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: HZA111789
Title: An open-label, non-randomised, pharmacokinetic and safety study of repeat doses of fluticasone furoate and GW642444M combination in healthy subjects and in subjects with mild, moderate or severe hepatic impairment.
Rationale: This was a study in subjects with hepatic impairment and in healthy subjects. The results of this study were to aid in deciding whether a dose adjustment is justified and in estimating any such adjustments in patients with impaired hepatic function.
Phase: Phase I.
Study Period: 18-OCT-2010 to 15-JUL-2011.
Study Design: An open-label, non-randomised, repeat-dose pharmacokinetic and safety study.
Centres: Two centres, one in the Czech Republic and one in Slovakia.
Indication: None.
Treatment: Subjects with mild and moderate hepatic impairment were recruited. Healthy controls were matched to subjects with moderate hepatic impairment by gender, ethnicity, age +/- 5 years and body mass index +/-15%. Subjects with severe hepatic impairment were enrolled after 9 subjects with moderate hepatic impairment and their matched healthy control subjects had completed the study. The dose for subjects with severe hepatic impairment was reduced to FF/VI 100/12.5 mcg due to an average 65% greater FF area under the plasma concentration-time curve from pre-dose to 24 h post-dose (AUC(0-24) in subjects with moderate hepatic impairment compared with healthy subjects. Subjects took fluticasone furoate (FF)/vilanterol (VI; GW642444) 200/25 mcg combination (FF 100 mcg/VI 12.5 mcg for subjects with severe hepatic impairment) once daily for 7 days. On Day 1, subjects were monitored for safety and had samples taken for pharmacokinetics over 8 h post-dose. All hepatically impaired subjects had safety assessments daily for 1 h post-dose. On Day 7 subjects were monitored for safety and had samples taken for pharmacokinetics over 48 h post-dose.
Objectives: To investigate the effect of varying degrees of hepatic impairment on the pharmacokinetics of FF and VI following repeat administration of FF 200 mcg/VI 25 mcg (FF 100 mcg/VI 12.5 mcg for subjects with severe hepatic impairment) via a novel dry powder inhaler (NDPI).
Statistical Methods: Sample size: There were 9 subjects planned in each of the groups: mild, moderate and severe hepatic impairment and healthy control subjects. Due to recruitment difficulties, only 8 subjects were enrolled in the severe hepatic impairment group. The sample size calculations were based on a non-inferiority approach for the primary endpoint, where lack of effect would be concluded if the upper 90% confidence limit for the ratio of hepatic/healthy was <2. All 35 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. Analysis: Plasma FF and VI concentration data and derived pharmacokinetic parameters were summarised. In addition, a formal statistical analysis was carried out. Following $\log_e$-transformation, maximum observed plasma concentration (Cmax) on Day 1 and 7, AUC from pre-dose to 8 h post-dose (AUC(0-8)) on Day 1, AUC(0-24)) on Day 7 and terminal phase half-life (t1/2) on Day 7 for FF and VI were separately analysed using a mixed model. Point estimates and their associated 90% confidence interval (CIs) were constructed for the difference between each hepatically impaired group and the healthy subject group for both FF and VI. The point estimates and their associated 90% CIs were back-transformed to provide point estimates and 90% CIs for the ratio. For AUC(0-8) on Day 1, and AUC(0-24) and t1/2 on Day 7, an analysis of variance model was used with group fitted as a fixed effect. Point estimates and their associated 90% CIs were constructed as described above for Cmax analyses. Similarly, the accumulation ratio was determined from comparison of AUC(0-8), Cmax at Day 1 and Day 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. Point estimates and their associated 90% CIs were constructed as described above. For the primary endpoints, non-inferiority was to be concluded if the upper 90% CI limit for the adjusted geometric mean ratio was less than 2. Selected safety endpoints were summarised as pharmacodynamic parameters. 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% CIs were constructed for

the difference between each hepatically impaired group and the healthy subject group.
Serum cortisol weighted mean (0–24 h) on Day 7 was analysed similarly to the other pharmacodynamic endpoints. However, data were log_e-transformed prior to analysis and baseline was defined as the log_e-transformed Day -1 serum cortisol weighted mean (0–24 h). Therefore, the ratio and corresponding two-sided 90% CI for each hepatic impairment group to healthy subjects was estimated. The ratio was calculated by back-transforming the difference in adjusted means.
All other safety data were summarised. No formal statistical analysis was performed on safety data not defined as pharmacodynamic endpoints.

