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.: BRL−049653−461

Title: A double−blind, randomised, placebo−controlled, parallel−group study to investigate the effects of rosiglitazone (extended release tablets) on cerebral glucose utilisation and cognition in subjects with mild to moderate Alzheimer's Disease (AD)

Rationale: Rosiglitazone (RSG) is currently marketed in an immediate release (IR) formulation for the treatment of type II diabetes (T2DM) and has shown a favorable safety profile in both elderly diabetic and Alzheimer's disease (AD) subjects. The overall profile for RSG suggested it could be uniquely suited to the symptomatic treatment of AD and prompted the initiation of development of RSG for this indication. This Phase IIb study was a supportive study for the Phase III development program evaluating RSG in AD. RSG was used as an extended-release (XR) formulation in this study. The XR formulation is being developed to allow once daily dosing which is expected to increase subject compliance in this study population. This study investigated the effects of a 12−month course of RSG on cerebral glucose metabolism and cognitive performance in subjects with mild−to−moderate AD. The study used the fluoro−deoxy−glucose positron emission tomography (FDG PET) signal from the brain as a potential surrogate endpoint for efficacy. Kinetic analysis of accumulation of the radiotracer, [18F]FDG in the brain was performed to determine glucose transport rates across the blood brain barrier and to provide evidence of the ability of RSG to modify cerebral glucose uptake. Structural and volumetric magnetic resonance imaging (MRI) scans of the brain also were performed to assess volumetric changes as a potential surrogate efficacy endpoint. Other markers of clinical status/disease progression and the polymorphism status of genes with a known or putative link to AD also were evaluated.

Phase: IIb

Study Period: 18 May 2004 to 10 July 2008

Study Design: Double−blind, randomized, placebo controlled, parallel−group study including a Screening Phase (1 month), a Double-blind Treatment Phase (12 months), and a Follow-up Phase (2 weeks).

Centers: Multicenter study conducted at 14 centers in 3 countries (Canada, United Kingdom, and United States).

Indication: Alzheimer's disease

Treatment: Subjects were randomized at the end of the Screening Phase to receive either 8mg RSG XR or placebo od for 12 months in a 1:1 ratio. All subjects randomized to 8mg RSG XR received one, 4mg RSG XR tablet od for the first 4 weeks of treatment followed by one, 8mg RSG XR od for the remainder of the 12 months of treatment. All subjects randomized to receive placebo received one placebo tablet matching 4mg RSG XR od for the first 4 weeks of treatment followed by one placebo tablet matching 8mg RSG XR od for the remainder of the 12 months of treatment. RSG XR and matching RSG XR placebo were provided by GlaxoSmithKline (GSK).

Objective: The primary objective was to compare changes in cerebral glucose metabolism in subjects receiving a 12−month course of RSG XR to those receiving placebo, including the time course of any changes.

Primary Endpoint: Change from baseline to Month 12 in Global and Regional Cerebral Metabolic Rate of glucose (CMRglu) Indices.

Secondary Endpoints:

- Changes between baseline and other scan time points in global and regional CMRglu Indices as measured by [18F]FDG uptake.
- Changes from baseline in cognitive tests and clinical scales of AD status.
- Global changes from baseline in brain structure as measured by structural MRI.
- Changes from baseline in the following blood borne biomarkers: markers of glucose metabolism (fasting plasma glucose, fasting plasma insulin, and glycosylated hemoglobin [Hb_{A1C}]); lipid and apolipoprotein levels; and inflammatory markers
- Changes from baseline in insulin sensitivity measured as follows: body mass index (BMI) and Homeostasis Model Assessment of Insulin Resistance (HOMA IR).
- Polymorphism status with respect to genetic markers: i.e., *Apolipoprotein ε4* (*APOE ε4*) gene variant.
- Measures of safety and tolerability including vital signs, 12−lead electrocardiograms (ECGs), hematology and clinical chemistry evaluations, adverse events (AEs), and fluid retention (i.e., body weight; hematocrit; clinical examination).

Statistical Methods: The planned sample size of 80 randomized and 60 evaluable subjects allowed ≥80% power to

detect a 33% treatment response with p≤0.05 (1−tailed uncorrected for multiple comparison) for a voxel in the left mid−frontal cortex showing a 1−year maximal decline in CMRglu Index. The calculation was based on a between−subject standard deviation of 0.33mg/100g/min and a dropout rate of 25%.

Pharmacodynamic/biomarker and efficacy data were analyzed using the Intent−to−Treat (ITT) Population (all randomized subjects who had taken at least one dose of study drug and had at least one post−baseline pharmacodynamic/biomarker, efficacy or PGx assessment). A Per Protocol (PP) Population was used to support the primary analysis and secondary analysis of Alzheimer's Disease Assessment Scale – Cognitive (ADAS−Cog) and Clinician Interview−Based Impression of Change Plus (CIBIC+) scores. The PP Population included all ITT subjects without a major protocol violation. Safety data were analyzed using the All Subjects Population (all randomized subjects who received at least one dose of study drug). Pharmacogenetic (PGx) analyses were performed for the PGx ITT Population (all ITT subjects with evaluable PGx data [i.e., consented to genotyping, had an identified genotyping sample, and were successfully genotyped for at least one of the genetic markers under study]).

