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.: AVA102670

Title: A 54-week, double-blind, randomized, placebo-controlled, parallel-group study to investigate the effects of rosiglitazone (extended release tablets) as adjunctive therapy to acetylcholinesterase inhibitors on cognition and overall clinical response in *APOE ε4*-stratified subjects with mild to moderate Alzheimer's disease (REFLECT-3)

Rationale: Rosiglitazone maleate (RSG) is currently marketed in an immediate release (IR) formulation for the treatment of type II diabetes (T2DM). The overall profile for RSG suggested a unique suitability for the treatment of Alzheimer's disease (AD) and prompted the initiation of development of RSG for this indication. Findings from a pilot study showed significant improvements in cognitive assessments with RSG IR 4 mg given for up to 6 months (n=20) relative to placebo (n=10) in subjects with mild AD or amnesic cognitive impairment. A Phase IIb, double-blind, placebo-controlled, 24-week study (Study AVA100193) followed which evaluated an extended-release (XR) formulation of RSG given once daily at 2 mg, 4 mg and 8 mg for mild-to-moderate AD. This study did not detect efficacy in the Intent-to-Treat (ITT) Population (n=511); but a prospectively-defined subgroup analysis showed subjects lacking an Apolipoprotein *(APOE) ε4* allele (i.e., *APOE ε4*-negative) improved with RSG XR relative to placebo; while carriers of the allele showed no improvement or decline regardless of treatment.

The current study, AVA102670 (REFLECT-3), evaluated the relationship between *APOE ε4* allele status and the effectiveness of 48 weeks of double-blind treatment with RSG XR versus placebo on cognitive function and overall clinical response in subjects who are maintained on a stable dose of an approved acetylcholinesterase inhibitor (AChEI; i.e., rivastigmine, galantamine, or donepezil).

Phase: III

Study Period: 12 July 2006 to 02 March 2009

Study Design: Double-blind, randomized, placebo-controlled, active-controlled, parallel-group study including a 4-week Screening Phase, a 48-week Double-blind Treatment Phase, and a 6-week Single-blind Treatment Phase. All subjects who completed the Double-blind Treatment Phase entered the Single-blind Treatment Phase and received placebo once daily while maintaining their regular AChEI regimen. Resumption of RSG XR dosing was offered to study completers in an open-label extension study (AVA102675) after completion of the Week 54 Visit.

Centres: There were 201 centers initiated in 22 countries. A total of 176 centers screened and enrolled at least one subject in the following countries: United Kingdom (UK), Canada, Poland, France, Spain, South Africa, Netherlands, Sweden, Czech Republic, Slovenia, Germany, Finland, Slovakia, Belgium, Bulgaria, Australia, Malaysia, Philippines, Korea, Hong Kong, Singapore, and the United States (US).

Indication: Alzheimer's disease

Treatment: Eligible subjects entered the Double-blind Treatment Phase and were stratified into *APOE ε4*-negative and positive groups and randomized within each stratum in a 1:1:1 ratio to receive placebo, 2 mg RSG XR or 8 mg RSG XR. GlaxoSmithKline (GSK) provided 2 mg, 4 mg and 8 mg tablets of RSG XR and matching RSG XR placebo tablets; AChEIs were obtained, as the commercially available products, from the subject's individual pharmacy.

Subjects took 1 tablet of randomized study drug daily in the morning with or without food. Subjects randomized to receive placebo or RSG XR 2 mg received the assigned dose (1 tablet once daily) throughout the 48 week treatment period. Subjects randomized to receive RSG XR 8 mg took one 4 mg tablet once daily for the first 4 weeks of treatment and then up-titrated to one 8 mg tablet once daily from Week 4 through the remaining 44 weeks of double-blind treatment. Starting at Week 48, all subjects received single-blind placebo as one tablet once daily, until Week 54. Additionally, all subjects continued receiving their stable dose of AChEI throughout the study. This dose could be decreased for tolerability reasons, provided the adjusted dose was within approved dosing guidelines.

Objectives: The primary objective was to investigate the add-on effects of daily dosing for 48 weeks with rosiglitazone extended-release (RSG XR) versus placebo on cognitive function and overall clinical response in acetylcholinesterase inhibitor (AChEI) treated subjects with mild-to-moderate Alzheimer's disease (AD) as a function of Apolipoprotein E *(APOE) ε4* status.

Primary Outcome/Efficacy Variable: The primary efficacy endpoints were changes from baseline at Week 48 in Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog) Total scores and Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) scores, both as a function of *APOE ε4* status.

Secondary Outcome/Efficacy Variables: The secondary efficacy endpoints were as follows: change from baseline in ADAS-Cog Total score for observed cases (OC) at Weeks 8, 16, 24, 36 and 48; change from baseline in CDR-SB score for OC at Weeks 12, 24, 36 and 48. (Note: Protocol, Section 3.2 incorrectly stated that the on-treatment assessments for CDR-SB were scheduled for Weeks 8, 16, 24, 36 and 48.); change from baseline (screening) in Mini Mental State Examination (MMSE) total score; change from baseline in Disability Assessment for Dementia (DAD) total score (i.e., percentage); Change from baseline in Neuropsychiatric Inventory (NPI) total score; domains of the Resource Utilization in Dementia (RUD); change from baseline in European Quality of Life – 5 Dimensions Proxy (EQ-5D) scale total score; change from baseline in Alzheimer's Carer Quality of Life Instrument (ACQLI) score; change in ADAS-Cog total score for OC and change in CDR-SB, at Week 54 compared to Week 48; and change from baseline in glycosylated hemoglobin (HbA_{1c}) at Week 48.

