The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: HZA113970
Title: An open-label, non-randomized pharmacokinetic and safety study of repeat doses of fluticasone furoate and GW642444M combination in healthy subjects and in subjects with severe renal impairment
Rationale: Fluticasone furoate (FF), a novel glucocorticoid, and vilanterol (VI; GW642444M), a potent, long-acting, beta2-receptor agonist, are currently under development in combination for use as a once-daily, inhaled treatment for asthma and chronic obstructive pulmonary disease. The aim of this study was to investigate whether there were any changes in systemic exposure or safety following once-daily dosing for 7 days with FF/VI in subjects with severe renal impairment.
Phase: I
Study Period: 14 October 2010 – 22 March 2011
Study Design: Open-label, non-randomised, repeat dose.
Centres: One centre in Prague, Czech Republic.
Indication: None.
Treatment: All subjects received FF/VI 200/25 mcg once-daily every morning for 7 days.
Objectives: To investigate the effect of severe renal impairment on the pharmacokinetics of FF and VI following repeat administration of FF/VI (200/25 mcg) via novel dry powder inhaler.
Statistical Methods: Sufficient subjects were enrolled to ensure 18 subjects completed the study: 9 in the severe renal impairment group and 9 healthy subjects. The sample size calculations were based on a non-inferiority approach for the primary endpoint; non-inferiority was to be concluded if the upper 90% confidence interval limit for the adjusted geometric mean ratio was less than 2. All 18 subjects enrolled completed the study and were included in the 'All Subjects' and 'Pharmacokinetic' populations. The 'All Subjects Population' was defined as all subjects who received at least one dose of study medication. This population was used in the evaluation of pharmacodynamics, safety and tolerability and for study population displays. The 'Pharmacokinetic Population' was defined as subjects in the 'All Subjects' population for whom a pharmacokinetic sample was obtained and analysed. This population was used in the evaluation of pharmacokinetic data. Pharmacokinetics: Plasma FF and VI concentration-time data and derived pharmacokinetic parameters were listed and summarised. Following $\log_e$-transformation, maximum observed concentration (Cmax) on Days 1 and 7, area under the concentration-time curve from zero (pre-dose) to 8 h (AUC(0–8)) on Day 1, area under the concentration-time curve from zero (pre-dose) to 24 h (AUC(0–24)) on Day 7 and terminal phase half-life (t½) on Day 7 for FF and VI were separately analysed using a mixed model. Cmax was analysed using a mixed model with fixed effects for group, day and day*group interaction and subject as a random effect. For AUC(0–8) on Day 1 and AUC(0–24) and t½ on Day 7, an analysis of variance model was used with group fitted as a fixed effect. Point estimates and their associated 95% confidence intervals were constructed for each group. Point estimates and their associated 90% confidence intervals were constructed for the difference between severely renally impaired and healthy groups for both FF and VI. The point estimates and their associated 90% confidence intervals were then back-transformed to provide point estimates and 90% confidence intervals for the ratio. Similarly, the accumulation ratio was determined from comparison of AUC(0–8) and Cmax at Days 1 and 7 for FF and VI, separately, fitting a model with fixed effects for group, day, and day*group interaction and subject as a random effect. Pharmacodynamics: Derived pharmacodynamic parameters were calculated and summarised, listed and presented graphically where appropriate. Maximum heart rate (0–4 h) and minimum serum potassium (0–4 h) were analysed on Day 7 using an analysis of covariance model with fixed effect terms for group and baseline. From these analyses, point estimates and their associated 90% confidence intervals were constructed for the difference between the severe renal impaired and healthy groups. Serum cortisol weighted mean (0–24 h) was analysed similarly but was $\log_e$-transformed prior to data analysis and the ratio and corresponding two-sided 90% confidence interval for severe renal impairment subjects to healthy subjects was estimated. The ratio was calculated by back transforming the difference in adjusted means.
Study Population: Male or female subjects aged between 18 and 70 years with a body mass index of 19.0–33.0 kg/m^2. Subjects had a QT interval corrected according to Fridericia's formula (QTcF) <450 msec or QTcF <480 msec in subjects with bundle branch block, and were able to use the dry powder inhaler. Female subjects

had to be of non-childbearing potential or be using adequate contraception.
Healthy subjects had aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and bilirubin ≤1.5 x upper limit of normal (ULN) and creatinine clearance >80 mL/minute. Renally impaired subjects had AST and ALT <2 x ULN, alkaline phosphatase and bilirubin ≤1.5 x ULN and creatinine clearance <30 mL/minute.