The primary endpoint was analyzed using separate mixed models for repeated measures model (MMRM). The MMRM was fitted with the fixed categorical terms of treatment, visit, and treatment by visit interaction; the fixed continuous covariates of baseline, baseline by visit interaction; the random effect of subject; and the repeated effect of visit. The primary model was adjusted for baseline PET.

Changes in structural MRI scans, and cognitive test and clinical scale scores were analyzed as change from baseline in normalized and percentage brain volume using the same approach used for the primary analysis. Changes from baseline in biomarker levels were summarized and evaluated for intercorrelation and correlation with changes in CMRglu Index and other selected endpoints. Covariates included for the cognitive tests were relevant baseline test score, baseline derived intelligence quotient score, and baseline Mini−Mental State Examination (MMSE) score. Covariates included for the clinical scales were relevant baseline score, and baseline MMSE and BMI.

Results for the PET, MRI, ADAS-Cog, CIBIC+ and cognitive test data were reported as least square mean (LSM) and 95% confidence intervals (95% CIs).

The primary endpoint and the secondary endpoints of ADAS−Cog and CIBIC+ scores were also analyzed by *APOE ε4* allele status subgroups, defined as follows: *APOE ε4*−negative (*APOE ε4*-neg) (subjects who were *ε2/2*, *ε2*/3, *APOE ε3/3*); and *APOE ε4*−positive (*APOE ε4*-pos) (subjects who were *ε2/4*, *ε3/4*, or *ε4/4*). These analyses were prospectively defined and were performed for this study in order to be consistent with planned analyses performed in the pivotal double−blind studies from the Phase III development program.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarized by overall incidence, maximum intensity, and relationship to study drug. Clinical laboratory values, vital signs and ECG values were summarized descriptively for absolute values, changes from baseline, incidence of values outside the reference range, and incidence of values of potential clinical concern.

Study Population: Eligible subjects were males or nonpregnant and nonlactating females, aged ≥50 to ≤85 years, who met the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS−ADRDA) criteria for AD; had an AD status of mild to-moderate, as classified by a Mini-Mental State Examination (MMSE) score of 16 to 26, inclusive at screening; and had a permanent caregiver who was willing to attend all visits, oversee the subject's compliance with protocol-specified procedures and study drug, and report on the subject's status.

Number of Subjects	**Placebo**	**8mg RSG XR**
Planned, N	40	40
Randomized, N	40	40
Completed, n (%)	31 (77.5)	31 (77.5)
Total Number of Subjects Withdrawn, n (%)	9 (22.5)	9 (22.5)
Withdrawn due to Adverse Events, n (%)	2 (5.0)	2 (5.0)
Withdrawn due to Insufficient Therapeutic Effect, n (%)	0	2 (5.0)
Withdrawn for Other Reasons, n (%)	7 (17.5)	5 12.5)
Demographics (ITT)	**Placebo**	**8mg RSG XR**
N	39	39
% Female: % Male	48.7:51.3	43.6:56.4
Mean Age (years), (Range)	70.2 (52−84)	72.5 (53−85)
Race: White/Caucasian, n (%)	37 (94.9)	37 (94.9)

APOE ε4 Allele Status (PGx ITT)	Placebo	8mg RSG XR
N	30	29
APOE ε4−positive	24 (80)	15 (52)
APOE ε4−negative	6 (20)	14 (48)
APOE ε4 Copies		
2	7 (23)	6 (21)
1	17 (57)	9 (31)
0	6 (20)	14 (48)

PHARMACODYNAMIC RESULTS:

PET Data – Primary Analysis

Global and Regional CMRglu Indices: Change from Baseline at Month 12 (Repeated Measures Analysis) (ITT)
(Note: Negative change indicates decline in cerebral glucose metabolism.)

Brain Region Evaluated	Treatment	Percent Change from Baseline		Absolute Change from Baseline (mg/cm³)		
		LSM	Difference	Difference	(95% CI)	p−value
Global (averaged grey matter)	Placebo (N=39) 8mg RSG XR (N=39)	−13.1% −6.3%	6.8%	0.13	(−0.058, 0.325)	0.1695
Posterior cingulate Gyrus	Placebo (N=39) 8mg RSG XR (N=39)	−13.5% −5.3%	8.3%	0.18	(0.038, 0.388)	0.1057
Frontal lobe	Placebo (N=39) 8mg RSG XR (N=39)	−13.7% −6.9%	6.7%	0.14	(−0.069, 0.354)	0.1833
Parietal lobe	Placebo (N=39) 8mg RSG XR (N=39)	−14.3% −7.5%	6.9%	0.14	(−0.057, 0.331)	0.1644
Posterior temporal lobe	Placebo (N=39) 8mg RSG XR (N=39)	−14.2% −7.4%	6.8%	0.13	(−0.047, 0.299)	0.1509
Cerebellum	Placebo (N=39) 8mg RSG XR (N=39)	−10.5% −3.7%	6.8%	0.14	(−0.075, 0.342)	0.2041
Medial Temporal Lobe	Placebo (N=39) 8mg RSG XR (N=39)	−12.5% −5.0%	7.6%	0.11	(−0.039, 0.257)	0.1445