Statistical Methods: A sample size of 174 subjects per treatment group and *APOE ε4* stratum level (*ε4*-negative or positive) allowed detection of a 2-point and 0.6-point treatment difference between placebo and RSG XR in change from baseline in ADAS-Cog and CDR-SB scores respectively, with 90% power in each *APOE ε4* stratum group, assuming underlying standard deviations (SD) of 5.74 and 1.725, respectively at a 0.05 significance level. To allow for 10% drop-out rate between baseline and the first post-baseline assessment of both primary efficacy variables, a minimum of 1158 randomized subjects were required. These 1158 subjects included 579 subjects per *APOE ε4* stratum (193 subjects per treatment group within each stratum). Enrolment continued in each *APOE ε4* stratum level until the required number of subjects in each stratum level had been enrolled.

In accordance with a protocol amendment made prior to unblinding, the primary statistical comparison was the RSG XR 2 mg vs. placebo comparison in the Full Population, with an associated 5% alpha level. Other comparisons were considered secondary.

All analyses were performed for 2 subgroups defined by *APOE* allele status; *APOE ε4*-negative subjects (i.e., *ε2/2, ε2/3 or ε3/3*) and All Except *ε4/4* subjects (i.e., *ε2/2, ε2/3, ε3/3, ε2/4, ε3/4*), as well as for all subjects (Full Population). Data were summarized using the following populations: Randomized, Safety (randomized subjects who took ≥1 dose of study drug); Intent-to-Treat (ITT) (Safety Population subjects who had at least one post-baseline ADAS-Cog or CDR-SB assessment).

Change from baseline in ADAS-Cog and CDR-SB scores were analyzed using a mixed model for repeated measures (MMRM). Primary inferences were based on the Week 48 treatment differences in the ITT Population.

Secondary efficacy and health outcomes endpoints were change from baseline in the following: ADAS-Cog Total and CDR-SB scores for Observed Cases (OC) at all time points evaluated, MMSE Total scores, DAD Total scores (i.e., percentage), NPI scores, RUD scores, EQ-5D scores, ACLQI scores, ADAS-Cog Total and CDR-SB scores at Week 54 relative to Week 48, and HbA_{1c}. Primary inferences were drawn from treatment differences at Week 48 from the MMRM model in the ITT Population. Change from baseline in MMSE and HbA_{1c} at Week 48 OC were analyzed by Analysis of covariance (ANCOVA).

Results are presented as Least Squares Means (LSM), standard errors (SE), with treatment differences and 95% confidence intervals. P-values are presented for the co-primary endpoints.
Safety data were evaluated for the Safety Population. No formal statistical testing was performed on safety data with the exception of $HbA_{1c,}$ which was a pre-specified secondary endpoint.

Study Population: Males or non-pregnant and non-lactating females, ≥50 and ≤90 years of age with a clinical diagnosis of probable AD in accordance with National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria; mild-to-moderate AD as defined by a MMSE score of 10 to 26, inclusive at screening, with a Hachinski Ischemia Score ≤4 at screening; with no evidence of any other potential cause of dementia other than AD; and who had been on ≥6 months of ongoing AChEI therapy for

AD before study entry including stable dosing for at least the last 2 months immediately before study entry. Subjects also had to live with (or have substantial periods of contact with) a regular 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.

	Placebo	2 mg RSG XR	8 mg RSG XR	Total
Number of Subjects:	Full Population	Full Population	Full Population	Full Population
Planned, N	483	483	483	1449
Randomised, N	494	496	495	1485
Safety Population, N	487	490	491	1468
Completed, n (%)	361 (74)	351 (72)	328 (67)	1040 (71)
Total Number Subjects Withdrawn, N (%)	126 (26)	139 (28)	163 (33)	428 (29)
Withdrawn due to Adverse Events n (%)	46 (9)	49 (10)	78 (16)	173 (12)
Withdrawn for other reasons n (%)	80 (16)	90 (18)	85 (17)	255 (17)

Demographics	**Placebo**	**2 mg RSG XR**	**8 mg RSG XR**	**Total**
	Full Population	Full Population	Full Population	Full Population
N (ITT)	479	480	470	1429
Mean (SD) age, years	72.8 (8.16)	73.4 (8.18)	73.5 (8.38)	73.2 (8.24)
% Females: % Males	56: 44	57: 43	54: 46	56: 44
% White	92	92	91	91
Mean (SD) age at 1st symptoms, years	68.2 (8.52)	68.8 (8.35)	69.0 (8.60)	68.6 (8.49)
Mean (SD) time since 1st symptoms, years	4.60 (2.678)	4.59 (2.575)	4.53 (2.960)	4.57 (2.739)
Mean (SD) age at diagnosis of probable AD, years	70.2 (8.22)	71.0 (8.17)	71.3 (8.25)	70.8 (8.22)
Mean (SD) time since diagnosis, years	2.53 (2.084)	2.41 (1.850)	2.20 (1.733)	2.38 (1.900)
Subjects with significant worsening in past 6 months, n/N (%)	189/479 (39)	207/480 (43)	178/470 (38)	574/1429 (40)
Mean (SD) full years of education completed	11.6 (4.02)	11.2 (3.65)	11.3 (4.01)	11.3 (3.90)

Primary Efficacy Results:

Co-Primary Efficacy Endpoints (ITT Population):

