a one-compartment model. However, it was not possible to obtain the covariance matrix when estimating all parameters and hence the volume of central compartment (V₂/F) was fixed to 0.225 and inter-compartmental clearance (Q/F) was fixed to 5.67 based on estimates from previous modeling work (personal communication).

Graphical exploration using the individual ETAs from the base model against covariates indicated that population (patients with

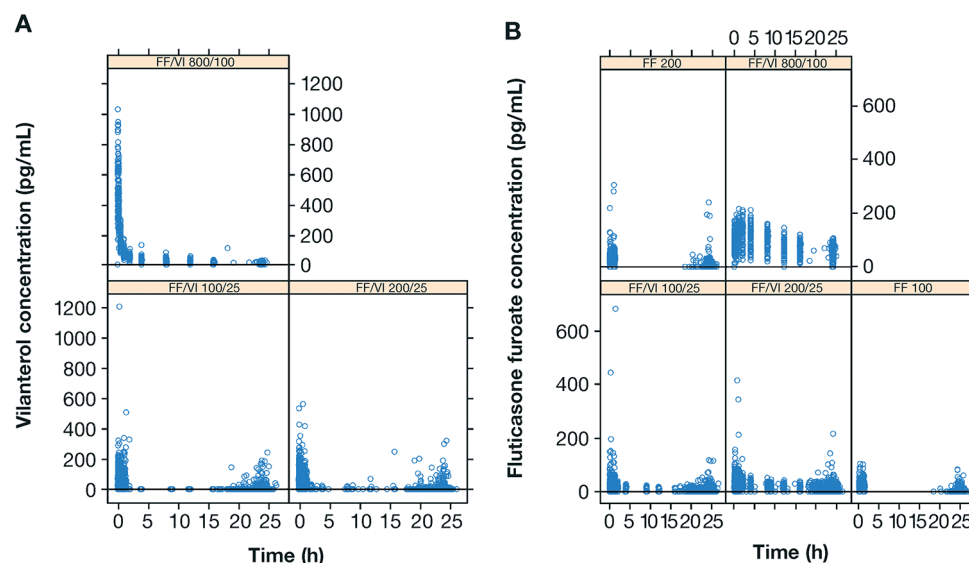


Figure 1. Concentrations relative to time of last dose following FF/VI (100/25, 200/25, and 800/100 μ g) and FF (100 and 200 μ g) to patients with asthma (studies 1, 2, 3, and 4) and healthy subjects (study 5) for (A) FF and (B) VI.

Table 3. Final FF PK model: log-transformed and untransformed parameter estimates.

Parameter	Ln estimate (95% CI)	Estimate (95% CI)	RSE, %
CL/F (RACE = 1 and 3)	5.21 (5.16 – 5.26)	183 (174 – 192)	0.476
Effect of RACE = 2 on CL/F	–0.331 (–0.451 – –0.211)	0.718 (0.637 – 0.810)	18.6
V2/F, L	0.225 FIXED	1.25 FIXED	FIXED
Q/F, L/h	5.67 FIXED	290 FIXED	FIXED
V3/F, L	5.14 (4.91 – 5.37)	171 (136, 215)	3.20
KA, h ^{–1}	–2.96 (–3.02 – –2.90)	0.0518 (0.0488 – 0.0550)	1.06

CI = confidence interval; CL/F = inhaled clearance; KA = absorption rate constant; Q/F = intercompartmental clearances; RSE = relative standard error; V2/F = volume of central compartment; V3/F = volume of peripheral compartment. RACE = 1 – White Caucasian; RACE = 2 – East Asian, Japanese, South East Asian; RACE = 3 – African American, Asian Central, White Arabic, American Indian/Native Alaskan, “Other”.

asthma or healthy subjects) and race category appeared influential on CL/F; no other covariates seemed to have any influence on all ETAs. Population and race were each included individually as covariates on CL/F. Including race category on CL/F (RACE = 2 vs. other race categories) resulted in a significant reduction in the OFV ($\Delta = 28$) compared with the base model. Inclusion of population on CL/F in the base model did not result in a significant OFV reduction ($\Delta < 6.64$). Therefore, only the race category was included in the model, and it was determined as the final model. The parameter estimates for the final model are presented in Table 3. All fixed effect parameters (θ s) were estimated with reasonable precision (%RSE < 20%). Inter-individual variances (exponential model) were

estimated with reasonable precision (%RSE $\leq 43\%$). The goodness-of-fit plot for the final model is presented in Figure 2 and the final model appears to provide a reasonable prediction of FF plasma concentrations.