PET Data – Secondary Analyses

Brain Region Evaluated	Treatment	Percent Change from Baseline		Absolute Change from Baseline (mg/cm³)	
		LSM	Difference	Difference	(95% CI)
Global and Regional CMRglu Indices: Change from Baseline at Month 1 (Repeated Measures Analysis) (ITT) (Note: Negative change indicates decline in cerebral glucose metabolism.)					
Global (averaged grey matter)	Placebo (N=39) 8mg RSG XR (N=39)	−4.7% 1.5%	6.2%	0.12	(−0.076, 0.319)
Posterior cingulate Gyrus	Placebo (N=39) 8mg RSG XR (N=39)	−5.9% 3.1%	9.0%	0.19	(−0.021, 0.401)
Frontal lobe	Placebo (N=39) 8mg RSG XR (N=39)	−5.2% 1.1%	6.3%	0.13	(−0.081, 0.346)
Parietal lobe	Placebo (N=39) 8mg RSG XR (N=39)	−4.9% 2.0%	6.9%	0.14	(−0.068, 0.342)
Posterior temporal lobe	Placebo (N=39) 8mg RSG XR (N=39)	−4.2% 2.7%	6.9%	0.13	(−0.067, 0.321)
Cerebellum	Placebo (N=39) 8mg RSG XR (N=39)	−4.2% 0.1%	4.3%	0.09	(−0.111, 0.281)
Medial Temporal Lobe	Placebo (N=39) 8mg RSG XR (N=39)	−4.1% 2.6%	6.6%	0.10	(−0.049, 0.241)
Global and Regional CMRglu Indices: Change from Baseline at Month 6 (Repeated Measures Analysis) (ITT) (Note: Negative change indicates decline in cerebral glucose metabolism.)					
Global (averaged grey matter)	Placebo (N=39) 8mg RSG XR (N=39)	−7.1% −2.6%	4.5%	0.09	(−0.064, 0.243)

Posterior cingulate Gyrus	Placebo (N=39) 8mg RSG XR (N=39)	−8.2% −2.2%	6.1%	0.13	(−0.042, 0.299)
Frontal lobe	Placebo (N=39) 8mg RSG XR (N=39)	−7.2% −3.0%	4.3%	0.09	(−0.087, 0.267)
Parietal lobe	Placebo (N=39) 8mg RSG XR (N=39)	−7.6% −3.2%	4.4%	0.09	(−0.074, 0.248)
Posterior temporal lobe	Placebo (N=39) 8mg RSG XR (N=39)	−7.3% −3.0%	4.4%	0.08	(−0.058, 0.221)
Cerebellum	Placebo (N=39) 8mg RSG XR (N=39)	−6.8% −1.9%	4.9%	0.10	(−0.058, 0.252)
Medial Temporal Lobe	Placebo (N=39) 8mg RSG XR (N=39)	−6.7% −0.1%	6.5%	1.00	(−0.019, 0.209)

MRI Data

Normalized Brain Volume: Changes from Baseline (Repeated Measures Analysis) (ITT)

				Treatment Comparison	
Visit	**Treatment**	**Baseline Mean (mm^3)**	**LSM (mm^3)**	**Difference (mm^3)**	**95% CI (mm^3)**
Month 6	Placebo (N=39) 8mg RSG XR (N=39)	1.38×10^6 1.38×10^6	−5820.7 −10792.3	−4971.6	(−25515.60, 15572.40)
Month 12	Placebo (N=39) 8mg RSG XR (N=39)	1.36×10^6 1.38×10^6	−23790.3 −11567.3	12223.0	(−7450.60, 31896.50)

Percentage Brain Volume: Percent Change from Baseline (Repeated Measures Analysis) (ITT)

			Treatment Comparison	
Visit	**Treatment**	**LSM Percent Change (%)**	**Difference (%)**	**95% CI (%)**
Month 6	Placebo (N=39) 8mg RSG XR (N=39)	−0.8% −1.4%	−0.6%	(−1.00, −0.10)
Month 12	Placebo (N=39) 8mg RSG XR (N=39)	−2.3% −2.5%	−0.2%	(−1.00, 0.60)

Biomarker Data

			Placebo	8mg RSG XR
Marker	**Study Visit**	**Statistic**	**N=40**	**N=40**
Glucose Metabolism Marker Levels: Change from Baseline (ITT)				
HbA_{1c} (%)	Baseline	n Mean (95% CI)	39 5.667 (5.480, 5.854)	39 5.564 (5.401, 5.727)
	Change at Month 1	n Mean (95% CI)	39 −0.180 (−0.344, −0.0153)	39 0.180 (0.033, 0.326)
	Change at Month 2	n Mean (95% CI)	37 −0.108 (−0.280, 0.064)	38 0.290 (0.075, 0.504)
	Change at Month 4	n Mean (95% CI)	34 −0.029 (−0.211, 0.153)	37 0.189 (0.016, 0.362)
	Change at Month 6	n Mean (95% CI)	34 0.000 (−0.172, 0.172)	35 0.229 (0.082, 0.375)
	Change at Month 8	n Mean (95% CI)	33 0.061 (−0.115, 0.237)	32 0.344 (0.170, 0.518)
	Change at Month 10	n Mean (95% CI)	31 0.032 (−0.145, 0.209)	31 0.258 (0.047, 0.469)
	Change at Month 12	n Mean (95% CI)	32 0.063 (−0.095, 0.220)	31 0.387 (0.206, 0.569)
Fasting Plasma Glucose (mmol/L)	Baseline	n Mean (95% CI)	34 5.115 (4.912, 5.318)	35 5.274 (5.092, 5.457)
	Change at Month 1	n Mean (95% CI)	30 −0.109 (−0.286, 0.068)	33 −0.082 (−0.220, 0.056)