Subject Group	**Treatment Group**	**n**	**LSM**	**SE**	**Treatment Comparison**		
					Difference	**(95% CI)**	**p-value**
Change from baseline in ADAS-Cog Total Scores at Week 48 (ADAS-Cog Total scores range from 0 to 70 with increasing scores implying worse cognition. Positive changes from 0 to 48 weeks indicate cognitive decline from baseline.) Positive difference in change scores relative to placebo indicates greater cognitive decline in the active treatment arm relative to placebo.							
APOE ε4-neg subgroup	Placebo (N=197)	145	3.2	0.54	---	---	---
	2 mg RSG XR (N=197)	142	3.5	0.53	0.3	(-1.2, 1.8)	0.739
	8 mg RSG XR (N=190)	137	4.0	0.63	0.8	(-0.8, 2.4)	0.343
All Except *ε4/4* subgroup	Placebo (N=395)	303	3.8	0.38	---	---	---
	2 mg RSG XR (N=420)	302	3.6	0.35	-0.1	(-1.1, 0.9)	0.783
	8 mg RSG XR (N=396)	274	3.8	0.41	0.0	(-1.1, 1.1)	0.940
Full Population	Placebo (N=479)	361	3.9	0.35	---	---	---
	2 mg RSG XR (N=480)	343	3.8	0.33	-0.1	(-1.1, 0.8)	0.763
	8 mg RSG XR (N=470)	331	3.8	0.36	-0.1	(-1.1, 0.9)	0.800

Change from baseline in CDR-SB scores at Week 48 (CDR-SB scores range from 0 to 18 with increasing scores indicating severity of impairment.)							
APOE ε4-neg subgroup	Placebo (N=197)	146	1.8	0.20	---	---	---
	2 mg RSG XR (N=197)	144	1.7	0.20	-0.1	(-0.7, 0.4)	0.611
	8 mg RSG XR (N=190)	138	1.7	0.17	-0.1	(-0.6, 0.4)	0.741
All Except *ε4/4* subgroup	Placebo (N=395)	302	1.8	0.13	---	---	---
	2 mg RSG XR (N=420)	311	1.8	0.13	0.0	(-0.4, 0.3)	0.913
	8 mg RSG XR (N=396)	272	1.7	0.13	-0.1	(-0.5, 0.2)	0.481
Full Population	Placebo (N=479)	360	1.9	0.12	---	---	---
	2 mg RSG XR (N=480)	349	1.8	0.13	-0.1	(-0.4, 0.2)	0.557
	8 mg RSG XR (N=470)	331	1.8	0.12	-0.1	(-0.5, 0.2)	0.404
Abbreviations: n = number of subjects with a change from baseline in ADAS-Cog Total score and CDR-SB score at Week 48, respectively; LSM = Least Squares Mean; SE = standard error for LSM; CI = confidence interval							
Secondary Outcome Variables:							
					Treatment Comparison		
Subject Group	**Treatment Group**	**n**	**LSM**	**SE**	**Difference**	**(95% CI)**	
ADAS-Cog Total Scores:							
Change from Baseline at Week 8 (Repeated Measures Analysis) (ITT Population)							
APOE ε4-negative	Placebo	189	0.3	0.36			
	2 mg RSG XR	186	0.2	0.33	-0.1	(-1.1, 0.8)	
	8 mg RSG XR	181	0.5	0.38	0.1	(-0.9, 1.1)	
All Except ε4/4	Placebo	381	0.2	0.25			
	2 mg RSG XR	397	0.1	0.23	0.0	(-0.7, 0.6)	
	8 mg RSG XR	373	0.3	0.25	0.2	(-0.5, 0.9)	
Full Population	Placebo	460	0.1	0.23			
	2 mg RSG XR	451	0.2	0.23	0.1	(-0.5, 0.8)	
	8 mg RSG XR	440	0.3	0.23	0.2	(-0.4, 0.8)	
Change from Baseline at Week 16 (Repeated Measures Analysis) (ITT Population)							
APOE ε4-negative	Placebo	180	0.3	0.35			
	2 mg RSG XR	178	0.3	0.35	0.1	(-0.9, 1.0)	
	8 mg RSG XR	167	0.2	0.38	0.0	(-1.0, 1.0)	
All Except ε4/4	Placebo	364	0.3	0.25			
	2 mg RSG XR	377	0.2	0.23	-0.1	(-0.8, 0.5)	
	8 mg RSG XR	343	0.2	0.26	-0.1	(-0.8, 0.7)	
Full Population	Placebo	440	0.2	0.24			
	2 mg RSG XR	430	0.3	0.23	0.1	(-0.6, 0.7)	
	8 mg RSG XR	411	0.2	0.24	0.0	(-0.7, 0.6)	
Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population)							
APOE ε4-negative	Placebo	171	0.6	0.41			
	2 mg RSG XR	171	1.5	0.41	1.0	(-0.2, 2.1)	
	8 mg RSG XR	156	0.8	0.45	0.2	(-1.0, 1.4)	
All Except ε4/4	Placebo	352	1.2	0.28			
	2 mg RSG XR	359	1.4	0.27	0.1	(-0.6, 0.9)	
	8 mg RSG XR	317	1.1	0.30	-0.1	(-0.9, 0.7)	
Full Population	Placebo	422	1.1	0.26			
	2 mg RSG XR	408	1.5	0.28	0.4	(-0.3, 1.1)	
	8 mg RSG XR	379	1.1	0.27	0.0	(-0.7, 0.7)	
Change from Baseline at Week 36 (Repeated Measures Analysis) (ITT Population)							
APOE ε4-negative	Placebo	152	2.2	0.49			
	2 mg RSG XR	158	2.4	0.46	0.2	(-1.1, 1.6)	
	8 mg RSG XR	147	2.7	0.54	0.5	(-0.9, 2.0)	
All Except ε4/4	Placebo	317	2.6	0.33			
	2 mg RSG XR	333	2.7	0.30	0.1	(-0.8, 0.9)	
	8 mg RSG XR	291	2.5	0.35	-0.1	(-1.0, 0.9)	

