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.: AVA102672
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 donepezil on cognition and overall clinical response in *APOE ε4*-stratified subjects with mild to moderate Alzheimer's disease (REFLECT-2)
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 declined regardless of treatment. The current study, AVA102672 (REFLECT-2), 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 donepezil.
Phase: III
Study Period: 06 July 2006 to 28 January 2009
Study Design: A randomized, double-blind, placebo-controlled, parallel-group study evaluating RSG XR as adjunctive therapy to donepezil in mild-to-moderate AD stratified by *APOE ε4* allele status. All subjects who completed the Double-blind Treatment Phase entered the Single-blind Treatment Phase and received placebo once daily while maintaining their regular donepezil 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 255 centers initiated in 19 countries. A total of 228 centers screened and enrolled at least one subject in the following countries: Argentina, Brazil, Chile, Mexico, India, Hungary, Czech Republic, Poland, Switzerland, Greece, Spain, Portugal, Canada, Japan, France, Germany, Italy, Austria, and the United States [US]).
Indication: Alzheimer's disease
Treatment: Eligible subjects were stratified at randomization according to APOE ε4 allele status; i.e., APOE ε4-negative (ε2/2, ε2/3, and ε3/3) or APOE ε4-positive (ε2/4, ε3/4, ε4/4), regardless of final proportions of each in the group. Subjects were then 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; donepezil 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 treatment as 1 tablet once daily, until Week 54. Additionally, all subjects continued receiving their stable dose of donepezil 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 RSG XR versus placebo on cognitive function in donepezil-treated subjects with mild-to-moderate AD, as a function of *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 Variable(s): 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). Enrollment continued in each *APOE ε4* stratum level until the required number of subjects in each stratum level had been enrolled, and it was expected that approximately 1400 subjects would be randomized in order to achieve the required total in each stratum.

