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.: ARA102198
Title: A randomised, double-blind, placebo-controlled, parallel group study to investigate the anti-inflammatory and metabolic effects of rosiglitazone XR, 8mg once daily, in subjects with rheumatoid arthritis
Rationale: In view of the anti-inflammatory properties of thiazolidinediones, drugs such as rosiglitazone (RSG) are potential new therapeutic leads for the treatment of rheumatoid arthritis (RA). The purpose of this study was to assess anti-inflammatory and metabolic effects of rosiglitazone XR, a new extended release formulation, as an adjunctive therapy in subjects with RA where their condition was insufficiently controlled with existing treatment options.
Phase: II
Study Period: 25 November 2004 – 8 December 2006
Study Design: Randomised, double-blind, placebo-controlled
Centres: Two centres in Lithuania and three centres in the UK
Indication: Rheumatoid arthritis
Treatment: Subjects received one tablet of either RSG XR 8mg or placebo (PBO) once daily for 26 weeks, with or without food, in addition to their current RA treatment.
Objectives: The primary objective of the study was to assess the anti-inflammatory efficacy of rosiglitazone XR 8mg administered once daily for a period of 6 months to subjects with RA who demonstrated active disease despite disease-modifying anti-rheumatic drug (DMARD) therapy.
Primary Outcome/Efficacy Variable: Change in disease activity score (DAS) based on a 28-joint count (DAS28) after 6 months of treatment.
Secondary Outcome/Efficacy Variables: **Efficacy:** American College of Rheumatology (ACR)20, ACR50 and ACR70 response at 3 and 6 months; changes in tender/painful joint count (TJC) and swollen joint count (SJC) at 3 and 6 months: change in DAS28 at 3 months; European League Against Rheumatism (EULAR) response at 3 and 6 months; changes in subject's and physician's global assessment of disease activity at 3 and 6 months; changes in subject's assessment of pain at 3 and 6 months. **Pharmacodynamics:** Changes in markers of insulin resistance (fasting glucose, fasting insulin, HbA1c and C-peptide) at 6 months; changes in lipids (high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides) at 6 months. **Biomarkers:** Changes in markers of inflammation: C-reactive protein (CRP), high sensitivity CRP (hsCRP) and ESR at 3 and 6 months. Changes in exploratory biomarkers: apoA1, apoB, adiponectin, interleukin-6 (IL-6), IL-10, tumour necrosis factor-α (TNF-α) and sCD40L at 6 months. **Health Outcomes:** Changes in the Functional Disability Index (FDI) of the Stanford Health Assessment Questionnaire (HAQ) at 3 and 6 months; changes in the Global Fatigue Index (GFI) of the Fatigue Symptom Inventory (FSI) at 6 months.
Statistical Methods: The Safety population consisted of all randomised subjects who received at least one dose of study medication. The modified intent-to-treat (MITT) population consisted of all randomised subjects who received at least one dose of study medication, had a baseline assessment and had at least one on-treatment assessment. The primary endpoint of interest was the comparison of DAS28 scores obtained from the rosiglitazone XR and placebo groups after 6 months of treatment. A repeated measures analysis was used to analyse the change from baseline in DAS28 scores. Adjusted means and treatment differences were presented along with their corresponding two-sided 95% confidence intervals (CIs). Change from baseline for TJC, SJC, subject's and physician's global assessments and subject's pain assessment were analysed using a repeated measures analysis. Adjusted means and treatment differences were presented along with their corresponding two-sided 95% CIs. Changes from baseline in markers of insulin resistance were analysed using a fixed effect model giving adjusted means and treatment differences together with the corresponding 95% CIs. For lipid data, the ratio to baseline was analysed, following a $\log_e$-transformation, using a fixed effect model giving adjusted means and treatment differences together with the associated 95% CIs. For CRP, hsCRP and ESR, the ratio to baseline was analysed, following a $\log_e$ transformation, using a mixed effect model for CRP and ESR and a fixed effects model for hsCRP. Adjusted geometric means and treatment ratios with corresponding 95% CIs were calculated. Since each laboratory used different assays to measure CRP and had different lower limits of quantification, two methods of analysing the CRP data were used: Method 1: all values <6 or recorded as '<6' set to 3 (half the lower limit of quantification); Method 2: values of '<6' from UK sites set to 3 and

values of '0' from Lithuanian sites set to 0.1. Results from Method 1 for CRP and results for ESR showed a significant country by treatment interaction and the treatment effect is presented for each country.
The safety parameters were summarised by treatment group.

