Online Resource

Population pharmacokinetics of inhaled fluticasone furoate and vilanterol in subjects with chronic obstructive pulmonary disease

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Table S1 Summary of studies in population pharmacokinetic meta-analysis

Study ID (NCT no.; protocol no.)	Design (Phase)	Disease	No. subjects ITT (M/F)	Formulation(s) Device	Nominal doses (μg)[‡] Frequency	Duration treatment (Day pharmacokinetic sampling)	Pharmacokinetic sampling post-dose
1 (NCT01053988; HZC112206)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group (Phase III)	COPD	1,030 (345/685)	FF/VI VI FF DPI	FF/VI: 50/25, 100/25 μg VI: 25 μg FF: 100 μg Placebo Once daily (am)	24 weeks (Days 84 & 168)	Pharmacokinetic:* pre-dose & post-dose 5–20 min, 0.5–1.5 h, & 2–4 h
2 (NCT01054885; HZC112207)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group (Phase III)	COPD	1,224 (339/885)	FF/VI VI FF DPI	FF/VI: 100/25, 200/25 μg VI: 25 μg FF: 100, 200 μg Placebo Once daily (am)	24 weeks (Days 84 & 168)	Pharmacokinetic:* pre-dose & post-dose 5–20 min, 0.5–1.5 h, & 2–4 h
3 (NCT01072149; HZC110946)	Multicenter, randomized, double-blind, placebo-controlled, 3-way incomplete cross-over (Phase III)	COPD	54 (25/29)	FF/VI DPI	50/25, 100/25, 200/25 μg Placebo Once daily (am)	4 weeks (Day 28)	Pharmacokinetic:** pre-dose & post-dose 5, 10, 15, 30, 60, & 90 min, 2, 3, 4, 6, 8, 12, 16, & 24 h
4 (NCT00731822; HZC111348***)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group (Phase II)	COPD	60 (40/20)	FF/VI DPI	400/25 μg (n = 40) Placebo (n = 20) Once daily (am)	4 weeks (Days 1, 14 & 2)	Pharmacokinetic:* pre-dose & post-dose 5, 10, 15, 20, 45, 60, & 90 min, 2, 3, & 4 h

5 (NCT01209026; HZA102936[†])	Randomized, placebo-controlled, 4-way cross-over (Phase I)	HVT	85 (49/36)	FF/VI DPI	200/25; 800/100 µg Placebo Once daily (am)	1 week (Day 7)	Pharmacokinetic:* pre-dose & post-dose 5, 10, & 30 min, 1, 2, 4, 8, 12, & 24 h

ITT population, intent-to-treat population; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; VI, vilanterol; DPI, dry powder inhaler; HVT, healthy volunteers

COPD: post-albuterol/salbutamol FEV_1/FVC ratio of ≤0.70 at screening (Visit 1) (Pellegrino, 2005), measured post-albuterol/salbutamol FEV_1 ≤70% of predicted normal values calculated (via centralized vendor equipment) using NHANES III reference equations (Hankinson, 1999) at screening (Visit 1)

COPD Study 4: post-albuterol/salbutamol FEV1/FVC ratio of ≤0.70 at screening (Visit 1) (Pellegrino, 2005) measured post-albuterol/salbutamol FEV1 ≥40% and ≤80% of predicted normal values calculated (via centralized vendor equipment) using NHANES III reference equations (Hankinson, 1999)

*Lower limit of quantification of the FF & VI analytical assays =10 pg/mL

**Lower limit of quantification of the VI analytical assay = 20 pg/mL, FF analytical assay = 10 pg/mL

***Steady-state (treatment days 14 and 28) included in analysis

[†]For 200/25 and 800/25 µg treatments single-dose placebo administered on Day 7. Placebo treatment administered with single-dose placebo and moxifloxacin (400 µg) on Day 7

[‡]Emitted doses 46/22, 92/22, 184/22 and 368/22 µg for FF/VI treatments, 22 µg for VI and 46, 92 and 184 µg for FF treatments

Supplementary References

Hankinson JL, Odencrantz JR, Fedan KB (1999) Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 159:179–187.

Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N,

McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J (2005) Interpretative strategies for lung function tests. Eur Respir J. 26:948–968

Table S2 Demographic characteristics

Demographic	FF dataset (*n* = 1,307)	VI dataset (*n* = 1,167)
Median age, years (range)	61.0 (18, 85)	61.0 (18, 84)
Sex, n (%)		
Male	427 (33)	327 (32)
Female	880 (67)	795 (68)
Mean BMI, kg/m^2 (range)	26.3 (13.2, 63.0)	26.0 (13.2, 63.0)
Mean height, cm (range)	169 (144, 200)	170 (143, 200)
Mean weight, kg (range)	75.7 (35.0, 174.6)	75.3 (34.6, 160.0)
Ethnicity, n (%)		
Hispanic or Latino	33 (3)	31 (3)
Not Hispanic or Latino	1,274 (97)	1,137 (97)
Race, n (%)		
White – White/Caucasian/European heritage	1,072 (82)	957 (82)
African American/African heritage	37 (3)	36 (3)
Asian – East Asian heritage	65 (5)	62 (5)
Asian – Central/South Asian heritage	9 (<1)	9 (<1)
Asian – Japanese heritage	48 (4)	37 (3)
Asian – South East Asian heritage	59 (5)	52 (5)
American Indian/Native Alaskan	5 (<1)	4 (<1)
White – Arabic/North African	11 (<1)	9 (<1)
Other	2 (<1)	1 (<1)
Smoker (COPD population), n (%)		
No	553 (45)	513 (47)
Yes	672 (55)	578 (53)
Population, n (%)		
COPD	1,225 (94)	1,091 (94)
Healthy	82 (6)	76 (6)
Reversibility (COPD population), n (%)		
No	837 (69)	728 (68)
Yes	371 (31)	348 (32)
% predicted FEV_1 (COPD population), mean (range)	48.1 (14.4, 70.0)	48.8 (14.3, 76.2)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second