In accordance with a protocol amendment made prior to unblinding, to control for type I error associated with multiple comparisons (RSG dose levels and *APOE ε4* subgroups) treatment comparisons for the co-primary endpoints were made according to a pre-specified hierarchy with two pathways. In the first pathway statistical tests at the 0.01 significance level were conducted in the following order. All Except *ε4/4* subjects 8mg versus placebo. All except *ε4/4* subjects 2mg versus placebo. Full Population 8mg versus placebo, Full Population 2mg versus placebo. In the second pathway statistical tests at the 0.04 significance level were conducted in the *APOE ε4* –negative subgroup for the 8mg group versus placebo and then for the 2mg group versus placebo. Within a pathway, testing stopped when a non-significant result was observed for either of the co-primary endpoints.

All analyses were performed for 2 populations based on *APOE ε4* 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 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, Disability Assessment for Dementia (DAD) Total scores, 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. Supportive data included treatment differences for other time points derived using the MMRM model. Change from baseline in MMSE and HbA_{1c} at Week 48 OC were analyzed by 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 Mini Mental State Examination (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 donepezil 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	467	467	467	1401
Randomised, N	500	497	499	1496
Safety Population, N	496	494	489	1479
Completed, n (%)	362 (73)	396 (80)	346 (71)	1104 (75)
Total Number Subjects Withdrawn, N (%)	134 (27)	98 (20)	143 (29)	375 (25)
Withdrawn due to Adverse Events n (%)	56 (11)	28 (6)	63 (13)	147 (10)
Withdrawn for other reasons n (%)	78 (16)	70 (14)	80 (16)	228 (15)
Demographics	Placebo	2 mg RSG XR	8 mg RSG XR	Total
	Full Population	Full Population	Full Population	Full Population
N (ITT)	461	473	459	1393
Mean (SD) age, years	74.0 (7.96)	74.2 (7.98)	74.1 (7.78)	74.1 (7.90)
% Females: % Males	61: 39	57: 43	61: 39	60: 40
% White	89	88	89	89
Mean (SD) age at 1st symptoms, years	69.8 (8.04)	69.7 (8.35)	69.8 (8.20)	69.8 (8.19)
Mean (SD) time since 1st symptoms, years	4.12 (2.238)	4.43 (2.524)	4.28 (2.593)	4.28 (2.458)
Mean (SD) age at diagnosis of probable AD, years	71.8 (7.93)	72.1 (8.13)	71.9 (7.78)	71.9 (7.94)
Mean (SD) time since diagnosis, years	2.11 (1.579)	2.13 (1.559)	2.30 (1.614)	2.18 (1.585)
Subjects with significant worsening in past 6 months, n/N (%)	185/461 (40)	187/473 (40)	165/459 (36)	537/1393 (39)
Mean (SD) full years of education completed	9.9 (4.12)	10.2 (4.20)	10.0 (4.13)	10.0 (4.15)

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=202)	153	2.9	0.54	---	---	---
	2 mg RSG XR (N=205)	172	1.6	0.42	−1.3	(−2.7, −0.0)	0.049
	8 mg RSG XR (N=202)	141	2.7	0.56	−0.2	(−1.7, 1.3)	0.808
