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: RES104033

Title: A 28-day, Randomised, Double-Blind, Active Comparator, Controlled Study to Assess the Effects of Rosiglitazone, Inhaled Corticosteroid, Theophylline and Theophylline Plus Inhaled Corticosteroid on Inflammation and Pulmonary Function in Asthmatic Smokers.

Rationale: This study used smoking asthmatics as a human model of smoke-induced steroid-insensitive airway inflammation to evaluate both the efficacy of rosiglitazone as an anti-inflammatory and the effect of low doses of theophylline on the response to inhaled corticosteroids (ICS).

Phase: I

Study Period: 05 August 2005 – 06 June 2007.

Study Design: Randomised, double-blind, active comparator, controlled.

Centres: One centre in Glasgow, Scotland, UK.

Indication: None.

Treatment: Following successful ICS weaning, subjects were randomly assigned (Baseline Visit, Day +1) to one of the following treatments for 28 days: low dose (LD) ICS bid (inhaled 200 μg); theophylline bid (200 mg oral tablet); theophylline bid (200 mg oral tablet) plus LD ICS bid (inhaled 200 μg); or rosiglitazone bid (4 mg oral tablet).

Primary Objective: Comparison of pre-bronchodilator forced expiratory volume in 1 second (FEV1) at 28 days between rosiglitazone and LD ICS treatment groups.

Statistical Methods: All lung function data in the Intent-To-Treat population were listed and summarised. For the primary endpoint, pre-bronchodilatory FEV1 following 28 days treatment, a repeated measures analysis was used on untransformed data. The model included fixed effects for treatment, day, treatment by day, baseline (pre-dose on Day 1) and baseline by day; subject was fitted as a random effect. The repeated measures model was also used for analysing the other lung function parameters following 14 and 28 days of dosing. Lung function variables were not log-transformed. Results from the statistical analyses were presented in tabular form as well as plots of adjusted means. All safety data (adverse events [AEs], vital signs, FEV1, electrocardiography and laboratory tests) were listed and summarised as appropriate to the data. Pharmacodynamic markers of inflammation from blood and sputum samples were listed and summarised as appropriate to the data.

Study Population: Male or female adults aged between 18 and 60 years of age (inclusive) with a clinical diagnosis of mild or moderate persistent asthma in accordance with the Global Initiative for Asthma criteria for a minimum of 6 months prior to entry to the study. Subjects were current cigarette smokers with a minimum five-pack-year smoking history. Subjects had a baseline FEV1 that was greater than 50% predicted and demonstrated a reversibility of FEV1 after nebulised albuterol of 12% or more at screening, washout or randomisation.

Number of Subjects:	Rosiglitazone	LD ICS	Theophylline	Theophylline + LD ICS	Total
Planned N	22	22	22	22	88
Randomised N	23	23	23	22	91
Completed n (%)	18 (78)	21 (91)	20 (87)	20 (91)	79 (87)
Total Number Subjects Withdrawn N (%)	5 (22)	2 (9)	3 (13)	2 (9)	12 (13)
Withdrawn due to Adverse Events n (%)	1 (4)	1 (4)	0	1 (5)	3 (3)
Lost to follow-up n (%)	2 (9)	0	1 (4)	0	3 (3)
Protocol violation n (%)	0	0	1 (4)	0	1 (1)
Decided to withdraw n (%)	2 (9)	0	1 (4)	0	3 (3)
Asthma exacerbation n (%)	0	1 (4)	0	1 (5)	2 (2)
Demographics					
N	23	23	23	22	91
Females: Males	13:10	14:9	15:8	12:10	54:37
Mean Age in Years (range)	42.4 (25–59)	43.3 (27–57)	43.8 (24–58)	41.8 (21–60)	42.8 (21–60)
Mean Height in Cm (range)	168.5 (155–183)	166.8 (152–183)	165.4 (152–188)	164.5 (142–180)	166.3 (142–188)