Study Population: Healthy subjects were males or females aged between 18 and 70 years. Hepatically impaired subjects had a known medical history of liver disease with or without a known history of alcohol abuse, and a Child-Pugh score of 5-15 to cover all severities (Mild = 5-6 points; Moderate = 7-9 points; Severe = 10-15 points). The components that contributed to the Child-Pugh score were directly related to the underlying hepatic disease and not to non-hepatic disease.

Number of Subjects:	**Healthy**	**Hepatic impairment**			**Total**
	FF/VI 200/25	**Mild FF/VI 200/25**	**Moderate FF/VI 200/25**	**Severe FF/VI 100/12.5**	
Planned N	9	9	9	9	36
Dosed N	9	9	9	8	35
Completed n (%)	9 (100)	9 (100)	9 (100)	8 (100)	35 (100)
Demographics	**Healthy**	**Hepatic impairment**			**Total**
	FF/VI 200/25	**Mild FF/VI 200/25**	**Moderate FF/VI 200/25**	**Severe FF/VI 100/12.5**	
N (All Subjects)	9	9	9	8	35
Females: Males	4: 5	4: 5	4: 5	3: 5	15: 20
Mean Age in years (range)	50.3 (33-61)	52.1 (31-65)	52.0 (37-63)	57.8 (45-64)	52.9 (31-65)
Mean Weight in kg (range)	77.3 (68-86)	74.0 (51-102)	78.1 (65-90)	78.0 (63-115)	76.8 (51-115)
Mean Height in cm (range)	172.8 (164–179)	171.2 (157–179)	170.3 (156–184)	169.8 (156–187)	171.1 (156–187)
Mean BMI in kg/m^2 (range)	25.97 (22.6–29.4)	24.98 (20.5–31.8)	27.02 (22.7–32.7)	26.98 (20.7–32.9)	26.21 (20.5–32.9)
White n (%)	9 (100)	9 (100)	9 (100)	8 (100)	35 (100)

Pharmacokinetics (PK): Selected FF pharmacokinetic parameters following single and repeated inhaled administration of FF/VI are summarised below.

FF parameter	**Group**	**Day**	**N**	**n**	**n***	**Geometric mean (CV%)**	**95% CI**
AUC(0-24) (pg.h/mL)	Healthy	7	9	9	0	472.7 (62.5)	(304.1, 734.9)
	Mild Hepatic		9	9	0	634.5 (27.3)	(516.3, 779.7)
	Moderate Hepatic		9	9	0	863.5 (61.8)	(557.6, 1337.3)
	Severe Hepatic		8	8	0	412.9 (117.3)	(189.7, 898.8)
AUC(0-8) (pg.h/mL)	Healthy	1	9	9	0	148.7 (40.8)	(110.0, 201.1)
	Mild Hepatic		9	9	0	99.7 (40.6)	(73.9, 134.6)
	Moderate Hepatic		9	9	0	146.4 (28.5)	(118.1, 181.5)
	Severe Hepatic		8	8	3	13.7 (427.7)	(3.3, 57.9)
	Healthy	7	9	9	0	237.6 (37.2)	(180.2, 313.3)
	Mild Hepatic		9	9	0	287.7 (28.2)	(232.6, 355.8)
	Moderate Hepatic		9	9	0	379.8 (40.5)	(281.5, 512.4)
	Severe Hepatic		8	8	0	188.1 (71.0)	(110.2, 320.8)
Cmax (pg/mL)	Healthy	1	9	9	0	36.1 (49.5)	(25.2, 51.7)
	Mild Hepatic		9	9	0	29.1 (37.1)	(22.1, 38.4)
	Moderate Hepatic		9	9	0	29.4 (35.6)	(22.5, 38.3)
	Severe Hepatic		8	8	3	10.8 (81.5)	(5.95-19.62)
	Healthy	7	9	9	0	43.5 (40.0)	(32.4, 58.5)
	Mild Hepatic		9	9	0	51.4 (36.6)	(39.1, 67.5)
	Moderate Hepatic		9	9	0	62.3 (39.7)	(46.4, 83.7)
	Severe Hepatic		8	8	0	29.8 (55.9)	(19.3, 46.1)
Tmax (h)[1]	Healthy	1	9	9	0	0.25 (0.08-2.00)	NA
	Mild Hepatic		9	9	0	0.25 (0.08-2.00)	NA