All Except *ε4/4* subgroup	Placebo (N=417)	317	3.1	0.36	---	---	---
	2 mg RSG XR (N=425)	350	2.1	0.29	−1.0	(−1.9, −0.1)	0.035
	8 mg RSG XR (N=395)	285	3.1	0.37	0.0	(−1.0, 1.0)	0.999
Full Population	Placebo (N=461)	356	3.4	0.35	---	---	---
	2 mg RSG XR (N=473)	391	2.4	0.30	−1.0	(−1.9, −0.2)	0.020
	8 mg RSG XR (N=459)	333	3.2	0.35	−0.2	(−1.2, 0.7)	0.661
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=202)	146	1.3	0.21	---	---	---
	2 mg RSG XR (N=205)	169	0.8	0.16	−0.5	(−1.0, 0.0)	0.056
	8 mg RSG XR (N=202)	139	1.5	0.20	0.2	(−0.4, 0.7)	0.587
All Except *ε4/4* subgroup	Placebo (N=417)	309	1.5	0.14	---	---	---
	2 mg RSG XR (N=425)	343	1.0	0.12	−0.5	(−0.9, −0.2)	0.004
	8 mg RSG XR (N=395)	283	1.7	0.14	0.2	(−0.2, 0.6)	0.402
Full Population	Placebo (N=461)	347	1.6	0.14	---	---	---
	2 mg RSG XR (N=473)	384	1.0	0.12	−0.5	(−0.9, −0.2)	0.002
	8 mg RSG XR (N=459)	331	1.7	0.13	0.1	(−0.2, 0.5)	0.478

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 Variable(s):

Subject Group	Treatment Group	n	LSM	SE	Treatment Comparison Difference	(95% CI)
ADAS-Cog Total Scores:						
Change from Baseline at Week 8 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	188	0.0	0.32		
	2 mg RSG XR	197	-0.8	0.33	-0.8	(-1.7, 0.1)
	8 mg RSG XR	187	-0.7	0.29	-0.7	(-1.5, 0.1)
All Except ε4/4	Placebo	392	-0.3	0.22		
	2 mg RSG XR	409	-0.6	0.23	-0.3	(-0.9, 0.3)
	8 mg RSG XR	375	-0.3	0.22	0.1	(-0.5, 0.7)
Full Population	Placebo	433	-0.2	0.22		
	2 mg RSG XR	455	-0.5	0.23	-0.3	(-0.9, 0.2)
	8 mg RSG XR	437	-0.2	0.22	0.0	(-0.6, 0.6)
Change from Baseline at Week 16 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	180	0.1	0.37		
	2 mg RSG XR	190	-0.7	0.30	-0.8	(-1.7, 0.1)
	8 mg RSG XR	171	-0.7	0.38	-0.8	(-1.9, 0.2)
All Except ε4/4	Placebo	379	-0.0	0.26		
	2 mg RSG XR	395	-0.7	0.23	-0.6	(-1.3, 0.1)
	8 mg RSG XR	352	-0.1	0.27	-0.1	(-0.8, 0.7)
Full Population	Placebo	420	-0.0	0.26		
	2 mg RSG XR	439	-0.5	0.24	-0.4	(-1.1, 0.2)

	8 mg RSG XR	411	0.2	0.26	0.2	(-0.5, 0.9)
Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	173	1.2	0.42		
	2 mg RSG XR	184	-0.5	0.37	-1.7	(-2.8, -0.6)
	8 mg RSG XR	164	0.3	0.47	-0.9	(-2.1, 0.3)
All Except ε4/4	Placebo	360	1.0	0.29		
	2 mg RSG XR	380	-0.3	0.25	-1.3	(-2.1, -0.6)
	8 mg RSG XR	330	0.9	0.31	-0.2	(-1.0, 0.7)
Full Population	Placebo	403	1.1	0.29		
	2 mg RSG XR	423	-0.1	0.26	-1.2	(-2.0, -0.5)
	8 mg RSG XR	386	0.9	0.29	-0.2	(-1.0, 0.6)
Change from Baseline at Week 36 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	162	1.5	0.47		
	2 mg RSG XR	176	0.9	0.40	-0.6	(-1.8, 0.7)
	8 mg RSG XR	151	1.8	0.50	0.3	(-1.1, 1.6)
All Except ε4/4	Placebo	335	1.8	0.31		
	2 mg RSG XR	361	1.2	0.29	-0.6	(-1.4, 0.3)