Study Population: Male or female subjects aged over 18 years with a diagnosis of RA according to the revised 1987 criteria of the ACR were entered into the study. They had active disease despite their current stable anti-rheumatic therapy. This was defined as at least 6 swollen joints (out of 28 joints) plus two out of the following three criteria: (i) 6 tender joints (out of 28), (ii) early morning stiffness lasting longer than 30 minutes, (iii) erythrocyte sedimentation rate (ESR) ≥28mm/h. Existing treatment for RA could include DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors and oral glucocorticoids (≤10mg/day), but subjects could not be on any biological anti-rheumatic therapy.

	PBO	**RSG XR**
Number of Subjects:		
Planned, N	48	48
Randomised, N	49	49
Completed, n (%)	37 (76)	30 (61)
Total Number Subjects Withdrawn, N (%)	12 (24)	19 (39)
Withdrawn due to Adverse Events n (%)	4 (8)	5 (10)
Withdrawn due to Lack of Efficacy n (%)	2 (4)	4 (8)
Withdrawn for other reasons n (%)	6 (12)	10 (20)
Demographics	**PBO**	**RSG XR**
N (Safety)	49	49
Females: Males	47:2	46:3
Mean Age, years (SD)	56.2 (9.3)	56.8 (11.6)
White, n (%)	49 (100)	49 (100)
Primary Efficacy Results:		
DAS28 at Month 6	**PBO**	**RSG XR**
Baseline: Mean	6.34	6.24
Model Adjusted Change from Baseline: mean (SE)	-1.37 (0.17)	-1.11 (0.20)
Difference from Placebo: mean (95% CI)		0.26 (-0.28, 0.79)
P-value		0.34
Secondary Outcome Variables:		
Efficacy Endpoints	**PBO**	**RSG XR**
ACR20 at Month 3		
Responders n (%)	13 (34.2)	11 (28.2)
Odds ratio compared with Placebo (95% CI)		0.79 (0.30, 2.08)
ACR20 at Month 6		
Responders n (%)	14 (40.0)	9 (36.0)
Odds ratio compared with Placebo (95% CI)		0.83 (0.30, 2.33)
ACR50 at Month 3		
Responders n (%)	0	2 (5.1%)
ACR50 at Month 6		
Responders n (%)	1 (2.9%)	5 (20.0%)
ACR70 at Month 3		
Responders n (%)	0	0
ACR70 at Month 6		
Responders n (%)	0	0
TJC at Month 3		
Model Adjusted Change from Baseline: mean (SE)	-4.23 (0.86)	-5.33 (0.86)
Difference from Placebo: mean (95% CI)		-1.09 (-3.53, 1.34)
TJC at Month 6		
Model Adjusted Change from Baseline: mean (SE)	-5.57 (1.06)	-5.14 (1.22)