Full Population	Placebo	383	2.6	0.31		
	2 mg RSG XR	381	2.8	0.29	0.2	(-0.6, 1.0)
	8 mg RSG XR	352	2.6	0.31	-0.1	(-0.9, 0.8)
CDR-SB Scores:						
Change from Baseline at Week 12 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	178	0.4	0.11		
	2 mg RSG XR	177	0.3	0.13	-0.1	(-0.4, 0.2)
	8 mg RSG XR	174	0.3	0.10	-0.1	(-0.4, 0.2)
All Except ε4/4	Placebo	363	0.3	0.07		
	2 mg RSG XR	381	0.3	0.08	0.0	(-0.2, 0.2)
	8 mg RSG XR	356	0.3	0.07	0.0	(-0.2, 0.2)
Full Population	Placebo	437	0.3	0.07		
	2 mg RSG XR	432	0.4	0.08	0.0	(-0.2, 0.2)
	8 mg RSG XR	422	0.3	0.07	0.0	(-0.2, 0.2)
Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	167	0.8	0.16		
	2 mg RSG XR	165	0.8	0.14	-0.1	(-0.5, 0.3)
	8 mg RSG XR	157	0.9	0.13	0.0	(-0.4, 0.5)
All Except ε4/4	Placebo	345	0.8	0.10		
	2 mg RSG XR	351	0.7	0.10	-0.1	(-0.4, 0.2)
	8 mg RSG XR	314	0.9	0.10	0.1	(-0.2, 0.3)
Full Population	Placebo	413	0.9	0.10		
	2 mg RSG XR	400	0.8	0.10	-0.1	(-0.4, 0.2)
	8 mg RSG XR	376	0.9	0.09	0.1	(-0.2, 0.3)
Change from Baseline at Week 36 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	152	1.4	0.18		
	2 mg RSG XR	155	1.2	0.17	-0.2	(-0.7, 0.3)
	8 mg RSG XR	143	1.2	0.15	-0.2	(-0.7, 0.3)
All Except ε4/4	Placebo	318	1.3	0.11		
	2 mg RSG XR	326	1.3	0.11	-0.1	(-0.4, 0.2)
	8 mg RSG XR	285	1.2	0.11	-0.2	(-0.5, 0.2)
Full Population	Placebo	382	1.4	0.11		
	2 mg RSG XR	374	1.3	0.11	-0.1	(-0.4, 0.2)
	8 mg RSG XR	350	1.3	0.10	-0.1	(-0.4, 0.2)
DAD Scores: Change from Baseline at Week 48 (Repeated Measures Analysis) (ITT Population) [The DAD scale assesses the ability of a subject to execute basic and instrumental activities of daily living (ADL) and leisure activities. A percentage score was calculated as (Total score/Total number of applicable items)*100. A score of 100% represents no impairment as measured by the DAD. A positive change from baseline in these scores indicates improvement in the subject's condition.]						
APOE ε4-negative	Placebo	149	-6.9	1.24		
	2 mg RSG XR	147	-7.8	1.20	-0.9	(-4.3, 2.5)
	8 mg RSG XR	142	-9.8	1.17	-2.9	(-6.2, 0.5)
All Except ε4/4	Placebo	311	-8.3	0.85		
	2 mg RSG XR	317	-9.2	0.87	-0.9	(-3.3, 1.5)
	8 mg RSG XR	283	-9.6	0.85	-1.3	(-3.6, 1.1)
Full Population	Placebo	373	-9.5	0.81		
	2 mg RSG XR	359	-9.4	0.81	0.1	(-2.1, 2.3)
	8 mg RSG XR	342	-10.4	0.82	-0.9	(-3.2, 1.3)