For patient/subjects categorized as RACE = 2 (East Asian, Japanese, South East Asian), the typical value of CL/F was lower vs. white Caucasian (183 and 131 L/h, respectively), resulting in estimates of FF AUC_(0–24) being on average 33 – 53% higher for Asians compared with other racial groups (Table 4). Comparison of the model predicted systemic exposure (final model) showed no notable difference between FF/VI combination treatment and FF monotherapy (Table 4).

The VPC plots by FF dose (Figure 3a) showed that most data are captured within

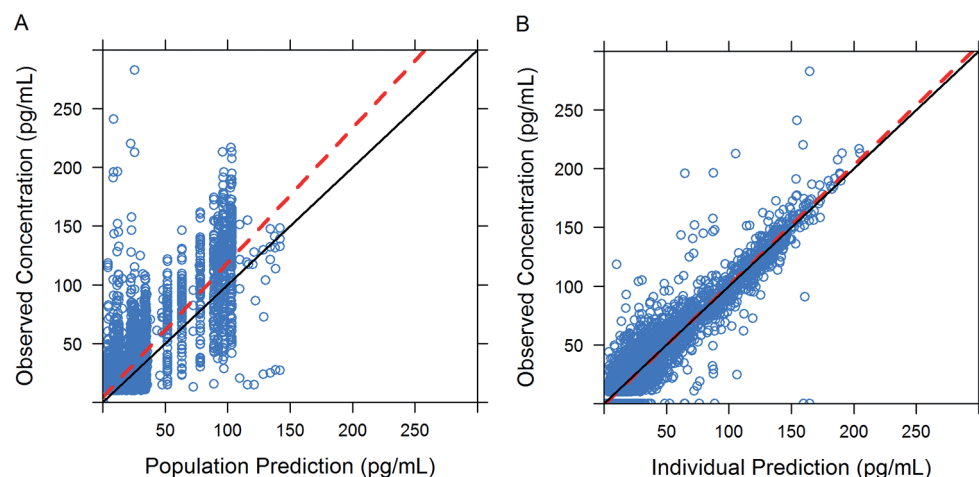


Figure 2. Diagnostic plots for the final FF model. Dashed lines represent lines of identity and solid lines depict smooth (LOESS) trends.

Table 4. Model predicted systemic exposure (geometric mean (95% CI)) for FF ($C_{\max}$ and $AUC_{(0-24)}$) following administration of FF (as FF/VI or FF) in patients with asthma (studies 1, 2, 3, and 4) and by race category.

Treatment	N	$C_{\max}$, pg/mL (95% CI)	$AUC_{(0-24)}$, pg·h/mL (95% CI)
FF/VI 100/25	434	16.01 (15.55 – 16.48)	244.25 (235.98 – 252.51)
FF 100	186	15.50 (14.81 – 16.19)	238.24 (228.01 – 248.47)
FF/VI 200/25	432	31.35 (30.33 – 32.37)	495.33 (480.06 – 510.60)
FF 200	161	30.63 (29.20 – 32.06)	477.77 (455.93 – 499.61)
FF dose/RACE			
100/1	492	15.24 (14.86 – 15.63)	232.23 (225.99 – 238.46)
100/2	80	20.44 (19.18 – 21.69)	335.69 (314.01 – 357.37)
100/3	48	15.56 (14.42 – 16.70)	218.97 (198.09 – 239.86)
200/1	471	29.96 (29.11 – 30.80)	471.57 (458.98 – 484.15)
200/2	71	41.63 (39.00 – 44.25)	642.92 (604.11 – 681.73)
200/3	51	29.88 (27.18 – 32.5)	484.10 (434.68 – 533.51)

AUC = area under curve; CI = confidence interval; $C_{\max}$ = maximum concentration; FF = fluticasone furoate; VI = vilanterol. RACE = 1 – White Caucasian; RACE = 2 – East Asian, Japanese, South East Asian; RACE = 3 – African American, Asian Central, White Arabic, American Indian/Native Alaskan, "Other".

the 5th and 95th percentile boundary, indicating that the model was valid for this asthma dataset. The VPC plots also showed that the model adequately describes the proportion of data reported as below the LLQ (Figure 3b).

VI PK model development

Based on the observed concentration-time profiles, and previous modeling in COPD and healthy subjects (unpublished data, GSK, 2012), a three-compartment linear model with zero order absorption and first order elimination was evaluated. Mod-

eling was conducted on log-transformed VI concentrations.