Difference from Placebo: mean (95% CI)		0.42 (-2.81, 3.65)
SJC at Month 3		
Model Adjusted Change from Baseline: mean (SE)	-5.37 (0.64)	-5.54 (0.64)
Difference from Placebo: mean (95% CI)		-0.16 (-1.98, 1.65)
SJC at Month 6		
Model Adjusted Change from Baseline: mean (SE)	-5.90 (0.76)	-6.09 (0.89)
Difference from Placebo: mean (95% CI)		-0.20 (-2.55, 2.15)
DAS28 at Month 3		
Model Adjusted Change from Baseline: mean (SE)	-1.02 (0.14)	-0.89 (0.15)
Difference from Placebo: mean (95% CI)		0.12 (-0.29, 0.54)
EULAR Response at Month 3		
Responders n (%)	19 (51.4)	15 (42.9)
Odds ratio compared with Placebo (95% CI)		0.73 (0.29, 1.84)
EULAR Response at Month 6		
Responders n (%)	22 (64.7)	13 (56.5)
Odds ratio compared with Placebo (95% CI)		0.67 (0.24, 1.88)
Subject's Global Assessment of Disease Activity at Month 3		
Model Adjusted Change from Baseline: mean (SE)	-14.10 (2.80)	-17.27 (2.78)
Difference from Placebo: mean (95% CI)		-3.17 (-11.01, 4.67)
Subject's Global Assessment of Disease Activity at Month 6		
Model Adjusted Change from Baseline: mean (SE)	-17.85 (3.29)	-20.00 (3.84)
Difference from Placebo: mean (95% CI)		-2.15 (-12.25, 7.95)
Physician's Global Assessment of Disease Activity at Month 3		
Model Adjusted Change from Baseline: mean (SE)	-11.29 (2.09)	-13.01 (2.08)
Difference from Placebo: mean (95% CI)		-1.72 (-7.67, 4.23)
Physician's Global Assessment of Disease Activity at Month 6		
Model Adjusted Change from Baseline: mean (SE)	-14.14 (2.27)	-15.13 (2.69)
Difference from Placebo: mean (95% CI)		-1.00 (-8.07, 6.08)
Subject's Assessment of Pain at Month 3		
Model Adjusted Change from Baseline: mean (SE)	-9.92 (3.11)	-14.19 (3.08)
Difference from Placebo: mean (95% CI)		-4.27 (-13.04, 4.50)
Subject's Assessment of Pain at Month 6		
Model Adjusted Change from Baseline: mean (SE)	-14.56 (3.28)	-17.18 (3.88)
Difference from Placebo: mean (95% CI)		-2.62 (-12.84, 7.60)
Early Morning Stiffness at Month 3		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.53 (0.29)	0.25 (0.29)
Ratio relative to Placebo: mean (95% CI)		0.47 (0.21, 1.06)
Early Morning Stiffness at Month 6		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.24 (0.34)	0.16 (0.41)
Ratio relative to Placebo: mean (95% CI)		0.67 (0.23, 1.95)
Pharmacodynamic Endpoints	**PBO**	**RSG XR**
Fasting Insulin (pmol/L) at Month 6		
Model Adjusted Change from Baseline: mean (SE)	-15.4 (6.2)	-37.3 (7.2)
Difference from Placebo: mean (95% CI)		-21.9 (-41.4, -2.3)
Fasting Glucose (mmol/L) at Month 6		
Model Adjusted Change from Baseline: mean (SE)	0.35 (0.09)	-0.02 (0.10)
Difference from Placebo: mean (95% CI)		-0.36 (-0.65, -0.08)
C-Peptide (nmol/L) at Month 6		
Model Adjusted Change from Baseline: mean (SE)	-0.58 (0.18)	-0.79 (0.22)
Difference from Placebo: mean (95% CI)		-0.21 (-0.79, 0.37)
Hba1c (%) at Month 6		
Model Adjusted Change from Baseline: mean (SE)	0.11 (0.06)	0.16 (0.07)
Difference from Placebo: mean (95% CI)		0.05 (-0.13, 0.23)
HDL-Cholesterol (mmol/L) at Month 6		