	Change at Month 2	n Mean (95% CI)	30 0.057 (−0.164, 0.277)	33 −0.158 (−0.310, −0.005)
	Change at Month 4	n Mean (95% CI)	28 0.004 (−0.202, 0.209)	33 −0.112 (−0.249, 0.025)
	Change at Month 6	n Mean (95% CI)	29 0.055 (−0.218, 0.329)	31 −0.074 (−0.245, 0.097)
	Change at Month 12	n Mean (95% CI)	27 0.256 (−0.140, 0.651)	28 −0.175 (−0.364, 0.014)
Fasting Plasma Insulin (pmol/L)	Baseline	n Mean (95% CI)	32 76.009 (57.788, 94.230)	34 76.203 (60.107, 92.299)
	Change at Month 1	n Mean (95% CI)	32 12.409 (−21.730, 46.549)	34 −6.156 (−15.677, 3.366)
	Change at Month 2	n Mean (95% CI)	27 −4.537 (−21.432,12.358)	32 −4.506 (−32.045, 23.033)
	Change at Month 4	n Mean (95% CI)	28 27.3178(−21.361, 75.996)	32 −16.003 (−29.081, −2.926)
	Change at Month 6	n Mean (95% CI)	27 −8.826 (−24.468, 6.816)	30 −20.203 (−31.599, −8.807)
	Change at Month 8	n Mean (95% CI)	25 14.140 (−6.523, 34.803)	28 −9.0179 (−22.970, 4.934)
	Change at Month 10	n Mean (95% CI)	24 0.304 (−18.383, 18.992)	28 −25.521 (−40.284, −10.758)
	Change at Month 12	n Mean (95% CI)	26 −10.258 (−27.556, 7.041)	28 −25.514 (−39.231, −11.797)
Lipid and Apolipoprotein Levels: Change from Baseline (ITT)				
ApoA (G/L)	Baseline	n Mean (95% CI)	39 1.737 (1.614, 1.859)	39 1.769 (1.646, 1.891)
	Change at Month 1	n Mean (95% CI)	39 0.001 (−0.066, 0.067)	39 −0.075 (−0.143, 0.008)
	Change at Month 2	n Mean (95% CI)	35 0.009 (−0.053, 0.070)	38 −0.141 (−0.210, −0.072)
	Change at Month 4	n Mean (95% CI)	34 0.008 (−0.084, 0.100)	37 −0.163 (−0.237, −0.089)
	Change at Month 6	n Mean (95% CI)	34 −0.023 (−0.133, 0.087)	34 −0.199 (−0.280, −0.118)
	Change at Month 12	n Mean (95% CI)	32 −0.048 (−0.153, 0.058)	31 −0.206 (−0.306, −0.105)
ApoB (G/L)	Baseline	n Mean (95% CI)	39 0.968 (0.887, 1.049)	39 0.999 (0.924, 1.073)
	Change at Month 1	n Mean (95% CI)	39 −0.033 (−0.075, 0.009)	39 0.053 (0.003,0.102)
	Change at Month 2	n Mean (95% CI)	35 −0.050 (−0.105, 0.005)	38 0.015 (−0.042, 0.073)
	Change at Month 4	n Mean (95% CI)	34 −0.023 (−0.076, 0.030)	37 0.031 (−0.040, 0.102)
	Change at Month 6	n Mean (95% CI)	34 −0.041 (−0.099, 0.017)	34 0.042 (−0.063, 0.146)
	Change at Month 12	n Mean (95% CI)	32 −0.019 (−0.087, 0.048)	31 −0.001 (−0.093, 0.091)
Total cholesterol (mmol/L)	Baseline	n Mean (95% CI)	39 5.251 (4.847, 5.654)	39 5.321 (5.014, 5.628)
	Change at Month 1	n Mean (95% CI)	39 −0.121 (−0.312, 0.069)	39 0.271 (0.030, 0.513)
	Change at Month 2	n Mean (95% CI)	36 −0.129 (−0.362, 0.103)	36 0.260 (0.033, 0.488)