	8 mg RSG XR	306	2.3	0.34	0.5	(-0.4, 1.4)
Full Population	Placebo	376	2.0	0.31		
	2 mg RSG XR	400	1.4	0.29	-0.7	(-1.5, 0.1)
	8 mg RSG XR	362	2.5	0.33	0.4	(-0.4, 1.3)
CDR-SB Scores:						
Change from Baseline at Week 12 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	179	0.3	0.12		
	2 mg RSG XR	195	0.2	0.11	-0.1	(-0.4, 0.3)
	8 mg RSG XR	173	0.2	0.09	0.0	(-0.3, 0.3)
All Except ε4/4	Placebo	379	0.3	0.08		
	2 mg RSG XR	400	0.3	0.07	-0.1	(-0.3, 0.1)
	8 mg RSG XR	357	0.4	0.07	0.0	(-0.2, 0.2)
Full Population	Placebo	421	0.4	0.08		
	2 mg RSG XR	444	0.2	0.07	-0.1	(-0.3, 0.1)
	8 mg RSG XR	414	0.3	0.07	-0.1	(-0.3, 0.1)
Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	175	0.6	0.16		
	2 mg RSG XR	184	0.4	0.13	-0.2	(-0.6, 0.2)
	8 mg RSG XR	159	0.7	0.15	0.1	(-0.3, 0.5)
All Except ε4/4	Placebo	360	0.7	0.10		
	2 mg RSG XR	376	0.5	0.09	-0.2	(-0.4, 0.1)
	8 mg RSG XR	326	0.8	0.10	0.1	(-0.1, 0.4)
Full Population	Placebo	401	0.7	0.10		
	2 mg RSG XR	419	0.5	0.09	-0.2	(-0.5, 0.0)
	8 mg RSG XR	382	0.8	0.09	0.0	(-0.2, 0.3)
Change from Baseline at Week 36 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	161	1.0	0.19		
	2 mg RSG XR	174	0.5	0.14	-0.4	(-0.9, 0.0)
	8 mg RSG XR	148	1.0	0.17	-0.0	(-0.4, 0.5)
All Except ε4/4	Placebo	332	1.0	0.12		
	2 mg RSG XR	357	0.7	0.10	-0.3	(-0.6, 0.0)
	8 mg RSG XR	303	1.2	0.12	0.2	(-0.1, 0.5)
Full Population	Placebo	372	1.1	0.11		
	2 mg RSG XR	398	0.7	0.10	-0.4	(-0.7, -0.1)
	8 mg RSG XR	357	1.2	0.12	0.1	(-0.2, 0.4)
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	150	-6.2	1.12		
	2mg RSG XR	173	-2.5	1.14	3.7	(0.6, 6.9)
	8mg RSG XR	146	-6.5	1.34	-0.2	(-3.7, 3.2)
All Except ε4/4	Placebo	315	-7.3	0.85		
	2mg RSG XR	353	-5.0	0.80	2.3	(0.0, 4.6)
	8mg RSG XR	293	-8.2	0.91	-1.0	(-3.4, 1.4)
Full Population	Placebo	356	-7.8	0.82		
	2mg RSG XR	394	-5.7	0.78	2.1	(-0.1, 4.2)
	8mg RSG XR	344	-8.4	0.84	-0.7	(-2.9, 1.6)
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	151	1.5	0.86		
	2 mg RSG XR	174	-0.2	0.58	-1.7	(-3.8, 0.3)
	8 mg RSG XR	148	0.8	0.82	-0.7	(-3.0, 1.7)
All Except ε4/4	Placebo	318	1.3	0.65		
	2 mg RSG XR	354	-0.2	0.46	-1.5	(-3.1, 0.0)
	8 mg RSG XR	294	1.6	0.61	0.3	(-1.4, 2.0)
Full Population	Placebo	359	1.6	0.61		
	2 mg RSG XR	395	0.1	0.44	-1.5	(-2.9, -0.0)
	8 mg RSG XR	345	1.8	0.55	0.2	(-1.4, 1.8)
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	-1.1	0.30		
	2 mg RSG XR	170	-1.1	0.28	0.0	(-0.8, 0.8)
	8 mg RSG XR	140	-1.4	0.31	-0.3	(-1.2, 0.5)
All Except ε4/4	Placebo	309	-1.4	0.21		
	2 mg RSG XR	347	-1.4	0.20	0.0	(-0.6, 0.5)
	8 mg RSG XR	285	-1.9	0.22	-0.5	(-1.1, 0.1)
Full Population	Placebo	348	-1.6	0.21		
	2 mg RSG XR	388	-1.6	0.20	0.0	(-0.5, 0.6)