Number of Subjects:	**Healthy**	**Severe renal impairment**
Planned N	9	9
Dosed N	9	9
Completed n (%)	9 (100)	9 (100)
Total Number Subjects Withdrawn N (%)	0	0
Demographics		
N	9	9
Females: Males	1:8	1:8
Mean Age in years (SD)	55.4 (9.76)	55.8 (10.00)
Mean Weight in kg (SD)	82.78 (6.48)	82.89 (9.20)
Mean Height in cm (SD)	176.4 (7.54)	174.1 (8.31)
Mean Body Mass Index in kg/m^2 (SD)	26.60 (1.54)	27.33 (2.55)
Not Hispanic or Latino n (%)	9 (100)	9 (100)
White n (%)	9 (100)	9 (100)
Calculated Creatinine Clearance in mL/min, Mean (SD)	143.4 (33.6)	26.0 (7.8)
Estimated Creatinine Clearance in mL/min, Mean (SD)	109.7 (20.8)	24.0 (5.5)

Pharmacokinetic Endpoints: A summary of selected FF pharmacokinetic parameters following single and repeated inhaled administration of FF/VI (200/25 mcg) is presented below.

Parameter	**Group**	**Day**	**N**	**n**	**n***	**Geometric mean (CV%)**	**95% CI**
AUC(0–24) (pg.h/mL)	Healthy	7	9	9	1	609.1 (56.5)	406.5, 912.6
	Severe renal impairment		9	8	0	554.1 (47.2)	381.0, 806.0
AUC(0–8) (pg.h/mL)	Healthy	1	9	7	1	131.8 (44.8)	88.8, 195.8
	Severe renal impairment		9	4	1	126.1 (68.7)	46.9, 339.3
	Healthy	7	9	9	1	252.9 (63.1)	162.1, 394.5
	Severe renal impairment		9	9	0	229.7 (49.7)	160.1, 330.0
t½ (h)	Healthy	7	9	8	0	35.1 (16.1)	30.7, 40.1
	Severe renal impairment		9	7	0	34.6 (32.4)	25.8, 46.3
Cmax (pg/mL)	Healthy	1	9	9	1	19.5 (69.5)	12.1, 31.7
	Severe renal impairment		9	9	1	18.0 (72.6)	10.9, 29.7
	Healthy	7	9	9	1	38.4 (90.9)	21.2, 69.8
	Severe renal impairment		9	9	0	36.9 (48.2)	26.0, 52.5
Tmax (h)[1]	Healthy	1	9	8	0	1.75 (0.08 - 3.00)	NA
	Severe renal impairment		9	8	0	1.75 (0.75 - 4.00)	
	Healthy	7	9	8	0	3.00 (0.25 – 4.00)	NA
	Severe renal impairment		9	8	0	1.50 (0.25 – 3.00)	

1. Median (range)

NA = not applicable; n = number of subjects with non-missing observations (including imputed non-calculable values); n* = number of subjects for whom parameter cannot be derived because of non-calculable concentrations. AUC non-calculable values imputed by 0.5 x lowest observed AUC, Cmax imputed with half the lower limit of quantification; CI = confidence interval; CV% = coefficient of variation

A summary of the results from the statistical analysis of FF pharmacokinetic parameters is presented below.

Parameter	Day	Group comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
AUC(0–8)	1	Severe renal impairment / healthy	126.11 / 131.82	0.96	(0.54, 1.70)
AUC(0–24)	7	Severe renal impairment / healthy	554.12 / 609.06	0.91	(0.60, 1.38)
Cmax	1	Severe renal impairment / healthy	17.99 / 19.54	0.92	(0.55, 1.54)
	7	Severe renal impairment / healthy	36.91 / 38.44	0.96	(0.57, 1.61)
t½	7	Severe renal impairment / healthy	34.55 / 35.07	0.98	(0.79, 1.23)

CI = confidence interval

A summary of the results from the statistical analysis of FF pharmacokinetic parameters to assess accumulation is presented below.

Parameter	Group	Adjusted geometric means Day 7 / Day 1	Ratio of adjusted geometric means	90% CI of the ratio
AUC(0–8)	Healthy	252.86 / 135.89	1.86	(1.50, 2.31)
	Severe renal impairment	229.71 / 103.15	2.23	(1.68, 2.95)
Cmax	Healthy	38.44 / 19.54	1.97	(1.48, 2.62)
	Severe renal impairment	36.91 / 17.99	2.05	(1.54, 2.73)

CI = confidence interval

A summary of selected VI pharmacokinetic parameters following single and repeated inhaled administration of FF/VI (200/25 mcg) is presented below.