Initial exploration indicated that CL/F, volume of the central and peripheral compartments ($V1/F$ and $V2/F$) needed to be separated by population (patients with asthma or healthy subjects). However, this model resulted in a very large (in the order of 10^5) estimate for $V3/F$, and a very small (~ 0.5 minute) estimate for input duration ($D1$), both of which were considered implausible. As a consequence, modeling was progressed with CL/F, $V1/F$, $V2/F$ (healthy subjects), inter-compartmental clearances ($Q2/F$, $Q3/F$), $D1$, and residual variability (σ^2) for patients with asthma and healthy subjects (and respective ETAs); these were fixed to population estimates reported for healthy subjects from a previous meta-analysis (unpublished data, GSK, UK, 2012). CL/F, $V1/F$, $V2/F$, and σ^2 for patients with asthma were estimated by the model. The change in OFV with the separation of CL/F by population was < 6.64 , therefore, modeling was progressed without this covariate on CL/F. Model estimation of the population parameters describing the inter-compartment clearances ($Q2/F$, $Q3/F$, and $V3/F$) in patients with asthma or healthy subjects was also investigated but did not add significant improvement to the model. Model estimation of $D1$ by population improved the model and was included in the structural base model.

Potential covariate-parameter relationships were explored graphically using the individual ETAs. Study 4 appeared influential

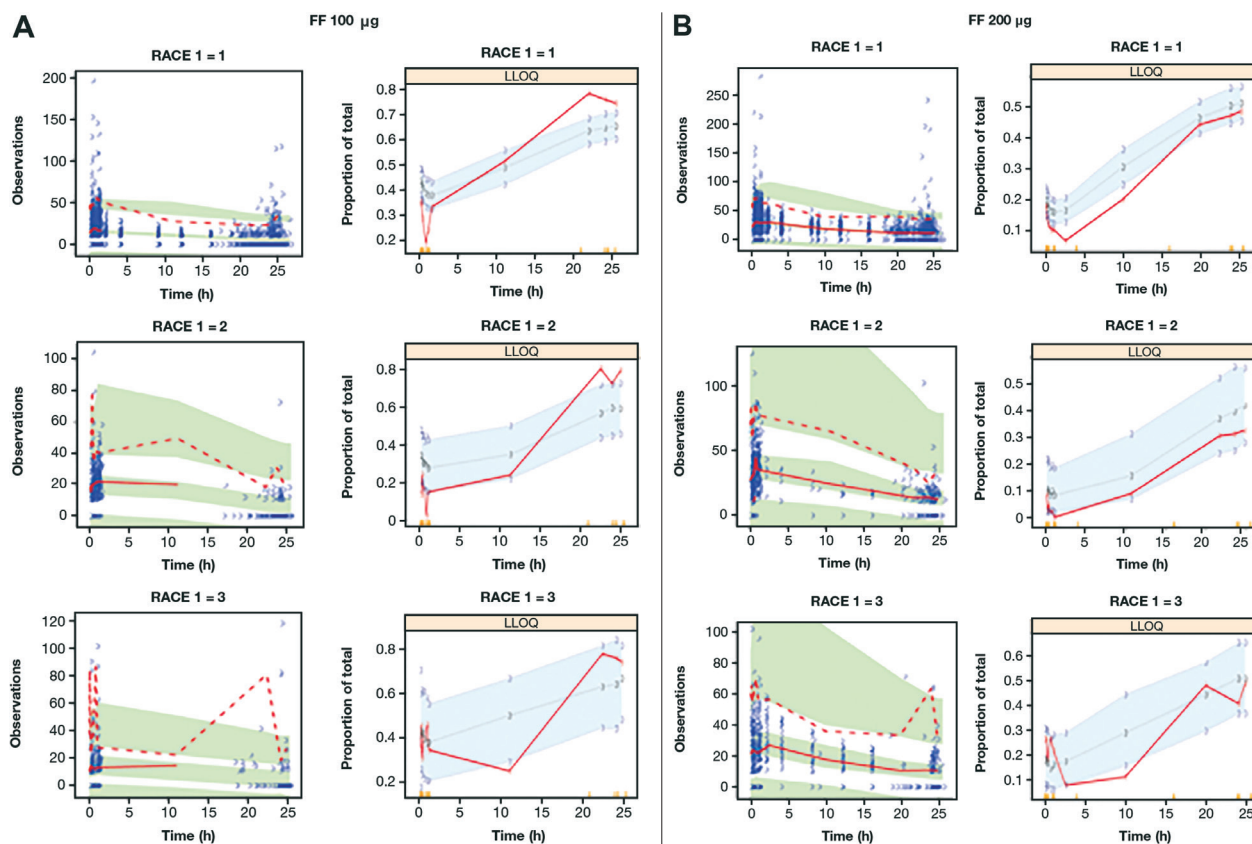


Figure 3. Visual predictive check plots stratified by dose regimen for the final FF model concentration vs. time and the proportion of BLQ values by time. The left plot in each panel shows the 95% CI (represented by the shaded area) for the predicted median and 95% prediction interval by time, overlaid with the median and 95% percentiles (solid and dashed lines, respectively) of the observed data (dots). The plots on the right show the same information for the BQL portion of the total data. RACE = 1 – White Caucasian; RACE = 2 – Asian East Asian, Japanese, South East Asian; RACE = 3 – African American; Asian Central, White Arabic, American Indian/Native Alaskan, “Other”.