	Change at Month 4	n Mean (95% CI)	34 −0.194 (−0.405, 0.018)	37 0.258 (−0.014, 0.531)
	Change at Month 6	n Mean (95% CI)	33 −0.074 (−0.323, 0.175)	34 0.470 (0.004, 0.937)
	Change at Month 12	n Mean (95% CI)	32 −0.256 (−0.507, −0.004)	30 0.134 (−0.274, 0.542)
HDL (high density lipoprotein) (mmol/L)	Baseline	n Mean (95% CI)	39 1.610 (1.428, 1.791)	39 1.580 (1.385, 1.776)
	Change at Month 1	n Mean (95% CI)	39 0.027 (−0.039, 0.094)	39 −0.038 (−0.110, 0.034)
	Change at Month 2	n Mean (95% CI)	36 0.011 (−0.055, 0.078)	36 −0.013 (−0.096, 0.0700)
	Change at Month 4	n Mean (95% CI)	34 0.029 (−0.071, 0.130)	37 −0.035 (−0.120, 0.049)
	Change at Month 6	n Mean (95% CI)	33 0.065 (−0.028, 0.158)	34 −0.033 (−0.132, 0.066)
	Change at Month 12	n Mean (95% CI)	32 0.002 (−0.080, 0.084)	30 −0.041 (−0.169, 0.086)
LDL (low density lipoprotein) (mmol/L)	Baseline	n Mean (95% CI)	38 2.975 (2.635, 3.314)	39 3.035 (2.781, 3.288)
	Change at Month 1	n Mean (95% CI)	38 −0.123 (−0.275, 0.028)	39 0.153 (−0.066, 0.372)
	Change at Month 2	n Mean (95% CI)	35 −0.152 (−0.359, 0.056)	36 0.144 (−0.061, 0.349)
	Change at Month 4	n Mean (95% CI)	33 −0.225 (−0.435, −0.015)	37 0.124 (−0.111, 0.359)
	Change at Month 6	n Mean (95% CI)	32 −0.102 (−0.318, 0.115)	32 0.321 (−0.163, 0.805)
	Change at Month 12	n Mean (95% CI)	31 −0.217 (−0.465, 0.032)	30 0.140 (−0.232, 0.513)
FFA (free fatty acid) (mmol/L)	Baseline	n Mean (95% CI)	38 0.475 (0.390, 0.559)	36 0.482 (0.405, 0.559)
	Change at Month 1	n Mean (95% CI)	38 −0.024 (−0.102, 0.054)	36 −0.039 (−0.102, −0.024)
	Change at Month 2	n Mean (95% CI)	32 0.000 (−0.093, 0.093)	35 −0.070 (−0.119, −0.020)
	Change at Month 4	n Mean (95% CI)	33 −0.102 (−0.216, 0.012)	34 −0.038 (−0.096, 0.021)
	Change at Month 6	n Mean (95% CI)	33 −0.012 (−0.098, 0.074)	30 −0.031 (−0.106, 0.044)
	Change at Month 12	n Mean (95% CI)	31 −0.006 (−0.102, 0.090)	28 −0.008 (−0.078, 0.063)
Triglycerides (mmol/L)	Baseline	n Mean (95% CI)	39 1.508 (1.184, 1.832)	39 1.538 (1.376, 1.700)
	Change at Month 1	n Mean (95% CI)	39 −0.158 (−0.384, 0.068)	39 0.332 (0.126, 0.538)
	Change at Month 2	n Mean (95% CI)	36 0.025 (−0.175, 0.225)	36 0.278 (0.073, 0.484)
	Change at Month 4	n Mean (95% CI)	34 −0.095 (−0.420, 0.230)	37 0.367 (0.082, 0.652)
	Change at Month 6	n Mean (95% CI)	33 −0.140 (−0.395, 0.116)	34 0.385 (0.047, 0.723)
	Change at Month 12	n Mean (95% CI)	32 −0.211 (−0.484, 0.063)	30 0.074 (−0.128, 0.275)

VLDL (very low (density lipoprotein) (mmol/L)	Baseline	n Mean (95% CI)	38 0.622 (0.523, 0.720)	39 0.699 (0.624, 0.775)
	Change at Month 1	n Mean (95% CI)	38 −0.013 (−0.079, 0.052)	39 0.157 (0.060, 0.253)
	Change at Month 2	n Mean (95% CI)	35 0.050 (−0.022, 0.122)	36 0.135 (0.041, 0.229)
	Change at Month 4	n Mean (95% CI)	33 0.033 (−0.053, 0.118)	37 0.169 (0.038, 0.300)
	Change at Month 6	n Mean (95% CI)	32 −0.007 (−0.088, 0.073)	32 0.103 (−0.005, 0.211)
	Change at Month 12	n Mean (95% CI)	31 −0.021 (−0.097, 0.056)	30 0.040 (−0.054, 0.134)
Inflammatory Marker Levels: Change from Baseline (ITT)				
CD−40L (CD−40 ligand) (ng/L)	Baseline	n Mean (95% CI)	38 5268.5 (4397.4, 6139.6)	37 4982.9 (4181.5, 5784.2)
	Change at Month 1	n Mean (95% CI)	38 392.0 (−459.6, 1243.6)	37 −14.7 (−911.6, 882.2)
	Change at Month 6	n Mean (95% CI)	33 329.5 (−998.2, 1657.2)	32 −550.8 (−1578.1, 476.5)
	Change at Month 12	n Mean (95% CI)	31 −236.8 (−1153.9, 680.3)	30 130.5 (−832.9, 1094.0)
hs−CRP (high sensitivity −C−reactive protein) (mg/L)	Baseline	n Mean (95% CI)	39 1.154 (0.297, 2.011)	38 2.282 (0.807, 3.757)
	Change at Month 1	n Mean (95% CI)	39 0.682 (−0.710, 2.074)	38 −1.413 (−2.668, −0.159)
	Change at Month 6	n Mean (95% CI)	32 1.528 (−1.453, 4.509)	33 −1.624 (−3.295, 0.046)
	Change at Month 12	n Mean (95% CI)	31 0.816 (−1.363, 2.995)	30 −1.480 (−3.211, 0.251)
IL−6 (interleukin−6) (pg/mL)	Baseline	n Mean (95% CI)	39 1.957 (1.335, 2.578)	38 2.401 (1.703, 3.099)
	Change at Month 1	n Mean (95% CI)	39 0.978 (−0.446, 2.402)	38 0.038 (−1.162, 1.238)
	Change at Month 6	n Mean (95% CI)	34 1.371 (−0.2413, 2.9836)	34 −0.048 (−0.815, 0.719)
	Change at Month 12	n Mean (95% CI)	31 6.339 (−1.918,14.596)	30 2.637 (−1.514, 6.788)
TNFα (tumor necrosis factor−alpha) (ng/L)	Baseline	n Mean (95% CI)	38 1.866 (1.204, 2.527)	37 2.295 (0.983, 3.606)
	Change at Month 1	n Mean (95% CI)	36 −0.300 (−1.039, 0.439)	36 1.778 (−2.329, 5.884)
	Change at Month 6	n Mean (95% CI)	33 −0.230 (−1.159, 0.698)	33 −0.452 (−1.935,1.032)
	Change at Month 12	n Mean (95% CI)	28 16.789 (−3.794, 37.372)	27 3.841 (−2.488,10.169)
Insulin Sensitivity Marker Levels: Change from Baseline (ITT)				
BMI (kg/m^2)	Baseline	n Mean (95% CI)	39 25.454 (24.249, 26.659)	39 26.141 (24.822, 27.460)
	Change at Week 2	n Mean (95% CI)	39 0.015 (−0.180, 0.211)	39 0.140 (−0.033, 0.314)
	Change at Month 1	n Mean (95% CI)	39 0.010 (−0.227, 0.247)	39 0.197 (−0.011, 0.406)
	Change at Month 2	n Mean (95% CI)	37 −0.054 (−0.329, 0.221)	38 0.276 (0.075, 0.478)
	Change at Month 4	n Mean (95% CI)	36 0.053 (−0.211, 0.317)	37 0.327 (−0.029, 0.683)