NPI Scores: Change from Baseline at Week 48 (Repeated Measures Analysis) (ITT Population) [NPI Total scores range from 0 to 120 with increasing scores reflecting an increase in behavioral disturbance. A positive change from baseline implies increased neuropsychiatric symptoms relative to baseline.]						
APOE ε4-negative	Placebo	150	2.4	0.83		
	2 mg RSG XR	148	0.6	0.63	-1.8	(-3.8, 0.3)
	8 mg RSG XR	143	2.8	0.77	0.4	(-1.9, 2.6)
All Except ε4/4	Placebo	312	2.2	0.54		
	2 mg RSG XR	318	1.3	0.48	-0.9	(-2.3, 0.5)
	8 mg RSG XR	283	1.9	0.53	-0.4	(-1.8, 1.1)
Full Population	Placebo	374	2.6	0.52		
	2 mg RSG XR	360	1.5	0.49	-1.0	(-2.4, 0.3)
	8 mg RSG XR	342	1.9	0.50	-0.7	(-2.1, 0.7)
MMSE Scores: Change from Baseline at Week 48 (ANCOVA) (ITT Population) [The MMSE briefly evaluates orientation, memory (recent and immediate), concentration, language and constructional praxis. Scores range from 0 to 30 and positive changes from baseline indicate improvement.]						
APOE ε4-negative	Placebo	149	-1.9	0.33		
	2 mg RSG XR	145	-1.9	0.34	0.0	(-1.0, 0.9)
	8 mg RSG XR	140	-1.8	0.34	0.0	(-0.9, 1.0)
All Except ε4/4	Placebo	307	-1.8	0.22		
	2 mg RSG XR	315	-2.1	0.22	-0.3	(-0.9, 0.3)
	8 mg RSG XR	277	-1.8	0.23	0.0	(-0.6, 0.7)
Full Population	Placebo	366	-2.0	0.21		
	2 mg RSG XR	356	-2.3	0.22	-0.3	(-0.8, 0.3)
	8 mg RSG XR	336	-2.0	0.22	0.0	(-0.6, 0.6)
ADAS-Cog Total Score: Change from Week 48 to Week 54 (ANCOVA) (ITT Population)						
APOE ε4-negative	Placebo	139	1.7	0.41		
	2 mg RSG XR	128	1.0	0.43	-0.7	(-1.9, 0.4)
	8 mg RSG XR	130	0.5	0.43	-1.2	(-2.3, 0.0)
All Except ε4/4	Placebo	285	1.1	0.28		
	2 mg RSG XR	282	0.5	0.28	-0.7	(-1.4, 0.1)
	8 mg RSG XR	258	0.7	0.30	-0.4	(-1.2, 0.4)
Full Population	Placebo	338	1.0	0.27		
	2 mg RSG XR	319	0.4	0.28	-0.6	(-1.3, 0.1)
	8 mg RSG XR	307	0.5	0.28	-0.4	(-1.2, 0.3)
CDR-SB Score: Change from Week 48 to Week 54 (ANCOVA) (ITT Population)						
APOE ε4-negative	Placebo	141	0.4	0.12		
	2 mg RSG XR	124	0.2	0.13	-0.2	(-0.5, 0.2)
	8 mg RSG XR	128	0.4	0.13	0.0	(-0.4, 0.3)
All Except ε4/4	Placebo	281	0.3	0.08		
	2 mg RSG XR	281	0.2	0.08	-0.1	(-0.3, 0.1)
	8 mg RSG XR	253	0.3	0.09	0.0	(-0.3, 0.2)
Full Population	Placebo	335	0.3	0.07		
	2 mg RSG XR	316	0.2	0.08	-0.1	(-0.3, 0.1)
	8 mg RSG XR	303	0.3	0.08	0.0	(-0.2, 0.2)
HbA_{1c} (%): Change from Baseline at Week 48 (ANCOVA) (ITT Population)						
APOE ε4-negative	Placebo	132	0.16	0.028		
	2 mg RSG XR	131	0.17	0.028	0.01	(-0.07, 0.08)
	8 mg RSG XR	125	0.27	0.029	0.11	(0.03, 0.18)
All Except ε4/4	Placebo	282	0.14	0.019		
	2 mg RSG XR	289	0.19	0.018	0.05	(-0.00, 0.10)
	8 mg RSG XR	251	0.26	0.020	0.12	(0.07, 0.17)
Full Population	Placebo	337	0.13	0.018		
	2 mg RSG XR	326	0.18	0.019	0.05	(0.00, 0.10)
	8 mg RSG XR	309	0.26	0.019	0.13	(0.08, 0.18)

EQ-5D Proxy Scores [The EQ-5D Proxy evaluates the subject's health status via Thermometer and Utility scores. The Thermometer score is the caregiver's rating of the subject's overall health status on a VAS (0 ["worst possible status"] to 100 ["best imaginable status"]). The Utility score is a caregiver rating of health status on dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.]						
Thermometer Score: Change from Baseline at Week 48 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	148	3.2	1.37		
	2 mg RSG XR	146	0.7	1.63	-2.5	(-6.7, 1.7)
	8 mg RSG XR	143	-0.5	1.49	-3.7	(-7.7, 0.3)
All Except ε4/4	Placebo	305	2.7	0.96		
	2 mg RSG XR	313	-0.2	1.02	-2.9	(-5.6, -0.1)
	8 mg RSG XR	283	-1.9	1.06	-4.5	(-7.3, -1.7)
Full Population	Placebo	366	2.1	0.91		
	2 mg RSG XR	354	-0.5	1.00	-2.6	(-5.2, -0.0)
	8 mg RSG XR	342	-1.4	0.96	-3.4	(-6.0, -0.9)
Utility Score: Change from Baseline at Week 48 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	148	-0.01	0.017		
	2 mg RSG XR	147	-0.03	0.019	-0.01	(-0.06, 0.04)
	8 mg RSG XR	143	-0.01	0.014	0.01	(-0.04, 0.05)
All Except ε4/4	Placebo	307	-0.03	0.011		
	2 mg RSG XR	314	-0.05	0.013	-0.03	(-0.06, 0.01)
	8 mg RSG XR	283	-0.03	0.011	-0.01	(-0.04, 0.03)
Full Population	Placebo	368	-0.03	0.011		
	2 mg RSG XR	355	-0.05	0.012	-0.01	(-0.05, 0.02)
	8 mg RSG XR	342	-0.04	0.010	-0.00	(-0.03, 0.02)
ACQLI Total Score: Change from Baseline at Week 48 (Repeated Measures Analysis) (ITT Population) [The ACQLI consists of 30 questions assessing various aspect of caregiver quality of life (QoL). The Total score ranged from 0 (good QoL) to 30 (very poor QoL). A negative change from baseline indicates improvement in QoL.]						
APOE ε4-negative	Placebo	150	0.6	0.45		
	2 mg RSG XR	147	1.0	0.42	0.4	(-0.8, 1.6)
	8 mg RSG XR	143	0.9	0.42	0.3	(-0.9, 1.5)
All Except ε4/4	Placebo	311	0.9	0.29		
	2 mg RSG XR	315	1.3	0.30	0.4	(-0.4, 1.2)
	8 mg RSG XR	282	1.0	0.30	0.1	(-0.7, 0.9)
Full Population	Placebo	373	1.1	0.27		
	2 mg RSG XR	356	1.3	0.29	0.2	(-0.5, 1.0)
	8 mg RSG XR	341	1.2	0.27	0.1	(-0.6, 0.9)
Caregiver Hours from RUD [The RUD was used to assess caregiver hours spent assisting the subject with basic activities (i.e., toilet visits, eating, dressing, grooming, walking, and bathing) and with instrumental activities (i.e., shopping, food preparation, housekeeping, laundry, transportation, taking medication, and managing financial matters).]						
Caregiver Hours Spent on Basic Activities: Change from Baseline at Week 48 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	148	13.9	6.50		
	2 mg RSG XR	146	30.7	8.04	16.8	(-3.6, 37.1)
	8 mg RSG XR	141	10.2	4.25	-3.7	(-19.1, 11.6)
All Except ε4/4	Placebo	310	15.7	4.81		
	2 mg RSG XR	316	18.5	4.18	2.8	(-9.7, 15.3)
	8 mg RSG XR	282	19.6	4.68	3.9	(-9.3, 17.1)
Full Population	Placebo	371	15.7	4.14		
	2 mg RSG XR	357	19.7	4.06	4.0	(-7.2, 15.2)
	8 mg RSG XR	341	19.2	4.54	3.4	(-8.5, 15.4)