	Moderate Hepatic		9	9	0	1.00 (0.08-4.00)	NA
	Severe Hepatic		8	8	0	2.00 (0.50-3.08)	NA
	Healthy	7	9	9	0	0.50 (0.08-2.00)	NA
	Mild Hepatic		9	9	0	1.00 (0.08-1.50)	NA
	Moderate Hepatic		9	9	0	1.00 (0.08-2.00)	NA
	Severe Hepatic		8	8	0	2.00 (0.25-4.00)	NA
t1/2 (h)	Healthy	7	9	7	0	23.9 (60.7)	(14.2, 40.1)
	Mild Hepatic		9	7	0	30.9 (17.8)	(26.3, 36.4)
	Moderate Hepatic		9	8	0	35.5 (82.1)	(19.5, 64.6)
	Severe Hepatic		8	5	0	53.5 (22.6)	(40.6, 70.6)

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

Results from statistical analysis of dose-normalised FF pharmacokinetic parameters are summarised in the table below.

FF parameter	Day	Group comparison	Adjusted geometric means	Ratio of adjusted geometric means	90% CI of the ratio
AUC(0-8)	1	Hepatic Mild /Healthy	99.71 / 148.73	0.67	(0.33, 1.35)
		Hepatic Moderate /Healthy	146.44 / 148.73	0.98	(0.49, 1.98)
		Hepatic Severe /Healthy	27.38 / 148.73	0.18	(0.09, 0.38)
AUC (0-24)	7	Hepatic Mild /Healthy	634.50 / 472.74	1.34	(0.82, 2.20)
		Hepatic Moderate /Healthy	863.50 / 472.74	1.83	(1.11, 2.99)
		Hepatic Severe /Healthy	825.75 / 472.74	1.75	(1.05, 2.91)
Cmax	1	Hepatic Mild /Healthy	29.10 / 36.05	0.81	(0.57, 1.15)
		Hepatic Moderate /Healthy	29.36 / 36.05	0.81	(0.57, 1.16)
		Hepatic Severe /Healthy	21.61 / 36.05	0.60	(0.42, 0.86)
	7	Hepatic Mild /Healthy	51.36 / 43.48	1.18	(0.83, 1.69)
		Hepatic Moderate /Healthy	62.33 / 43.48	1.43	(1.00, 2.04)
		Hepatic Severe /Healthy	59.58 / 43.48	1.37	(0.95, 1.98)

Results from statistical analysis of dose-normalised FF pharmacokinetic parameters to assess accumulation are summarised in the table below. The estimated ratio of 13.7 for the severe group was confounded by a large extent of non-quantifiable data on Day 1 (including 3 subjects who had no quantifiable values) due to the lower dose administered to this group and hence is likely to be an over-estimate.

FF parameter	Group	Adjusted geometric means Day 7 / Day 1	Ratio of adjusted geometric means	90% CI of the ratio
AUC(0-8)	Healthy	237.62 / 148.73	1.60	(1.05, 2.44)
	Hepatic Mild	287.69 / 99.71	2.89	(1.89, 4.40)
	Hepatic Moderate	379.77 / 146.44	2.59	(1.70, 3.96)
	Hepatic Severe	376.11 / 27.38	13.7	(8.77, 21.5)
Cmax	Healthy	43.48 / 36.05	1.21	(0.90, 1.61)
	Hepatic Mild	51.36 / 29.10	1.77	(1.32, 2.36)
	Hepatic Moderate	62.33 / 29.36	2.12	(1.59, 2.84)
	Hepatic Severe	59.58 / 21.61	2.76	(2.03, 3.75)

Selected VI pharmacokinetic parameters following single and repeated inhaled administration of FF/VI are summarised in the table below.