	Change at Month 6	n Mean (95% CI)	34 0.062 (−0.457, 0.581)	34 0.185 (−0.203, 0.574)
	Change at Month 8	n Mean (95% CI)	33 0.030 (−0.326, 0.387)	33 0.124 (−0.318, 0.566)
	Change at Month 10	n Mean (95% CI)	31 −0.010 (−0.408, 0.389)	31 0.481 (−0.300, 1.262)
	Change at Month 12	n Mean (95% CI)	33 −0.097 (−0.471, 0.277)	31 0.161 (−0.445, 0.768)
HOMA IR	Baseline	n Mean (95% CI)	38 19.704 (15.037, 24.371)	39 18.777 (14.709, 22.844)
	Change at Month 1	n Mean (95% CI)	38 0.738 (−5.716, 7.192)	39 −1.704 (−3.939, 0.530)
	Change at Month 2	n Mean (95% CI)	36 −1.103 (−4.651, 2.446)	38 −1.319 (−6.933, 4.295)
	Change at Month 4	n Mean (95% CI)	34 5.803 (−3.920,15.525)	37 −3.733 (−6.578, −0.888)
	Change at Month 6	n Mean (95% CI)	33 −1.511 (−5.371, 2.349)	35 −3.945 (−7.328, −0.561)
	Change at Month 8	n Mean (95% CI)	32 1.277 (−2.731, 5.284)	32 −1.609 (−5.424, 2.206)
	Change at Month 10	n Mean (95% CI)	30 0.491 (−2.962, 3.944)	31 −5.446 (−9.328, −1.564)
	Change at Month 12	n Mean (95% CI)	31 −0.270 (−4.893, 4.353)	31 −5.991 (−9.584, −2.398)

EFFICACY RESULTS:

Clinical Scales (Note: The overall values represent the mean of values at Months 1, 6 and 12.)

Visit	**Treatment**	**LSM**	**Treatment Difference (95% CI)**
ADAS−Cog Total Scores: Change from Baseline (Repeated Measures Analysis) (ITT) (Note: ADAS-Cog Total scores range from 0 to 70 with negative changes from baseline indicating an improvement in condition. A negative treatment difference favors 8mg RSG XR relative to placebo.)			
Month 1	Placebo (N=39) 8mg RSG XR (N=39)	−0.41 −0.60	−0.20 (−2.38, 1.99)
Month 6	Placebo (N=39) 8mg RSG XR (N=39)	1.73 3.17	1.44 (−1.43, 4.32)
Month 12	Placebo (N=39) 8mg RSG XR (N=39)	5.44 7.62	2.18 (−1.68, 6.04)
CIBIC+ Scores: Repeated Measures Analysis (ITT) (Note: CIBIC+ is scored on a 7-point scale to determine global clinical change from baseline: 1=marked improvement; 2=moderate improvement; 3=minimal improvement; 4= no change; 5=minimal worsening; 6=moderate worsening; 7=marked worsening. A negative treatment difference favors 8mg RSG XR relative to placebo.)			
Month 1	Placebo (N=39) 8mg RSG XR (N=39)	3.90 3.90	−0.00 (−0.46, 0.46)
Month 6	Placebo (N=39) 8mg RSG XR (N=39)	4.73 4.51	−0.22 (−0.72, 0.28)
Month 12	Placebo (N=39) 8mg RSG XR (N=39)	4.96 4.86	−0.10 (−0.70, 0.49)