	8 mg RSG XR	335	-1.7	0.21	-0.1	(-0.7, 0.4)
ADAS-Cog Total Score: Change from Week 48 to Week 54 (ANCOVA) (ITT Population)						
APOE ε4-negative	Placebo	143	0.2	0.41		
	2 mg RSG XR	155	1.1	0.39	0.9	(-0.2, 2.0)
	8 mg RSG XR	132	0.5	0.43	0.3	(-0.8, 1.5)
All Except ε4/4	Placebo	295	0.7	0.27		
	2 mg RSG XR	328	1.0	0.26	0.3	(-0.4, 1.1)
	8 mg RSG XR	263	1.0	0.29	0.3	(-0.4, 1.1)
Full Population	Placebo	332	0.7	0.28		
	2 mg RSG XR	366	1.1	0.27	0.4	(-0.3, 1.1)
	8 mg RSG XR	305	1.1	0.29	0.4	(-0.3, 1.1)
CDR-SB Score: Change from Week 48 to Week 54 (ANCOVA) (ITT Population)						
APOE ε4-negative	Placebo	141	0.2	0.11		
	2 mg RSG XR	155	0.1	0.10	0.0	(-0.3, 0.2)
	8 mg RSG XR	127	-0.0	0.11	-0.2	(-0.5, 0.1)
All Except ε4/4	Placebo	293	0.2	0.07		
	2 mg RSG XR	324	0.2	0.07	-0.1	(-0.3, 0.1)
	8 mg RSG XR	259	0.1	0.08	-0.2	(-0.4, 0.0)
Full Population	Placebo	328	0.2	0.07		
	2 mg RSG XR	364	0.2	0.07	0.0	(-0.2, 0.1)

	8 mg RSG XR	302	0.1	0.07	-0.2	(-0.4, 0.0)
HbA_{1c} (%): Change from Baseline at Week 48 (ANCOVA) (ITT Population)						
APOE ε4-negative	Placebo	137	0.15	0.034		
	2 mg RSG XR	155	0.23	0.031	0.08	(-0.01, 0.17)
	8 mg RSG XR	127	0.16	0.035	0.01	(-0.08, 0.11)
All Except ε4/4	Placebo	287	0.16	0.020		
	2 mg RSG XR	319	0.22	0.019	0.07	(0.01, 0.12)
	8 mg RSG XR	264	0.17	0.021	0.02	(-0.04, 0.08)
Full Population	Placebo	321	0.14	0.020		
	2 mg RSG XR	352	0.21	0.020	0.07	(0.02, 0.12)
	8 mg RSG XR	313	0.18	0.020	0.04	(-0.01, 0.09)
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	151	1.1	1.51		
	2 mg RSG XR	173	0.1	1.40	-1.0	(-5.0, 3.0)
	8 mg RSG XR	142	0.0	1.48	-1.1	(-5.2, 3.0)
All Except ε4/4	Placebo	313	-1.6	1.08		
	2 mg RSG XR	348	-0.3	0.95	1.3	(-1.5, 4.1)
	8 mg RSG XR	286	-2.3	1.16	-0.7	(-3.8, 2.4)
Full Population	Placebo	352	-1.5	1.05		
	2 mg RSG XR	389	-0.3	0.96	1.2	(-1.5, 3.8)
	8 mg RSG XR	337	-2.4	1.08	-0.9	(-3.7, 2.0)
Utility Score: Change from Baseline at Week 48 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	150	-0.02	0.017		
	2 mg RSG XR	172	0.02	0.017	0.04	(-0.00, 0.09)
	8 mg RSG XR	142	-0.04	0.021	-0.01	(-0.07, 0.04)
All Except ε4/4	Placebo	312	-0.03	0.012		
	2 mg RSG XR	348	-0.02	0.012	0.02	(-0.02, 0.05)
	8 mg RSG XR	286	-0.05	0.014	-0.02	(-0.05, 0.02)
Full Population	Placebo	351	-0.04	0.012		
	2 mg RSG XR	389	-0.02	0.011	0.03	(-0.00, 0.06)
	8 mg RSG XR	337	-0.05	0.013	-0.01	(-0.04, 0.03)
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	136	0.9	0.41		
	2 mg RSG XR	156	-0.2	0.43	-1.1	(-2.3, 0.0)
	8 mg RSG XR	137	0.9	0.47	0.0	(-1.2, 1.2)
All Except ε4/4	Placebo	279	1.0	0.31		
	2 mg RSG XR	315	0.2	0.29	-0.8	(-1.6, 0.0)
	8 mg RSG XR	266	1.1	0.33	0.1	(-0.8, 1.0)
Full Population	Placebo	315	1.2	0.30		