VI parameter	Group	Day	N	n	n*	Geometric mean (CV%)	95% CI
AUC(0-24) (pg.h/mL)	Healthy	7	9	9	0	511.1 (26.1)	(419.6, 622.6)
	Mild Hepatic		9	9	0	335.7 (32.1)	(263.9, 427.1)
	Moderate Hepatic		9	7	0	678.3 (17.4)	(578.2, 795.6)
	Severe Hepatic		8	8	0	183.8 (173.1)	(68.7, 491.8)
AUC(0-8)	Healthy	1	9	9	0	204.6 (32.2)	(160.8, 260.4)

	Mild Hepatic		9	9	0	81.8 (63.3)	(52.3, 127.8)
	Moderate Hepatic		9	7	0	189.7 (43.6)	(129.1, 279.0)
	Severe Hepatic		8	8	0	59.1 (90.3)	(31.0, 112.7)
	Healthy	7	9	9	0	306.2 (24.7)	(254.0, 369.0)
	Mild Hepatic		9	9	0	210.1 (26.4)	(172.1, 256.5)
	Moderate Hepatic		9	7	0	342.8 (18.5)	(289.2, 406.3)
	Severe Hepatic		8	8	0	128.6 (114.3)	(59.9, 276.1)
Cmax (pg/mL)	Healthy	1	9	9	0	225.7 (45.6)	(161.6, 315.3)
	Mild Hepatic		9	9	0	107.1 (71.6)	(65.3, 175.6)
	Moderate Hepatic		9	7	0	167.9 (68.1)	(94.9, 297.2)
	Severe Hepatic		8	8	0	83.5 (47.8)	(57.2, 122.0)
Cmax (pg/mL)	Healthy	7	9	9	0	246.8 (31.4)	(195.0, 312.5)
	Mild Hepatic		9	9	0	154.5 (48.6)	(108.5, 220.1)
	Moderate Hepatic		9	7	0	193.3 (31.2)	(145.9, 256.2)
	Severe Hepatic		8	8	0	103.0 (46.0)	(71.4, 148.6)
Tmax (h)[1]	Healthy	1	9	9	0	0.08 (0.08-0.25)	NA
	Mild Hepatic		9	9	0	0.08 (0.08-0.25)	NA
	Moderate Hepatic		9	7	0	0.08 (0.08-0.25)	NA
	Severe Hepatic		8	8	0	0.08 (0.08-0.25)	NA
	Healthy	7	9	9	0	0.08 (0.08-0.08)	NA
	Mild Hepatic		9	9	0	0.08 (0.08-0.25)	NA
	Moderate Hepatic		9	7	0	0.08 (0.08-0.25)	NA
	Severe Hepatic		8	8	0	0.08 (0.08-0.08)	NA
t1/2 (h)	Healthy	7	9	4	0	11.1 (53.1)	(5.03, 24.6)
	Mild Hepatic		9	3	0	28.7 (83.9)	(4.68, 175.7)
	Moderate Hepatic		9	3	0	45.1 (31.2)	(21.1, 96.2)
	Severe Hepatic		8	5	0	4.76 (741.6)	(0.39, 57.5)

1. median (range).

Subject 403 had non-calculable value for AUC(0-24) and subsequently appeared as an outlier in the statistical analyses for AUC(0-24). Results excluding data from this subject led to a change in inference for the Moderate/Healthy comparison for AUC(0-24) on Day 7 (geometric mean ratio 1.33 [95% CI: 0.92, 1.91]). All other inferences remained the same.

Results from statistical analysis of dose-normalised VI pharmacokinetic parameters are summarised in the table below.