Treatment Group **Visit**		**Placebo** **N=39**	**8mg RSG XR** **N=39**
NPI Scores: Change from Baseline (ITT) (Note: NPI scores range from 0 [no burden] to 120 [maximum burden]. Negative changes from baseline indicate improvement and positive changes indicate increasing symptoms.			
Baseline, n Mean (95% CI)		31 7.4 (3.7, 11.1)	33 8.0 (4.8, 11.3)
Change at Month 1, n Mean change (95% CI)		31 −1.6 (−3.9, 0.7)	32 −2.6 (−5.1, −0.2)
Change at Month 6, n Mean change (95% CI)		28 2.1 (−1.2, 5.5)	30 −0.8 (−5.2, 3.5)
Change at Month 12, n Mean change (95% CI)		25 0.9 (−2.5, 4.4)	27 1.8 (−3.7, 7.3)
MMSE Scores: Change from Baseline (ITT) (Note: MMSE scores range from 0 to 30 with lower scores indicating greater cognitive impairment. Negative changes from baseline indicate cognitive decline.)			
Baseline, n Mean (95% CI)		39 20.7 (19.8, 21.7)	39 20.9 (19.7, 22.1)
Change at Month 12, n Mean change (95% CI)		30 −3.3 (−4.9, −1.8)	30 −2.6 (−3.9, −1.4)
Cognitive Tests (Note: The overall values represent the mean of values at Months 1, 6 and 12.)			
Visit	**Treatment**	**LSM**	**Treatment Difference (95% CI)**
Buschke Selective Reminding (BSR) Test (Delayed Free Recall) Scores: Change from Baseline: Repeated Measures Analysis (ITT) [Note: Higher scores indicate better short-term memory and a positive treatment difference favors 8mg RSG XR relative to placebo.]			
Month 1	Placebo (N=39) 8mg RSG XR (N=39)	0.07 0.17	0.11 (−0.59, 0.80)
Month 6	Placebo (N=39) 8mg RSG XR (N=39)	−0.11 −0.04	0.06 (−0.53, 0.66)
Month 12	Placebo (N=39) 8mg RSG XR (N=39)	−0.28 −0.41	−0.14 (−0.78 0.51)
Stroop Color−Word Interference (SCWI) Test Scores: Change from Baseline: Repeated Measures Analysis (ITT) [Note: A negative treatment difference favors 8mg RSG XR relative to placebo.]			
Month 1	Placebo (N=39) 8mg RSG XR (N=39)	−0.16 −0.23	−0.07 (−0.44, 0.30)
Month 6	Placebo (N=39) 8mg RSG XR (N=39)	−0.10 −0.14	−0.04 (−0.40, 0.32)
Month 12	Placebo (N=39) 8mg RSG XR (N=39)	0.08 −0.01	−0.09 (−0.71, 0.53)

PGx RESULTS:

Demographic Characteristics by *APOE ε4* Allele Status (PGx ITT)

Treatment	**Placebo** **N=30**		**8mg RSG XR** **N=29**		**Total** **N=59**
Allele Status	***APOE ε4-neg*** **n=6**	***APOE ε4-pos*** **n=24**	***APOE ε4-neg*** **n=14**	***APOE ε4-pos*** **n=15**	**---** **---**
Age (years), Mean (SD)	73.1 (6.61)	68.4 (10.41)	73.8 (10.43)	69.2 (9.04)	70.4 (9.82)
% Female: % Male	17/83	63/38	14/86	53/47	44/56
% Causcasian	100	92	100	87	93

PET Data by *APOE ε4* Allele Status: Change from Baseline (Repeated Measures Analysis) (PGx ITT)						
	Visit	**Allele Status**	**Placebo Estimate (mg/cm³)**	**8mg RSG XR Estimate (mg/cm³)**	**Difference (mg/cm³)**	**(95% CI) (mg/cm³)**
Global CMRglu Index (PGx ITT)	Month 1	*APOE ε4*-pos	−0.0636	0.2081	0.2717	(−0.0018, 0.5452)
		APOE ε4-neg	−0.0883	−0.0315	0.0568	(−0.3563, 0.4698)
	Month 6	*APOE ε4*-pos	−0.1027	−0.0926	0.0101	(−0.2147, 0.2350)
		APOE ε4-neg	−0.1737	0.0148	0.1885	(−0.1661, 0.5431)
	Month 12	*APOE ε4*-pos	−0.1883	−0.1239	0.0643	(−0.2193, 0.3479)
		APOE ε4-neg	−0.2193	−0.0636	0.1558	(−0.2948, 0.6063)
Clinical Scale Data by *APOE ε4* Allele Status: Change from Baseline (Repeated Measures Analysis) (PGx ITT)						
Changes in ADAS-Cog Total Scores Adjusted for *APOE ε4* Allele Status (PGx ITT)	Month 1	*APOE ε4*-pos	−1.37	−1.72	−0.34	(−3.00, 2.31)
		APOE ε4-neg	4.58	−0.24	−4.82	(−8.73, −0.92)
	Month 6	*APOE ε4*-pos	2.54	1.22	−1.32	(−5.41, 2.77)
		APOE ε4-neg	−0.07	4.02	4.09	(−2.00, 10.18)
	Month 12	*APOE ε4*-pos	4.05	5.06	1.01	(−4.23, 6.26)
		APOE ε4-neg	7.50	10.26	2.76	(−5.01, 10.53)
CIBIC+ Scores Adjusted for *APOE ε4* Allele Status (PGx ITT)	Month 1	*APOE ε4*-pos	3.85	3.83	−0.02	(−0.67, 0.63)
		APOE ε4-neg	3.67	3.58	−0.09	(−1.05, 0.87)
	Month 6	*APOE ε4*-pos	4.67	4.65	−0.02	(−0.79, 0.75)
		APOE ε4-neg	5.05	3.96	−1.08	(−2.25, 0.08)
	Month 12	*APOE ε4*-pos	4.65	4.62	−0.03	(−0.92, 0.85)
		APOE ε4-neg	5.43	5.04	−0.39	(−1.71, 0.93)