Caregiver Hours Spent on Instrumental Activities: Change from Baseline at Week 48 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	148	13.4	7.46		
	2 mg RSG XR	146	34.2	10.34	20.8	(-4.3, 45.9)
	8 mg RSG XR	141	16.8	6.14	3.4	(-15.6, 22.4)
All Except ε4/4	Placebo	310	19.2	5.87		
	2 mg RSG XR	315	27.5	6.17	8.3	(-8.4, 25.0)
	8 mg RSG XR	282	22.0	5.27	2.8	(-12.7, 18.4)
Full Population	Placebo	371	21.8	5.62		
	2 mg RSG XR	356	26.0	5.69	4.2	(-11.3, 19.6)
	8 mg RSG XR	341	21.6	4.92	-0.2	(-14.7, 14.2)

Safety Results: An on-treatment adverse event (AE) or serious adverse event (SAE) was defined as an AE with onset on or after the start date of double-blind randomized treatment and before or on the last day of randomized treatment + 1 day OR with onset missing and stop date after the first day of double blind randomized treatment.

Most Frequent Adverse Events – On-Therapy (10 most frequent AEs in each treatment group)

Subjects with any AE(s), n(%)

Treatment Group Subject Group Preferred Term	Placebo Full Population N=487	2 mg RSG XR Full Population N=490	8 mg RSG XR Full Population N=491
ANY EVENT	275 (56)	298 (61)	319 (65)
Edema Peripheral	9 (2)	32 (7)	91 (19)
Fall	13 (3)	27 (6)	17 (3)
Dizziness	17 (3)	21 (4)	15 (3)
Urinary tract infection	16 (3)	12 (2)	11 (2)
Back pain	11 (2)	13 (3)	14 (3)
Anemia	2 (<1)	10 (2)	25 (5)
Nausea	11 (2)	7 (1)	19 (4)
Upper respiratory tract infection	12 (2)	14 (3)	10 (2)
Weight increased	4 (<1)	10 (2)	22 (4)
Agitation	8 (2)	12 (2)	15 (3)
Depression	14 (3)	11 (2)	9 (2)
Fatigue	8 (2)	10 (2)	15 (3)
Nasopharyngitis	10 (2)	12 (2)	10 (2)
Vomiting	7 (1)	14 (3)	11 (2)
Bronchitis	11 (2)	11 (2)	8 (2)
Headache	10 (2)	10 (2)	9 (2)
Cough	7 (1)	12 (2)	9 (2)
Diarrhoea	8 (2)	9 (2)	10 (2)
Hypercholesterolaemia	8 (2)	10 (2)	7 (1)
Hypertension	10 (2)	8 (2)	6 (1)
Anxiety	8 (2)	5 (1)	8 (2)
Arthralgia	9 (2)	5 (1)	7 (1)
Syncope	10 (2)	4 (<1)	7 (1)
Confusional state	9 (2)	8 (2)	3(<1)
Insomnia	7 (1)	5 (1)	8 (2)
Muscle spasms	4 (<1)	2 (<1)	14 (3)
Constipation	7 (1%)	6 (1%)	4 (<1%)
Musculoskeletal pain	10 (2)	2 (<1)	4 (<1)
Abdominal pain upper	1 (<1)	8 (2)	4 (<1)
Weight decreased	7 (1%)	3 (<1%)	1 (<1%)

Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**			
Subjects with any SAEs, n (%) [related] -includes both fatal and non-fatal events			
Treatment Group	Placebo	2 mg RSG XR	8 mg RSG XR
Subject Group	Full Population N=487	Full Population N=490	Full Population N=491
Preferred Term	n (%) [related]	n (%) [related]	n (%) [related]
ANY EVENT	60 (12%) [8]	58 (12%) [4]	66 (13%) [10]
Syncope	5 (1%) [2]	1 (<1%)	3 (<1%)
Fall	3 (<1%) [1]	3 (<1%)	1 (<1%)
Pneumonia	1 (<1%)	3 (<1%)	3 (<1%)
Bronchitis	2 (<1%)	1 (<1%)	3 (<1%)
Hip fracture	3 (<1%)	1 (<1%)	2 (<1%) [1]
Cerebrovascular accident	1 (<1%)	3 (<1%)	1 (<1%)
Cardiac failure	1 (<1%)	0	3 (<1%) [2]
Myocardial infarction	1 (<1%) [1]	0	3 (<1%) [1]
Urinary tract infection	0	1 (<1%)	3 (<1%)
Confusional state	2 (<1%)	1 (<1%)	0
Dehydration	2 (<1%)	0	1 (<1%)
Femur fracture	2 (<1%)	0	1 (<1%)
Pelvic fracture	1 (<1%)	2 (<1%)	0
Prostate cancer	2 (<1%)	0	1 (<1%)
Transient ischaemic attack	1 (<1%)	1 (<1%)	1 (<1%)
Abnormal behaviour	0	1 (<1%)	1 (<1%)
Arrhythmia	0	2 (<1%) [1]	0
Breast cancer	1 (<1%)	0	1 (<1%)
Bronchitis chronic	1 (<1%)	1 (<1%)	0
Contusion	0	1 (<1%)	1 (<1%)
Convulsion	1 (<1%) [1]	0	1 (<1%)
Cystitis	1 (<1%)	0	1 (<1%)
Hallucination	1 (<1%)	1 (<1%)	0
Humerus fracture	2 (<1%)	0	0
Hypotension	0	0	2 (<1%)
Loss of consciousness	0	1 (<1%)	1 (<1%)
Melaena	0	1 (<1%) [1]	1 (<1%)
Nervous system disorder	0	2 (<1%)	0
Orthostatic hypotension	0	1 (<1%)	1 (<1%)
Radius fracture	1 (<1%)	0	1 (<1%)
Abdominal hernia	0	0	1 (<1%)
Adjustment disorder	0	0	1 (<1%)
Aggression	1 (<1%)	0	0
Angina pectoris	0	0	1 (<1%) [1]
Ankle fracture	0	1 (<1%) [1]	0
Anxiety	1 (<1%)	0	0
Aortic aneurysm	1 (<1%)	0	0
Atrioventricular block	1 (<1%)	0	0
Atrioventricular block complete	0	1 (<1%)	0
Back pain	0	1 (<1%)	0
Basal cell carcinoma	0	0	1 (<1%)
Bile duct stenosis	1 (<1%)	0	0
Bipolar disorder	1 (<1%)	0	0

Bradycardia	0	1 (<1%)	0
Bronchopneumonia	1 (<1%)	0	0
Bronchopneumopathy	0	1 (<1%)	0
Bursitis infective	0	0	1 (<1%)
Carbon monoxide poisoning	1 (<1%)	0	0
Cardiac failure congestive	0	0	1 (<1%) [1]
Cardiac pacemaker malfunction	1 (<1%)	0	0
Cataract	1 (<1%)	0	0
Cerebral haematoma	1 (<1%)	0	0
Cerebral haemorrhage	0	1 (<1%)	0
Cerebral hypoperfusion	0	0	1 (<1%)
Cerebral infarction	1 (<1%)	0	0
Cerebral ischaemia	0	1 (<1%)	0
Cholecystitis	1 (<1%)	0	0
Cholelithiasis	0	1 (<1%)	0
Cholestasis	1 (<1%)	0	0
Chronic obstructive pulmonary disease	0	0	1 (<1%)
Clavicle fracture	0	1 (<1%)	0
Concussion	0	0	1 (<1%)
Coronary artery disease	0	1 (<1%)	0
Death	0	0	1 (<1%)
Deep vein thrombosis	1 (<1%)	0	0
Dementia Alzheimer's type	0	0	1 (<1%)
Depressed level of consciousness	0	0	1 (<1%)
Dizziness	1 (<1%) [1]	0	0
Dyspepsia	0	1 (<1%)	0
Dyspnoea	0	0	1 (<1%)
Encephalitis herpes	0	1 (<1%)	0
Encephalopathy	0	1 (<1%) [1]	0
Epididymitis	1 (<1%)	0	0
Epilepsy	0	0	1 (<1%)
Epistaxis	1 (<1%) [1]	0	0
Exposure to toxic agent	0	1 (<1%)	0
Facial bones fracture	0	0	1 (<1%)
Femoral neck fracture	1 (<1%) [1]	0	0
Food poisoning	0	0	1 (<1%)
Forearm fracture	0	0	1 (<1%)
Fractured ischium	0	1 (<1%)	0
Gastric cancer	0	1 (<1%)	0
Gastroenteritis	1 (<1%)	0	0
Gastrointestinal haemorrhage	0	1 (<1%)	0
General physical health deterioration	0	0	1 (<1%)
Generalised oedema	1 (<1%)	0	0
Haemorrhage intracranial	0	0	1 (<1%)
Haemorrhoids	0	1 (<1%)	0
Hepatic cirrhosis	0	1 (<1%)	0
Hyperthyroidism	0	0	1 (<1%)
Ilium fracture	1 (<1%)	0	0
Intervertebral disc protrusion	0	1 (<1%)	0
Intestinal obstruction	0	0	1 (<1%)
Iron deficiency anaemia	0	1 (<1%)	0
Joint injury	0	0	1 (<1%)