Table 5. Final VI PK model: log-transformed and untransformed parameter estimates.

Parameter	Ln estimate (95% CI)	Estimate (95% CI)	RSE, %
CL/F, L/h	4.90 (4.84 – 4.96)	134.3 (126.5 – 142.6)	0.588
Study 4 on CL/F	0.659 (0.490 – 0.828)	1.93 (1.63 – 2.29)	13.1
V1/F (HVT), L	5.08 FIXED	160.8 FIXED	FIXED
V1/F (asthma), L	6.59 (6.45 – 6.73)	727.8 (632.7 – 873.1)	1.08
Study 4 on V1/F (asthma)	–0.776 (–1.13 – –0.425)	0.460 (0.323 – 0.654)	23.1
RACE = 2 on V1/F (asthma)	–1.68 (–2.18 – –1.18)	0.186 (0.113 – 0.307)	15.2
Q2/F, L/h	5.54 FIXED	254.7 FIXED	FIXED
V2/F(HVT), L	6.25 FIXED	518.0 FIXED	FIXED
V2/F (asthma), L	4.53 (4.34 – 4.72)	92.8 (76.7 – 112.2)	2.18
Q3/F, L/h	4.91 FIXED	135.6 FIXED	FIXED
V3/F, L/h	7.73 FIXED	2,275.6 FIXED	FIXED
D1 (HVT), h	–2.52 (–2.65 – –2.39)	0.08 (0.07 – 0.09)	2.57
D1 (asthma) h	–3.15 (–3.47 – –2.83)	0.04 (0.03 – 0.06)	5.21

CI = confidence interval; CL/F = inhaled clearance; D1 = input duration; Q2/F & Q3/F = intercompartmental clearances; VI = vilanterol; V1/F = volume of central compartment; V2/F & V3/F = volumes of peripheral compartments, PK = pharmacokinetic; RSE = relative standard error. RACE = 2 – East Asian, Japanese, South East Asian.

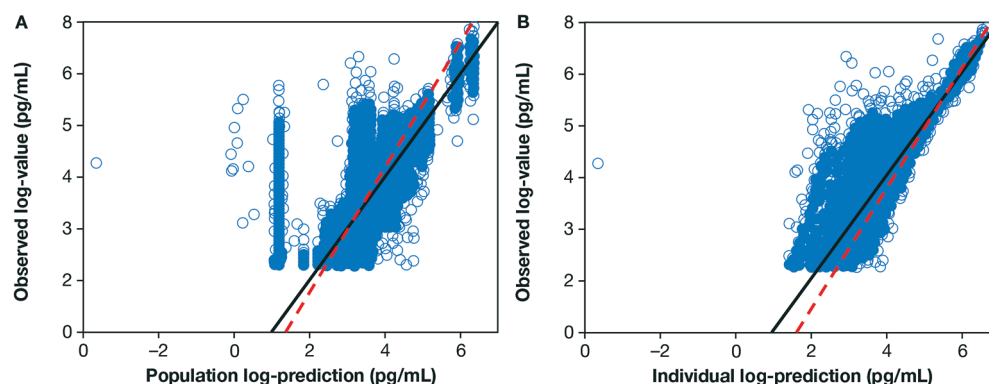


Figure 4. Diagnostic plots for the final VI model. Dashed lines represent lines of identity and solid lines depict smooth (LOESS) trends.

Table 6. Model predicted systemic exposure (geometric mean (95% CI)) for VI ($C_{\max}$ and $AUC_{(0-24)}$) following 25 μ g VI (as FF/VI 100/25 μ g or 200/25 μ g) in patients with asthma by study and by race categorization.