Model Adjusted Ratio to Baseline: geometric mean (SE logs)	1.02 (0.04)	0.94 (0.05)
Ratio relative to Placebo: mean (95% CI)		0.92 (0.81, 1.05)
LDL-Cholesterol (mmol/L) at Month 6		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.98 (0.04)	1.18 (0.05)
Ratio relative to Placebo: mean (95% CI)		1.20 (1.06, 1.35)
Triglycerides (mmol/L) at Month 6		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.78 (0.08)	0.96 (0.08)
Ratio relative to Placebo: mean (95% CI)		1.23 (0.98, 1.55)
Inflammatory Biomarker Endpoints	**PBO**	**RSG XR**
C-Reactive Protein (mg/L) Method 1: Month 1 Lithuania		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.73 (0.15)	0.79 (0.16)
Ratio relative to Placebo: mean (95% CI)		1.07 (0.69, 1.66)
C-Reactive Protein (mg/L) Method 1: Month 1 UK		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	1.02 (0.13)	0.61 (0.13)
Ratio relative to Placebo: mean (95% CI)		0.60 (0.41, 0.87)
C-Reactive Protein (mg/L) Method 1: Month 3 Lithuania		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.67 (0.16)	1.04 (0.16)
Ratio relative to Placebo: mean (95% CI)		1.54 (0.99, 2.38)
C-Reactive Protein (mg/L) Method 1: Month 3 UK		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.95 (0.14)	0.58 (0.14)
Ratio relative to Placebo: mean (95% CI)		0.61 (0.41, 0.92)
C-Reactive Protein (mg/L) Method 1: Month 6 Lithuania		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.88 (0.13)	0.85 (0.15)
Ratio relative to Placebo: mean (95% CI)		0.96 (0.64, 1.44)
C-Reactive Protein (mg/L) Method 1: Month 6 UK		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.94 (0.14)	0.69 (0.17)
Ratio relative to Placebo: mean (95% CI)		0.74 (0.48, 1.14)
C-Reactive Protein (mg/L) Method 2: Month 1		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.78 (0.15)	0.59 (0.15)
Ratio relative to Placebo: mean (95% CI)		0.75 (0.50, 1.13)
C-Reactive Protein (mg/L) Method 2: Month 3		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.82 (0.11)	0.71 (0.11)
Ratio relative to Placebo: mean (95% CI)		0.87 (0.64, 1.19)
C-Reactive Protein (mg/L) Method 2: Month 6		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.97 (0.11)	0.68 (0.13)
Ratio relative to Placebo: mean (95% CI)		0.71 (0.51, 0.98)
hs C-Reactive Protein (mg/L) at Month 6		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.95 (0.11)	0.64 (0.13)
Ratio relative to Placebo: mean (95% CI)		0.67 (0.48, 0.93)
ESR (mm/h): Month 1 Lithuania		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.81 (0.90)	1.11 (0.09)
Ratio relative to Placebo: mean (95% CI)		1.38 (1.07, 1.77)
ESR (mm/h): Month 1 UK		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.99 (0.08)	0.90 (0.08)
Ratio relative to Placebo: mean (95% CI)		0.91 (0.73, 1.12)
ESR (mm/h): Month 3 Lithuania		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.73 (0.12)	1.13 (0.12)
Ratio relative to Placebo: mean (95% CI)		1.56 (1.12, 2.17)
ESR (mm/h): Month 3 UK		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.94 (0.11)	1.09 (0.11)
Ratio relative to Placebo: mean (95% CI)		1.17 (0.87, 1.58)
ESR (mm/h): Month 6 Lithuania		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.76 (0.12)	1.17 (0.14)
Ratio relative to Placebo: mean (95% CI)		1.54 (1.07, 2.22)