Left ventricular failure	0	0	1 (<1%) [1]
Lip neoplasm malignant stage unspecified	0	0	1 (<1%)
Lip oedema	0	1 (<1%) [1]	0
Lordosis	0	0	1 (<1%)
Lower limb fracture	0	0	1 (<1%)
Lower respiratory tract infection	1 (<1%)	0	0
Lumbar vertebral fracture	0	0	1 (<1%)
Lung neoplasm malignant	0	1 (<1%)	0
Meningitis viral	0	1 (<1%)	0
Mental disorder due to a general medical condition	0	0	1 (<1%)
Metabolic encephalopathy	1 (<1%)	0	0
Metastases to lymph nodes	0	0	1 (<1%)
Metastatic neoplasm	0	0	1 (<1%)
Muscular weakness	0	1 (<1%)	0
Myocardial ischaemia	0	1 (<1%)	0
Non-cardiac chest pain	0	1 (<1%)	0
Oedema peripheral	0	0	1 (<1%) [1]
Osteoarthritis	0	0	1 (<1%) [1]
Pain in extremity	0	0	1 (<1%)
Palpitations	0	0	1 (<1%)
Pneumothorax	0	0	1 (<1%)
Post procedural pulmonary embolism	0	1 (<1%)	0
Psychotic disorder	1 (<1%)	0	0
Pulmonary embolism	1 (<1%)	0	0
Pyelonephritis	0	1 (<1%)	0
Pyelonephritis acute	1 (<1%)	0	0
Pyelonephritis chronic	0	1 (<1%)	0
Renal colic	1 (<1%)	0	0
Renal failure acute	0	1 (<1%)	0
Renal neoplasm	0	0	1 (<1%)
Respiratory failure	1 (<1%)	0	0
Respiratory tract infection	0	1 (<1%)	0
Reversible ischaemic neurological deficit	0	0	1 (<1%)
Right ventricular failure	0	0	1 (<1%) [1]
Salivary gland cancer	1 (<1%)	0	0
Sepsis	0	1 (<1%)	0
Septic shock	0	1 (<1%)	0
Sick sinus syndrome	1 (<1%)	0	0
Sinus bradycardia	0	0	1 (<1%)
Skin laceration	0	1 (<1%)	0
Soft tissue injury	0	1 (<1%)	0
Squamous cell carcinoma	0	0	1 (<1%)
Subarachnoid haemorrhage	1 (<1%)	0	0
Subdural haematoma	0	1 (<1%)	0
Sudden cardiac death	0	1 (<1%)	0
Syncope vasovagal	0	1 (<1%)	0
Tenosynovitis	1 (<1%)	0	0
Tonic convulsion	0	0	1 (<1%)
Upper limb fracture	1 (<1%)	0	0
Urosepsis	0	1 (<1%)	0
Uterine cancer	0	0	1 (<1%)

Ventricular tachycardia	0	0	1 (<1%)
Victim of sexual abuse	0	1 (<1%)	0
Weight decreased	1 (<1%)	0	0

Subjects with fatal SAEs, n (%) [related]

Treatment Group	Placebo	2 mg RSG XR	8 mg RSG XR
Subject Group	Full Population N=487	Full Population N=490	Full Population N=491
Preferred Term	n (%) [related]	n (%) [related]	n (%) [related]
ANY EVENT	7 (1) [0]	7 (1) [0]	8 (2) [0]
Cerebrovascular accident	1 (<1)	2 (<1)	0
Aortic aneurysm	1 (<1)	0	0
Bronchopneumonia	1 (<1)	0	0
Cardiac failure	1 (<1)	0	0
Cerebral haematoma	1 (<1)	0	0
Cerebral infarction	1 (<1)	0	0
Cerebral ischaemia	0	1 (<1)	0
Death	0	0	1 (<1)
Epilepsy	0	0	1 (<1)
General physical health deterioration	0	0	1 (<1)
Intestinal obstruction	0	0	1 (<1)
Metastases to lymph nodes	0	0	1 (<1)
Metastatic neoplasm	0	0	1 (<1)
Myocardial infarction	0	0	1 (<1)
Pneumonia	0	1 (<1)	0
Pneumothorax	0	0	1 (<1)
Pyelonephritis chronic	0	1 (<1)	0
Renal neoplasm	0	0	1 (<1)
Respiratory failure	1 (<1)	0	0
Sepsis	0	1 (<1)	0
Septic shock	0	1 (<1)	0
Sudden cardiac death	0	1 (<1)	0
Urosepsis	0	1 (<1)	0

Conclusion:

- The study failed to detect significant efficacy with 2 mg or 8 mg RSG XR on either co-primary endpoint, change from baseline at Week 48 in ADAS-Cog Total and CDR-SB scores in the Full ITT Population, *APOE ε4*-negative subjects or the All Except *ε4/4* subjects.
- Overall, the safety and tolerability profile for RSG XR, during up to 48 weeks of treatment at 2 mg and 8 mg, was consistent with the safety profile for RSG immediate-release (IR) in type 2 diabetes mellitus (T2DM).

Publications: None at the time of this report.