	N	$C_{\max}$, pg/mL (95% CI)	$AUC_{(0-24)}$, pg $\times$ h/mL (95% CI)
Study 1	178	35.2 (30.9 – 40.9)	177.0 (166.5 – 188.2)
Study 2	183	46.6 (41.7 – 52.1)	189.9 (180.1 – 200.4)
Study 3	385	54.4 (49.8 – 59.6)	184.6 (178.8 – 190.6)
Study 4	110	66.8 (56.6 – 78.9)	93.3 (87.1 – 100.0)
RACE = 1	660	42.2 (39.7 – 44.9)	165.7 (160.2 – 171.4)
RACE = 2	128	135.1 (121.5 – 150.1)	173.2 (165.3 – 181.6)
RACE = 3	68	34.9 (28.5 – 42.8)	190.5 (170.5 – 212.9)
All studies	856	49.5 (46.6 – 52.5)	168.7 (164.0 – 173.5)

$AUC_{(0-24)}$ = area under curve; CI = confidence interval; $C_{\max}$ = maximum concentration; FF = fluticasone furoate; VI = vilanterol. RACE = 1 – White Caucasian; RACE = 2 – East Asian, Japanese, South East Asian; RACE = 3 – African American/African, White Arabic, American Indian/Native Alaskan, "Other".

on CL/F and V1/F, and height, weight, and race category (RACE = 2 vs. others) appeared influential on V1/F. Each of these was evaluated as a potential covariate on CL/F and V1/F, as appropriate. The final population PK model incorporated the effect of study (4 vs. others) on CL/F, race category (RACE = 2) and study (4) on V1/F for patients with asthma. The population parameter estimates from the final model are shown in Table 5. The fixed effect parameters (CL/F, V1/F, V2/F, and D1) and the inter-individual variance on CL/F and V1/F were estimated with good precision (< 5%). The goodness-of-fit plot for the final model presented in Figure 4 shows the final model appears to provide a reasonable prediction of VI plasma concentrations.

For patients with asthma in study 4 (n = 110; 12% of the VI dataset) the typical value of CL/F was greater and V1/F

smaller vs. estimates for studies 1, 2, and 3 (746 subjects in total; 80% of the data). As a consequence, predicted VI $C_{\max}$ was higher (~ 23 – 90%), and estimated $AUC_{(0-24)}$ was up to 49% lower in patients with asthma in study 4 compared with that predicted in the other phase III trials (studies 1, 2, and 3) (Table 6).

For V1/F, RACE = 2 was also identified as a significant covariate with the typical value of V1/F in patients of East Asian heritage estimated to be lower than that for patients of a non-Asian heritage in studies 1, 2, and 3. As a consequence, the predicted VI $C_{\max}$ in patients/subjects of Asian heritage was higher (~ 220 – 287%) vs. that predicted for patients with asthma in the other race groups, whilst $AUC_{(0-24)}$ estimates were comparable (Table 6).

A predictive check for the final model was performed using the final parameter estimates from the model. Since study 4 had a higher LLQ (20 pg/mL) compared with the other studies (LLQ 10 pg/mL), a separate VPC was performed. The plot for VPC (Figure 5) showed that most data are captured in the prediction interval encompassing 90% of the data, indicating that the model was reasonable for this asthma dataset. The model appears to slightly under-predict the proportion (%) of BLQ data at early time points, < 15 minutes post-dose (Figure 5).

The FF PK dataset for patients with asthma included 121 aged 12 – 17 years (10% of the overall asthma population), and the VI PK dataset for patients with asthma included 96 aged 12 – 17 years (11% of the overall asthma population). Box and whisker plots by treatment and by age group (12 – 17 years