Mean Weight in Kg (range)	73.66 (51.0–105.0)	71.25 (46.0–104.0)	72.69 (45.0–104.0)	70.16 (50.2–98.0)	71.96 (45.0–105.0)
Mean Body Mass Index (kg/m^2)	26.05 (19.5–38.6)	25.45 (18.4–34.2)	26.60 (18.6 –37.1)	25.91 (17.3–36.1)	26.00 (17.3–38.6)
White n (%)	23 (100)	23 (100)	23 (100)	22 (100)	91 (100)
Mean Smoking History in Pack Years (range)	28.8 (10–86)	23.3 (6–45)	27.0 (6–60)	24.7 (5–54)	26.0 (5–86)

Efficacy Endpoints: Treatment differences and 95% confidence intervals for pre-bronchodilator FEV1 (L) are presented below.

Treatment Comparison	Day	Difference in Adjusted Mean [95% CI]	p-value
Rosiglitazone vs. LD ICS	14	0.164 [-0.001, 0.329]	0.0507
	28	0.183 [-0.001, 0.367]	0.0510
Rosiglitazone vs. theophylline + LD ICS	14	0.031 [-0.134, 0.197]	0.7068
	28	0.019 [-0.167, 0.204]	0.8423
Theophylline + LD ICS vs. theophylline	14	0.080 [-0.081, 0.242]	0.3252
	28	0.036 [-0.144, 0.217]	0.6883
Theophylline + LD ICS vs. LD ICS	14	0.133 [-0.027, 0.293]	0.1026
	28	0.165 [-0.013, 0.342]	0.0692

On average rosiglitazone yielded 183mL [95% confidence intervals:-1, 367] greater FEV1 value on Day 28 than LD ICS when adjusted for the baseline value (pre-dose on Day 1). On average rosiglitazone yielded 164mL [95% confidence intervals: -1, 329] greater FEV1 value on Day 14 than LD ICS. Resullts from the statistical analysis of post-bronchodilator FEV1 indicate that on average rosiglitazone yields a 130 mL [95% confidence intervals:-60, 320] greater post-bronchodilator FEV1 value on Day 28 than LD ICS, when adjusted for baseline post-bronchodilator FEV1 (pre-dose on Day 1). Post-bronchodilator FEV1 was not measured on Day 14. Treatment differences and 95% confidence intervals for pre-bronchodilator forced vital capacity (FVC) (L) are presented below.

Treatment Comparison	Day	Difference in Adjusted Mean [95% CI]	p-value
Rosiglitazone vs. LD ICS	14	0.045 (-0.114 , 0.204)	0.5764
	28	0.156 (-0.042 , 0.354)	0.1219
Rosiglitazone vs. theophylline + LD ICS	14	-0.087 (-0.247 , 0.073)	0.2843
	28	-0.098 (-0.298 , 0.101)	0.3300
Theophylline + LD ICS vs. theophylline	14	0.117 (-0.040 , 0.273)	0.1411
	28	0.078 (-0.116 , 0.272)	0.4242
Theophylline + LD ICS vs. LD ICS	14	0.132 (-0.023 , 0.286)	0.0939
	28	0.254 (0.063 , 0.445)	0.0100

On average rosiglitazone yielded 156 mL [95% confidence intervals: -42, 354] greater pre-bronchodilator FVC value on Day 28 than LD ICS. On average rosiglitazone yielded 45 mL [95% confidence intervals:-114, 204] greater pre-bronchodilator FVC value on Day 14 than LD ICS. Resullts from the statistical analysis of post-bronchodilator FVC indicate that on average rosiglitazone yielded a 42 mL [95% confidence intervals:-266, 350] greater FVC value on Day 28 than LD ICS. Post-bronchodilator FVC was not measured on Day 14.

Results from the statistical analysis of other secondary lung function endpoints were similar to that of the primary endpoint pre-bronchodilator FEV1.

Safety results: Adverse events were collected from first dose of investigational product to follow-up. A summary of all on-therapy AEs (n[%]) reported by more than one subject in any group during the study is presented below.