	2 mg RSG XR	350	0.3	0.28	-0.9	(-1.6, -0.1)
	8 mg RSG XR	309	1.1	0.31	-0.1	(-0.9, 0.7)
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	139	9.4	4.13		
	2 mg RSG XR	156	17.4	6.23	8.0	(-6.6, 22.7)

	8 mg RSG XR	136	13.6	5.25	4.3	(-8.9, 17.4)
All Except ε4/4	Placebo	284	17.6	4.02		
	2 mg RSG XR	316	16.4	4.45	-1.2	(-12.9, 10.6)
	8 mg RSG XR	267	16.8	5.21	-0.8	(-13.7, 12.1)
Full Population	Placebo	320	21.7	4.16		
	2 mg RSG XR	351	17.0	4.17	-4.6	(-15.9, 6.7)
	8 mg RSG XR	310	18.1	4.72	-3.6	(-15.7, 8.6)
Caregiver Hours Spent on Instrumental Activities: Change from Baseline at Week 48 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	139	5.0	8.13		
	2 mg RSG XR	157	16.8	7.53	11.8	(-9.9, 33.6)
	8 mg RSG XR	137	29.2	9.63	24.2	(-0.5, 48.9)
All Except ε4/4	Placebo	284	14.7	5.54		
	2 mg RSG XR	317	11.9	5.02	-2.8	(-17.4, 11.8)
	8 mg RSG XR	268	31.2	6.87	16.6	(-0.7, 33.8)
Full Population	Placebo	320	10.8	5.51		
	2 mg RSG XR	352	8.4	4.88	-2.4	(-16.2, 11.4)
	8 mg RSG XR	311	27.0	6.24	16.2	(0.3, 32.0)

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	Placebo	2mg RSG XR	8mg RSG XR
Subject Group	Full Population	Full Population	Full Population
Preferred Term	N=496	N=494	N=489
ANY EVENT	304 (61)	273 (55)	327 (67)
Edema peripheral	11 (2%)	29 (6%)	70 (14%)
Diarrhea	23 (5%)	23 (5%)	19 (4%)
Nasopharyngitis	19 (4%)	23 (5%)	18 (4%)
Fall	17 (3%)	15 (3%)	16 (3%)
Headache	19 (4%)	14 (3%)	8 (2%)
Back pain	11 (2%)	10 (2%)	14 (3%)
Weight increased	8 (2%)	9 (2%)	18 (4%)
Nausea	14 (3%)	7 (1%)	11 (2%)
Arthralgia	13 (3%)	8 (2%)	9 (2%)
Bronchitis	4 (<1%)	12 (2%)	14 (3%)
Hypercholesterolaemia	7 (1%)	12 (2%)	11 (2%)
Aggression	10 (2%)	8 (2%)	11 (2%)
Anaemia	2 (<1%)	2 (<1%)	24 (5%)
Blood creatine phosphokinase increased	4 (<1%)	8 (2%)	16 (3%)
Dizziness	5 (1%)	10 (2%)	13 (3%)
Muscle spasms	2 (<1%)	10 (2%)	15 (3%)
Vertigo	9 (2%)	11 (2%)	7 (1%)
Asthenia	9 (2%)	9 (2%)	8 (2%)
Constipation	12 (2%)	4 (<1%)	10 (2%)
Depression	5 (1%)	9 (2%)	11 (2%)
Contusion	10 (2%)	6 (1%)	8 (2%)
Fatigue	9 (2%)	7 (1%)	8 (2%)
Insomnia	5 (1%)	12 (2%)	6 (1%)
Agitation	5 (1%)	6 (1%)	11 (2%)
Pain in extremity	7 (1%)	7 (1%)	8 (2%)
Urinary tract infection	8 (2%)	7 (1%)	7 (1%)

Hypertension	11 (2%)	7 (1%)	3 (<1%)
Anxiety	12 (2%)	2 (<1%)	6 (1%)
Cough	5 (1%)	7 (1%)	4 (<1%)
Irritability	3 (<1%)	7 (1%)	4 (<1%)
Tremor	1 (<1%)	8 (2%)	4 (<1%)
Face oedema	0	0	12 (2%)
Delusion	2 (<1%)	7 (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=496	Full Population N=494	Full Population N=489
Preferred Term	n (%) [related]	n (%) [related]	n (%) [related]
ANY EVENT	62 (13%) [9]	45 (9%) [3]	50 (10%) [6]
Pneumonia	5 (1%)	1 (<1%)	6 (1%)
Femoral neck fracture	0	1 (<1%)	3 (<1%)
Atrial fibrillation	0	0	2 (<1%)[1]