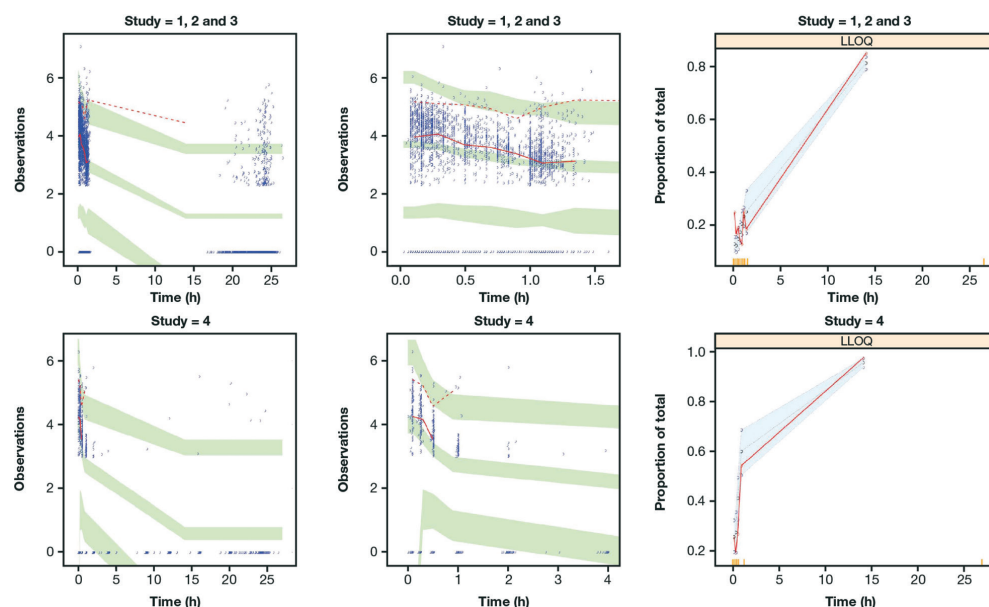


Figure 5. Visual predictive check plots stratified by study for the final VI model concentration vs. time and the proportion of BLQ values by time. The plots on the left of each panel show the 95% CI (represented by the shaded area) for the predicted median and 95% prediction interval by time, overlaid with the median and 95% percentiles (solid and dashed lines, respectively) of the observed data (dots). The plots on the right show the same information for the BLQ portion of the total data.

and ≥ 18 years) showed there was no notable difference in either FF or VI $AUC_{(0-24)}$ and C_{max} estimates between adults and adolescents (Figure 6).

Discussion

This meta-analysis showed plasma FF concentration-time profile following inhaled FF/VI or FF was adequately described by a two-compartment model with first order absorption and first order elimination. The only significant covariate was race (East Asian, Japanese, South East Asian) on CL/F. Based on the final model, the population mean estimate for CL/F was 185 L/h for a patient with asthma. FF $AUC_{(0-24)}$ estimates for East Asian, Japanese, South East Asian patients/subjects were on average 33 – 53% higher than in other racial groups, consistent with higher FF systemic exposure seen previously in healthy subjects of East Asian origin following inhaled dosing [12]. The exact reasons for the differences are not known; it could be a consequence of differences in the mucociliary clearance, lung solubility, and/or regional lung deposition of inhaled FF. Although there is evidence for higher FF

systemic exposure in Asian patients/subjects than in those of non-Asian heritage, exposure values are still below those associated with systemic effects on the hypothalamic–pituitary–adrenal axis [13] and there was no evidence for effect on 24-hour urinary cortisol excretion in patients with asthma at FF doses up to 600 μg [14].

Comparison of the model-predicted systemic FF exposure showed no notable difference between FF or FF/VI, consistent with data following single-dose administration of FF and FF/VI to healthy subjects [1]. Systemic FF exposure (C_{max} and $AUC_{(0-24)}$) increased in proportion to dose irrespective of whether administered as FF/VI or FF.

The VI population PK analysis showed that a three-compartment model with zero order absorption and first order elimination provided a good fit of the VI concentration-time data. Reflecting the sparse nature of the VI PK data available > 1.5 hours post-dose, some population parameters were fixed to population estimates reported for healthy subjects in a previous meta-analysis (data on file, GSK). Significant covariates were study (study 4) on CL/F and V1/F, and race category (RACE = 2) on V1/F.