SAFETY RESULTS

AEs were collected and recorded on the CRF from the time the subject was randomized into the study until the subject completed participation in the study (Month 12/Early Withdrawal or Follow−up Visit). SAEs were collected from the time the subject consented to enter the study (SV1) through completion of the study (Month 12/Early Withdrawal or Follow−up Visit).

	Placebo	**8mg RSG XR**
	N=40	**N=40**
Most Frequent Adverse Events – On−Therapy	**n (%)**	**n (%)**
Subjects with any AE, n (%)	32 (80.0)	33 (82.5)
Most Frequent AEs: (≥5% in any treatment group):		
Upper respiratory tract infection	3 (7.5)	4 (10.0)
Dizziness	3 (7.5)	3 (7.5)
Edema peripheral	0	3 (7.5)
Herpes zoster	1 (2.5)	3 (7.5)
Urinary tract infection	2 (5.0)	3 (7.5)
Back pain	1 (2.5)	2 (5.0)
Dementia Alzheimer's type	0	2 (5.0)
Depression	1 (2.5)	2 (5.0)
Fall	5 (12.5)	2 (5.0)
Fatigue	1 (2.5)	2 (5.0)
Gait disturbance	0	2 (5.0)
Headache	0	2 (5.0)
Joint sprain	0	2 (5.0)
Procedural pain	0	2 (5.0)
Basal cell carcinoma	3 (7.5)	1 (2.5)
Diarrhea	3 (7.5)	1 (2.5)
Muscle Spasms	2 (5.0)	1 (2.5)
Pneumonia	2 (5.0)	1 (2.5)

Nausea	3 (7.5)	1 (2.5)
Cough	3 (7.5)	0
Rash	3 (7.5)	0
Vomiting	3 (7.5)	0
Agitation	2 (5.0)	0
Blood pressure increased	2 (5.0)	0
Excoriation	2 (5.0)	0
Frequent bowel movements	2 (5.0)	0
Intervertebral disc protrusion	2 (5.0)	0

Serious Adverse Events − On−Therapy: No fatal SAEs or drug−related, non−fatal SAEs were reported during the study. The incidence of on−therapy, non−fatal SAEs is tabulated below:

	Placebo	**8mg RSG XR**
	N=40	**N=40**
Preferred Term	**n (%) [related]**	**n (%) [related]**
Subjects with any non−fatal SAE	6 (15)	4 (10)
Labyrinthitis	1 (2.5) [0]	0 [0]
Pneumonia	1 (2.5) [0]	0 [0]
Urosepsis	1 (2.5) [0]	0 [0]
Abdominal pain	1 (2.5) [0]	0 [0]
Fecaloma	0 [0]	1 (2.5) [0]
Compression fracture	1 (2.5) [0]	0 [0]
Pelvic fracture	0 [0]	1 (2.5) [0]
Interstitial lung disease	1 (2.5) [0]	0 [0]
Pulmonary embolism	0 [0]	1 (2.5) [0]
Myocardial infarction	1 (2.5) [0]	0 [0]
Hyponatremia	1 (2.5) [0]	0 [0]
Abnormal behavior	0 [0]	1 (2.5) [0]

Conclusions:

- Treatment with 8mg RSG XR did not achieve statistical significance relative to placebo on the primary outcome of change from baseline after 12 months of treatment in cerebral glucose metabolism as measured by [18]FDG PET scan. There was a numerical advantage for 8mg RSG XR relative to placebo on the primary outcome in all brain regions supporting the hypothesis that RSG XR has a beneficial effect on cerebral glucose metabolism (slowing progressive decline in glucose metabolism).
- Treatment with 8mg RSG XR resulted in beneficial changes in marker levels for fasting plasma glucose and fasting plasma insulin, insulin sensitivity, and inflammation (with the exception of CD40-L). These changes were apparent at 1 month and maintained through 12 months of therapy.
- No statistically significant treatment differences were detected for any of the cognitive tests or clinical assessments; change from baseline in ADAS-Cog Total scores favored the placebo group whereas change from baseline for CIBIC+ scores favored the 8mg RSG XR group.
- Exploratory analyses, based on *APOE ε4* allele status, showed changes at Month 12 in the CMRglu and CIBIC+ scores were more favorable, although not statistically significantly different, for *APOE ε4* -negative subjects treated with 8mg RSG XR relative to such subjects receiving placebo. This treatment difference was minimal for *APOE ε4* -positive subjects. This analysis was limited by small sample sizes and imbalance in *APOE* alleles in the placebo treated group.
- Overall, the safety and tolerability profile for RSG XR, during up to 1 year of treatment at 8mg, was consistent with the safety and tolerability profile for RSG IR in T2DM.

Publications: None at time of this report