Parameter	Group	Day	N	n	n*	Geometric mean (CV%)	95% CI
AUC(0–24) (pg.h/mL)	Healthy	7	9	9	1	386.3 (28.3)	312.1, 478.3
	Severe renal impairment		9	9	0	604.3 (22.2)	510.5, 715.3
AUC(0–8) (pg.h/mL)	Healthy	1	9	9	1	103.4 (96.4)	55.4, 192.8
	Severe renal impairment		9	9	0	181.1 (55.5)	121.6, 269.8
	Healthy	7	9	9	1	190.5 (104.2)	98.6, 368.1
	Severe renal impairment		9	9	0	316.6 (25.5)	261.1, 383.8
Cmax (pg/mL)	Healthy	1	9	9	1	107.8 (181.4)	42.6, 272.3
	Severe renal impairment		9	9	0	126.7 (61.9)	81.8, 196.3
	Healthy	7	9	9	1	152.9 (209.4)	56.4, 414.5
	Severe renal impairment		9	9	0	164.7 (45.4)	118.1, 229.7
Tmax (h)[1]	Healthy	1	9	8	0	0.08 (0.08 – 0.25)	NA
	Severe renal impairment		9	9	0	0.08 (0.08 – 0.25)	
	Healthy	7	9	8	0	0.08 (0.08 – 0.08)	NA
	Severe renal impairment		9	9	0	0.08 (0.08 – 0.25)	

1. Median (range)

NA = not applicable; n = number of subjects with non-missing observations (including imputed non-calculable values); n* = number of subjects for whom parameter cannot be derived because of non-calculable concentrations. AUC non-calculable values imputed by 0.5 x lowest observed AUC, Cmax imputed with half the lower limit of quantification; CI = confidence interval; CV% = coefficient of variation

A summary of the results from the statistical analysis of VI pharmacokinetic parameters is presented below.

Parameter	Day	Group comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
AUC(0–8)	1	Severe renal impairment / healthy	181.12 / 103.38	1.75	(1.00, 3.07)
AUC(0–24)	7	Severe renal impairment / healthy	604.26 / 386.35	1.56	(1.27, 1.92)
Cmax	1	Severe renal impairment / healthy	126.70 / 107.80	1.18	(0.54, 2.56)
	7	Severe renal impairment / healthy	164.73 / 152.88	1.08	(0.49, 2.35)

CI = confidence interval

One subject had non-calculable values for AUC(0–8) and Cmax and subsequently appeared as an outlier in the statistical analyses for these parameters. Results excluding data from this subject led to a change in inference for Cmax on Day 1.

A summary of the results from the statistical analysis of VI pharmacokinetic parameters – excluding data from this subject – is presented below.

Parameter	Day	Group comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
AUC(0–8)	1	Severe renal impairment / healthy	181.12 / 127.20	1.42	(0.90, 2.25)
Cmax	1	Severe renal impairment / healthy	126.70 / 158.24	0.80	(0.56, 1.14)
	7	Severe renal impairment / healthy	164.73 / 234.44	0.70	(0.49, 1.00)

CI = confidence interval

A summary of the results from the statistical analysis of VI pharmacokinetic parameters to assess accumulation is presented below.

Parameter	Group	Adjusted geometric means Day 7 / Day 1	Ratio of adjusted geometric means	90% CI of the ratio
AUC(0–8)	Healthy	190.47 / 103.38	1.84	(1.36, 2.49)
	Severe renal impairment	316.55 / 181.12	1.75	(1.29, 2.37)
Cmax	Healthy	152.88 / 107.80	1.42	(1.05, 1.92)
	Severe renal impairment	164.73 / 126.70	1.30	(0.96, 1.76)

CI = confidence interval

Pharmacodynamic Endpoints: A summary of the results of the statistical analysis of maximum heart rate (0–4 h) (bpm) on Day 7 is presented below.

Comparison	Adjusted means test/reference	Difference of adjusted means	90% CI of the difference
Severe renal impairment/ healthy	74.4/74.1	0.3	(-7.3, 7.9)

A summary of the results of the statistical analysis of minimum serum potassium (0–4 h) (mmol/L) on Day 7 is presented below.

Comparison	Adjusted means test/reference	Difference of adjusted means	90% CI of the difference
Severe renal impairment/ healthy	4.43/4.04	0.4	(-0.02, 0.81)

A summary of the results of the statistical analysis of serum cortisol weighted mean (0–24 h) (nmol/L) on Day 7 is presented below.

Comparison	Adjusted means test/reference	Ratio of adjusted means	90% CI of the ratio
Severe renal impairment/ healthy	207.08/201.91	1.03	(0.79, 1.33)

Safety results: There were no clinically relevant changes in laboratory, vital signs or ECG parameters over the course

of the study in either group.		
Adverse Events:	**Healthy**	**Severe renal impairment**
N	9	9
No. subjects with AEs n (%)	0	0
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:		
	Healthy	**Severe renal impairment**
N	9	9
No. subjects with SAEs n (%)	0	0