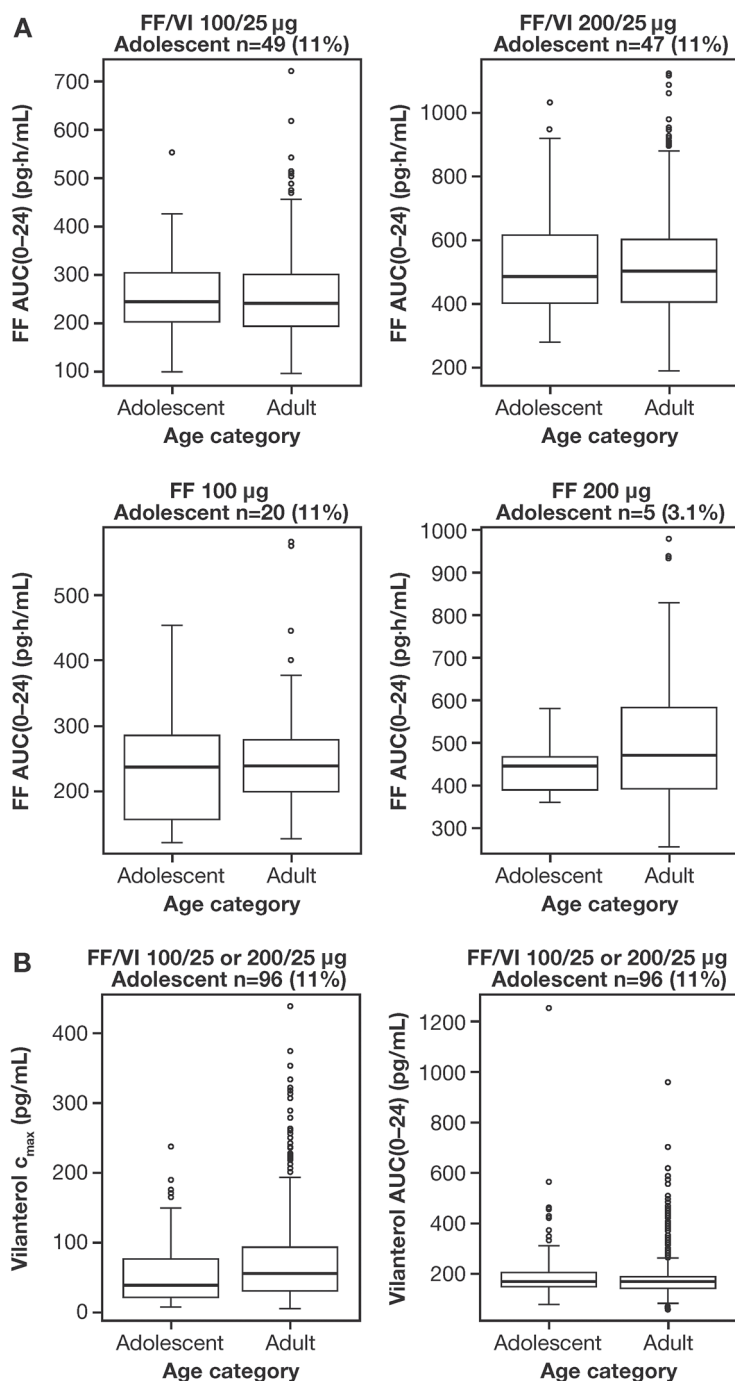


Figure 6. Box and whisker plots in adolescent (12–17 years) and adult (≥ 18 years) patients with asthma for (A) FF AUC and $C_{\max}$ and (B) VI AUC and $C_{\max}$. The number of adolescents in each dose group (FF/VI 200/25, FF/VI 100/25, FF 100 or FF 200) is presented on top of the box plots. Values in brackets indicate the proportion of patients within each dose group who are adolescents.

The typical value of VI CL/F in study 4 was predicted to be up to 93% higher than the typical value for the other studies conducted in patients with asthma (studies 1,

2, and 3). Patients in this study were also predicted to have a smaller VI/F. The demographic characteristics in this study were comparable with the other phase III trials, so do not provide an explanation for the difference. Therefore the reason for the difference is not clear. As a result of the higher CL/F and a smaller VI/F, VI $C_{\max}$ was predicted to be higher (23–90%) and AUC_(0–24) lower (up to 49%) in patients with asthma recruited to study 4 vs. the other three phase III studies. However, the VI $C_{\max}$ values estimated for patients with asthma in study 4 (geometric mean; 66.8 pg/mL) were still lower than those estimated for healthy subjects using non-compartmental methods in study 5 (geometric mean; 115 pg/mL) [15]. This finding may just reflect a faster rate of absorption of VI from the lung in study 4 and/or between-study variability, however additional analyses would be needed to confirm this hypothesis.

In patients with asthma, VI $C_{\max}$ is predicted to be 220–287% higher, whilst AUC_(0–24) is comparable for those from an East Asian heritage vs. subjects from a non-East Asian heritage. VI $C_{\max}$ in East Asian patients with asthma (135 pg/mL) was estimated to be similar to that for healthy subjects using non-compartmental methods (geometric mean; 115 pg/mL) [15] where FF/VI 200/25 µg did not have a significant effect on the QTc interval as measured by either QTcF or QTcI. Furthermore, in the current analysis there was no clear relationship between VI $C_{\max}$ and change from baseline heart rate in any of the race categories, including those with Asian heritage. In addition, FF/VI (100/25 and 200/25 µg) administered q.d. over 52 weeks has been shown to be well tolerated by patients with asthma aged ≥ 12 years with the overall safety profile of FF/VI not revealing any findings of clinical concern [3].

Although the reason for the differences by heritage is unclear, the lack of effect on CL/F would suggest that this effect on VI/F could reflect differences in the rate of lung absorption of VI between patients from an East Asian heritage and a non-East Asian heritage.

Overall, 10% of the patients with asthma included in these meta-analyses were aged 12–17 years. Age was not a significant co-

variate on either FF or VI PK parameters, therefore there were no notable differences between adults (≥ 18 years) and adolescents (12 – 17 years) in the $AUC_{(0-24)}$ or C_{max} estimates for FF or VI. Furthermore, there was very little difference in the exposure distribution; with a similar percentage of each population having exposure (C_{max} or $AUC_{(0-24)}$) which exceeded the 75% percentile.