Three subjects were withdrawn due to AEs: Subject 63 had eyelid oedema and palpitations for 6 days after the first day of dosing with rosiglitazone 4 mg. Both AEs were of mild intensity and were judged to be related to investigational product by the Investigator. The subject was withdrawn from the study on Day 4. Subject 69 had diarrhoea, nausea and vomiting, all of severe intensity, on the second day of dosing with LD ICS. All AEs were judged to be related to investigational product by the Investigator. The diarrhoea lasted for 6 days, while the nausea and vomiting resolved after 1 day. The subject was withdrawn from the study on Day 4. Subject 54 had a headache of severe intensity 1 day after the first dose of theophylline plus LD ICS that was judged to be related to investigational product by the Investigator. The headache resolved after 7 days. The subject was withdrawn on Day 5 of the study.

Adverse Events:	Rosiglitazone	LD ICS	Theophylline	Theophylline + LD ICS
N	23	23	23	22

No. subjects with AEs n (%)	10 (43)	12 (52)	18 (78)	12 (55)
Most Frequent AEs				
Headache	4 (17)	5 (22)	6 (26)	8 (36)
Nasopharyngitis	2 (9)	3 (13)	5 (22)	0
Dyspepsia	0	1 (4)	5 (22)	1 (5)
Nausea	0	1 (4)	3 (13)	3 (14)
Diarrhoea	0	1 (4)	4 (17)	0
Vomiting	0	1 (4)	3 (13)	1 (5)
Pharyngolaryngeal pain	0	2 (9)	2 (9)	1 (5)
Cough	0	1 (4)	2 (9)	0
Neck pain	0	1 (4)	2 (9)	0
Asthma	1 (4)	2 (9)	0	0
Abdominal distension	0	0	1 (4)	1 (5)
Toothache	1 (4)	1 (4)	0	0
Dizziness	0	0	1 (4)	1 (5)
Pain in extremity	1 (4)	0	0	1 (5)
Chest pain	0	1 (4)	1 (4)	0
Dysmenorrhoea	1 (4)	0	1 (4)	0

Serious Adverse Events, n (%) [n considered by the Investigator to be related, possibly related or probably related to study medication]: Two subjects had SAEs while taking theophylline; neither subject was withdrawn from the study due to these SAEs and both resolved before the end of the study.
Subject 42, a 38-year-old White female, had viral meningitis of 92 days duration 15 days after the first dose of theophylline. This SAE was judged to be of moderate intensity and unrelated to theophylline by the Investigator.
Subject 113, a 40-year-old White male, had severe chest pain for 3 h 15 days after the first dose of theophylline. This SAE was judged to be unrelated to theophylline by the Investigator.
Subject 596 was due to be randomised; however, during the last week of weaning from inhaled corticosteroid he was admitted to the local hospital (Western Infirmary) with chest pain. The subject was diagnosed with an acute coronary syndrome and the cardiology team proceeded to coronary angioplasty. Subject 596 was withdrawn from the study as a result and was not allocated to a treatment group. The SAE form was completed and sent once the team was made aware of admission

Health Outcomes Endpoint: The median Asthma Control Questionnaire score on Day 28 for the rosiglitazone group was consistent with the score on Day 1. Scores had decreased from Day 1 to Day 28 for the other three groups, especially for the theophylline and theophylline + LD ICS groups.

Pharmacodynamic Endpoints: No trend was identified in histone deacetylase levels following 28 days with any treatment. Data must be interpreted with caution due to the substantial number of missing results in each of the treatment arms due to sample quality issues. Exhaled breath pH and exhaled nitric oxide levels were similar across all four groups, and there were no differences between Day 1 and Day 28. There were no evident trends in the four groups in terms of percentages of eosinophils, neutrophils, macrophages, lymphocytes or bronchial epithelial cells on Day 28. There were no evident trends in sputum or blood biomarker levels following 28 days with any treatment.

Publications: No publication

Date updated: 6-Feb-2008