ESR (mm/h): Month 6 UK		
Model Adjusted Ratio to Baseline: geometric mean (SE logs)	0.78 (0.13)	1.09 (0.15)
Ratio relative to Placebo: mean (95% CI)		1.40 (0.95, 2.05)
Inflammatory Biomarker Endpoints	**PBO**	**RSG XR**
apoA1 (mg/dL)		
Baseline: mean (SD)	146.5 (30.6)	139.6 (28.4)
Month 6: mean (SD)	159.0 (32.7)	132.0 (36.4)
apoB (mg/dL)		
Baseline: mean (SD)	91.8 (25.1)	96.6 (31.9)
Month 6: mean (SD)	91.8 (29.2)	104.3 (32.8)
Adiponectin (µg/mL)		
Baseline: mean (SD)	12.5 (6.1)	10.8 (5.3)
Month 6: mean (SD)	12.9 (6.3)	25.6 (16.5)
IL-6		
Baseline: mean (SD)	18.6 (31.6)	19.7 (26.1)
Month 6: mean (SD)	11.0 (14.7)	10.7 (12.0)
IL-10		
Baseline: mean (SD)	2.47 (2.31)	2.42 (2.19)
Month 6: mean (SD)	2.47 (2.90)	2.52 (3.40)
TNF-α		
Baseline: mean (SD)	2.07 (1.59)	3.42 (3.16)
Month 6: mean (SD)	2.50 (2.42)	2.95 (2.57)
sCD40L		
Baseline: mean (SD)	543.8 (1156.9)	827.4 (2001.9)
Month 6: mean (SD)	773.4 (1169.9)	1700.9 (3341.1)
Health Outcomes Endpoints	**PBO**	**RSG XR**
FDI at Month 3		
Model Adjusted Change from Baseline: mean (SE)	-0.19 ± 0.06	-0.12 ± 0.06
Difference from Placebo: mean (95% CI)		0.07 (-0.10, 0.24)
FDI at Month 6		
Model Adjusted Change from Baseline: mean (SE)	-0.17 ± 0.06	-0.33 ± 0.07
Difference from Placebo: mean (95% CI)		-0.16 (-0.35, 0.03)
FSI at Month 6		
Model Adjusted Change from Baseline: mean (SE)	-6.05 ± 1.92	-3.07 ± 2.39
Difference from Placebo: mean (95% CI)		2.98 (-3.27, 9.23)
Safety Results: An on-therapy adverse event (AE) or serious AE (SAE) was defined as an AE or SAE that started on or after the date/time of the first dose of study medication.		
	PBO	**RSG XR**
Most Frequent (>5% in either treatment group) Adverse Events – On-Therapy	**n (%)**	**n (%)**
Subjects with any AE(s), n/N (%)	36/49 (73)	33/49 (67)
Headache	4/49 (8)	6/49 (12)
Lower respiratory tract infection	7/49 (14)	5/49 (10)
Nausea	6/49 (12)	4/49 (8)
Upper respiratory tract infection	5/49 (10)	3/49 (6)
Rheumatoid arthritis/Arthritis[1]	5/49 (10)	3/49 (6)
Nasopharyngitis	3/49 (6)	3/49 (6)
Pharyngolaryngeal pain	3/49 (6)	3/49 (6)
Leukopenia	2/49 (4)	3/49 (6)
Upper abdominal pain	1/49 (2)	3/49 (6)
Vomiting	1/49 (2)	3/49 (6)
Myalgia	0	3/49 (6)

Peripheral oedema	0	3/49 (6)
Pruritus	0	3/49 (6)
Dizziness	4/49 (8)	2/49 (4)
Back pain	3/49 (6)	2/49 (4)
Diarrhoea	3/49 (6)	2/49 (4)
Cough	4/49 (8)	1/49 (2)
Constipation	3/49 (6)	1/49 (2)
Musculoskeletal pain	3/49 (6)	1/49 (2)
[1]. All events described as flares, exacerbations or degenerative changes		
Serious Adverse Events – On-Therapy **n (%) [n considered by the investigator to be related to study medication]**		
	PBO	**RSG XR**
Subjects with non-fatal SAEs, n (%)	4 (8) [0]	2 (4) [1]
Pleuritic pain	0	1 (2) [0]
Pneumonia	0	1 (2) [1]
Upper abdominal pain	0	1 (2) [0]
Costochondritis	1 (2) [0]	0
Constipation	1 (2) [0]	0
C-reactive protein increased	1 (2) [0]	0
Lower respiratory tract infection	1 (2) [0]	0
Osteoporosis	1 (2) [0]	0
Osteoporotic fracture	1 (2) [0]	0
Paraesthesia	1 (2) [0]	0
Red blood cell sedimentation rate increased	1 (2) [0]	0
Rotator cuff syndrome	1 (2) [0]	0
Subjects with fatal SAEs, n (%)	0	0

Conclusion:
Relative to placebo, 6 months of treatment with RSG did not reduce the DAS28 in subjects who had active RA despite DMARD therapies. There was no difference between treatments in secondary efficacy outcomes, with the exception of a statistically significantly larger reduction from baseline in hsCRP for RSG compared with placebo (33%) at 6 months. In the placebo group, 36 subjects reported adverse events with the most frequently reported being lower respiratory tract infection and nausea. In the RSG XR group, 33 subjects reported adverse events with the most frequently reported being headache and lower respiratory tract infection. Five subjects, all in the RSG group, reported peripheral oedema (three subjects) or swollen ankles (two subjects) and for two of these subjects, the events led to premature withdrawal. Four subjects in the placebo group reported serious adverse events none of which was considered treatment–related. Two subjects in the RSG XR group reported serious adverse events of which, one report of pneumonia was considered treatment-related. There were no fatalities reported in the study.

Publications: No Publications

Date updated: 13-Nov-2007