Despite the use of sensitive analytical methods (LLQ 10 pg/mL) a significant proportion of the data was still below the LLQ for both FF and VI. In these analyses, the use of a methodology that maximized the likelihood for all the data, treating those data below the LLQ as censored, enabled robust modeling of the data and evaluation of potential covariates affecting the FF and VI PK.

Conclusions

Combined administration of FF/VI does not appear to affect the PK of FF or VI. The effect of race on FF or VI PK does not have impact on dose adjustments for FF/VI in East Asian patients with asthma.

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Conflict of interest

All studies used in this analysis were funded by GSK. AA, SS, and SY had support from GSK for the submitted work; AA, SS, and SY have been employed by GSK in the previous 3 years; SS, and SY are currently employed by and hold shares in GSK; Ann Allen was an employee of GSK at the time of these analyses.

References

- [1] Kempford R, Allen A, Bareille P, Bishop H, Hamilton M, Cheesbrough A. The safety, tolerability, pharmacodynamics and pharmacokinetics of inhaled fluticasone furoate (FF) and vilanterol (VI) are unaffected by administration in combination. *Eur Respir J*. 2011; 38 (Suppl 55): 138s.
- [2] Lötvall J, Bakke PS, Bjerner L, Steinshamn S, Scott-Wilson C, Crim C, Sanford L, Haumann B. Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. *BMJ Open*. 2012; 2: e000370. [CrossRef PubMed](#)
- [3] Busse WW, O'Byrne PM, Bleecker ER, Lötvall J, Woodcock A, Andersen L, Hicks W, Crawford J, Jacques L, Apoux L, Bateman ED. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β_2 agonist vilanterol administered once daily for 52 weeks in patients ≥ 12 years old with asthma: a randomised trial. *Thorax*. 2013; 68: 513-520. [CrossRef PubMed](#)
- [4] Boscia JA, Pudi KK, Zvarich MT, Sanford L, Siederer SK, Crim C. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. *Clin Ther*. 2012; 34: 1655-66.e5. [CrossRef PubMed](#)
- [5] Agusti A, de Teresa L, De Backer W, Zvarich MT, Locantore N, Barnes N, Bourbeau J, Crim C. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with fluticasone propionate/salmeterol in COPD patients. *Eur Respir J*. 2014; 43: 763-772. [CrossRef PubMed](#)
- [6] Bleecker ER, Lötvall J, O'Byrne PM, Woodcock A, Busse WW, Kerwin EM, Forth R, Medley HV, Nunn C, Jacques L, Bateman ED. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. *J Allergy Clin Immunol Pract*. 2014; 2: 553-561. [CrossRef PubMed](#)
- [7] O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, Toler WT, Jacques L, Lötvall J. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. *Eur Respir J*. 2014; 43: 773-782. [CrossRef PubMed](#)
- [8] Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, Ellsworth A, Jacques L, Busse WW. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest*. 2013; 144: 1222-1229. [CrossRef PubMed](#)
- [9] Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. *J Pharmacokin Pharmacodyn*. 2008; 35: 401-421. [CrossRef PubMed](#)
- [10] R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: <http://www.R-project.org>. [Accessed March 20, 2015].

- [11] *Jonsson EN, Karlsson MO.* Xpose – an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed.* 1999; 58: 51-64. [CrossRef PubMed](#)
- [12] *Post TM, Freijer JL, Ploeger BA, Danhof M.* Extensions to the visual predictive check to facilitate model performance evaluation. *J Pharmacokinet Pharmacodyn.* 2008; 35: 185-202. [CrossRef PubMed](#)
- [13] *Allen A, Bal J, Cheesbrough A, Hamilton M, Kempsford R.* Pharmacokinetics and pharmacodynamics of intravenous and inhaled fluticasone furoate in healthy Caucasian and East Asian subjects. *Br J Clin Pharmacol.* 2014; 77: 808-820. [CrossRef PubMed](#)
- [14] *Allen A.* The relationship between fluticasone furoate systemic exposure and cortisol suppression. *Clin Pharmacokinet.* 2013; 52: 885-896. [CrossRef PubMed](#)
- [15] *Kempsford R, Allen A, Kelly K, Saggu P, Crim C.* A repeat-dose thorough QT study of inhaled fluticasone furoate/vilanterol combination in healthy subjects. *Br J Clin Pharmacol.* 2014; 77: 466-479. [CrossRef PubMed](#)
- [16] *Hankinson JL, Odencrantz JR, Fedan KB.* Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999; 159: 179-187. [CrossRef PubMed](#)
- [17] *Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG.* Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. *Chest.* 2010; 137: 138-145. [CrossRef PubMed](#)

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