VI parameter	**Day**	**Group comparison**	**Adjusted geometric means**	**Ratio of adjusted geometric means**	**90% CI of the ratio**
AUC(0-8)	1	Hepatic Mild /Healthy	81.76 / 204.61	0.40	(0.26, 0.62)
		Hepatic Moderate /Healthy	189.74 / 204.61	0.93	(0.58, 1.48)
		Hepatic Severe /Healthy	118.17 / 204.61	0.58	(0.37, 0.91)
AUC (0-24)	7	Hepatic Mild /Healthy	335.74 / 511.10	0.66	(0.40, 1.08)
		Hepatic Moderate /Healthy	678.27 / 511.10	1.33	(0.78, 2.26)
		Hepatic Severe /Healthy	367.69 / 511.10	0.72	(0.43, 1.20)
Cmax	1	Hepatic Mild /Healthy	107.08 / 225.69	0.47	(0.33, 0.69)
		Hepatic Moderate /Healthy	167.93 / 225.69	0.74	(0.50, 1.11)
		Hepatic Severe /Healthy	167.02 / 225.69	0.74	(0.50, 1.09)
	7	Hepatic Mild /Healthy	154.51 / 246.82	0.63	(0.43, 0.91)
		Hepatic Moderate /Healthy	193.31 / 246.82	0.78	(0.52, 1.17)
		Hepatic Severe /Healthy	206.04 / 246.82	0.83	(0.57, 1.23)

Results from statistical analysis of dose-normalised VI pharmacokinetic parameters to assess accumulation are summarised in the table below.

VI parameter	**Group**	**Adjusted geometric means Day 7 / Day 1**	**Ratio of adjusted geometric means**	**90% CI of the ratio**
AUC(0-8)	Healthy	306.17 / 204.61	1.50	(1.21, 1.85)
	Hepatic Mild	210.09 / 81.76	2.57	(2.07, 3.18)
	Hepatic Moderate	342.79 / 189.74	1.81	(1.42, 2.30)
	Hepatic Severe	257.12 / 118.17	2.18	(1.73, 2.73)

Cmax	Healthy	246.82 / 225.69	1.09	(0.89, 1.35)
	Hepatic Mild	154.51 / 107.08	1.44	(1.17, 1.78)
	Hepatic Moderate	193.31 / 167.93	1.15	(0.91, 1.46)
	Hepatic Severe	206.04 / 167.02	1.23	(0.99, 1.54)

Pharmacodynamics (PD): Statistical analysis of maximum heart rate (0-4 h) on Day 7 is summarised below.

Maximum heart rate (0-4 h) (bpm) **Group comparison**	**Adjusted means test/reference**	**Difference of adjusted means**	**90% CI of the difference**
Hepatic mild/healthy	76.9 / 73.1	3.8	(-1.2, 8.8)
Hepatic moderate/healthy	76.3 / 73.1	3.2	(-1.7, 8.1)
Hepatic severe/healthy	70.7 / 73.1	-2.4	(-7.7, 3.0)

Statistical analysis of minimum serum potassium (0-4 h) on Day 7 is summarised in the table below.

Minimum potassium (0-4 h) (mmol/L) **Group comparison**	**Adjusted means test/reference**	**Difference of adjusted means**	**90% CI of the difference**
Hepatic mild/healthy	3.88 / 3.84	0.04	(-0.19, 0.27)
Hepatic moderate/healthy	3.73 / 3.84	-0.11	(-0.34, 0.12)
Hepatic severe/healthy	3.99 / 3.84	0.15	(-0.10, 0.40)

Statistical analysis of serum cortisol weighted mean (0-24 h) on Day 7 is summarised in the table below.

Cortisol weighted mean (0-24 h) (nmol/L) **Group comparison**	**Adjusted geometric means Test/reference**	**Ratio of adjusted geometric means**	**90% CI of the ratio**
Hepatic mild/healthy	176.18 / 156.24	1.13	(0.85, 1.50)
Hepatic moderate/healthy	103.27 / 156.24	0.66	(0.49, 0.89)
Hepatic severe/healthy	178.38 / 156.24	1.14	(0.84, 1.55)

Safety results: Adverse events were collected from the start of dosing until follow-up. Serious AEs (SAEs) were collected once the consent form had been signed until follow-up. A summary of all AEs is presented in the table below.

Preferred term	**Healthy**	**Hepatic impairment**		
		Mild	**Moderate**	**Severe**
	FF/VI 200/25	**FF/VI 200/25**	**FF/VI 200/25**	**FF/VI 100/12.5**
	N = 9	**N = 9**	**N = 9**	**N = 8**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Subjects with any AE	1 (11)	0	1 (11)	0
Back pain	1 (11)	0	0	0
Nasopharyngitis	0	0	1 (11)	0

Serious Adverse Events: There were no SAEs.