Fig. S1 Fluticasone furoate (FF) and vilanterol (VI) concentrations relative to time of last dose following FF/VI (50/25, 100/25, 200/25 and 400/25 µg), FF (100 and 200 µg) or VI (25 µg) to subjects with COPD (Studies 1, 2, 3, and 4) and following FF/VI (200/25 and 800/25 µg) to healthy subjects (Study 5)

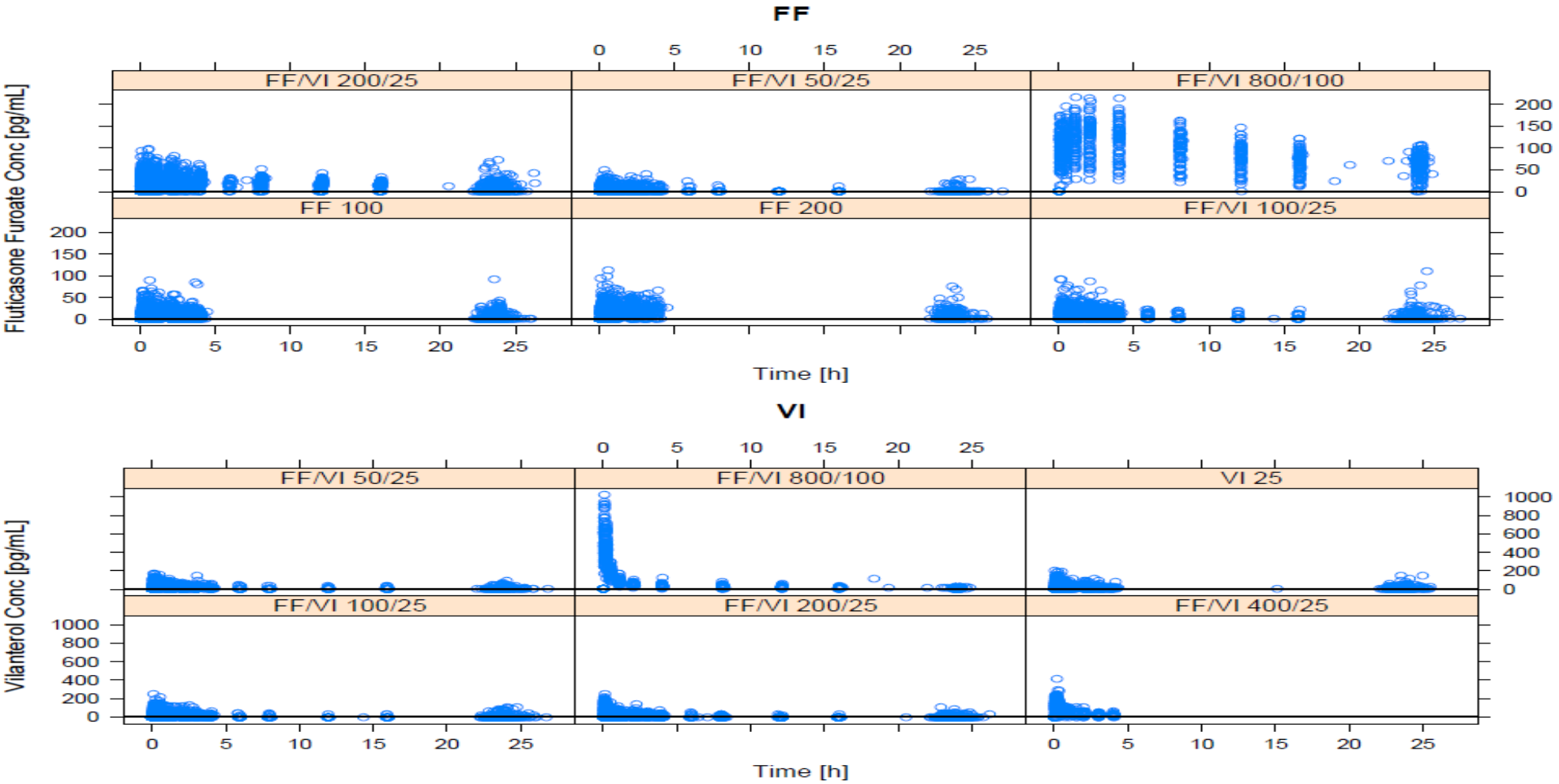

Fig. S2 Plots for vilanterol C_{max} and AUC_{0-24} by age and weight following 25 µg vilanterol (as FF/VI or vilanterol) to subjects with COPD