Lymphoma	0	0	2 (<1%)
Myocardial ischaemia	0	0	2 (<1%)[1]
Syncope	1 (<1%)	3 (<1%)	2 (<1%)
Urinary tract infection	1 (<1%)	0	2 (<1%)
Agitation	1 (<1%)	0	1 (<1%)
Anaemia	0	0	1 (<1%)
Anxiety	0	0	1 (<1%)
Aortic aneurysm	1 (<1%)	1 (<1%)	1 (<1%)
Bile duct cancer	0	0	1 (<1%)
Bradycardia	0	1 (<1%)	1 (<1%)
Bronchitis	1 (<1%)	0	1 (<1%)
Bronchospasm	0	0	1 (<1%)
Cardiac arrest	2 (<1%)	2 (<1%)	1 (<1%)
Cardiac failure	0	0	1 (<1%)
Cerebrovascular accident	0	1 (<1%)	1 (<1%)
Concussion	0	0	1 (<1%)
Confusional state	2 (<1%)[1]	0	1 (<1%)
Convulsion	0	0	1 (<1%)
Coronary artery stenosis	0	1 (<1%)	1 (<1%)
Death	0	0	1 (<1%)
Dementia Alzheimer's type	0	0	1 (<1%)[1]
Depression	0	0	1 (<1%)
Diarrhoea	0	0	1 (<1%)
Diverticulitis	0	0	1 (<1%)
Diverticulum intestinal	0	0	1 (<1%)
Dizziness	0	0	1 (<1%)
Duodenal ulcer haemorrhage	0	0	1 (<1%)
Epilepsy	0	0	1 (<1%)[1]
Fall	1 (<1%)	1 (<1%)	1 (<1%)[1]
Gastrointestinal infection	0	0	1 (<1%)
Haematoma	0	0	1 (<1%)
Hallucination	0	0	1 (<1%)[1]
Hip fracture	3 (<1%)	4 (<1%)[1]	1 (<1%)
Humerus fracture	1 (<1%)	1 (<1%)	1 (<1%)

Injury	0	0	1 (<1%)
Interstitial lung disease	0	0	1 (<1%)
Lung disorder	2 (<1%)	0	1 (<1%)[1]
Lung infection	0	0	1 (<1%)
Malaise	1 (<1%)	0	1 (<1%)
Normochromic normocytic anaemia	0	0	1 (<1%)
Oedema peripheral	0	0	1 (<1%)
Pain in extremity	0	0	1 (<1%)
Panic attack	0	0	1 (<1%)
Peptic ulcer perforation	0	0	1 (<1%)
Pneumonia primary atypical	0	0	1 (<1%)
Pulmonary embolism	1 (<1%)	0	1 (<1%)
Pyelonephritis	0	0	1 (<1%)
Radius fracture	0	0	1 (<1%)
Rectal polyp	0	0	1 (<1%)
Sick sinus syndrome	0	0	1 (<1%)
Suicidal ideation	0	0	1 (<1%)
Uterine neoplasm	0	0	1 (<1%)
Venous thrombosis	0	0	1 (<1%)
Vertebrobasilar insufficiency	0	0	1 (<1%)
Acute myocardial infarction	1 (<1%)	0	0
Aggression	1 (<1%)	1 (<1%)	0
Angina pectoris	1 (<1%)	1 (<1%)	0
Angle closure glaucoma	0	1 (<1%)	0
Aortic dissection	1 (<1%)[1]	0	0
Appendicitis	0	2 (<1%)	0
Arthralgia	1 (<1%)	1 (<1%)	0
Arthropathy	0	1 (<1%)	0
Basal cell carcinoma	1 (<1%)	0	0
Benign prostatic hyperplasia	2 (<1%)	0	0
Bile duct cancer recurrent	1 (<1%)	0	0
Bile duct stone	0	1 (<1%)	0
Breast cancer	0	1 (<1%)	0
Bronchopneumonia	1 (<1%)	1 (<1%)	0
Cardiac failure congestive	1 (<1%)	1 (<1%)[1]	0
Cardio-respiratory arrest	1 (<1%)[1]	0	0
Cataract	1 (<1%)	0	0
Cerebral haemorrhage	1 (<1%)[1]	0	0
Cholecystitis	0	1 (<1%)	0
Cholelithiasis	1 (<1%)	0	0
Colonic polyp	1 (<1%)	0	0
Contusion	1 (<1%)	0	0
Coronary artery disease	0	1 (<1%)	0
Deep vein thrombosis	1 (<1%)	0	0
Dehydration	1 (<1%)	2 (<1%)	0
Delirium	1 (<1%)	0	0
Delusion	1 (<1%)	0	0
Dislocation of joint prosthesis	0	1 (<1%)	0
Face injury	1 (<1%)	0	0
Femur fracture	2 (<1%)	0	0
Gastroenteritis	1 (<1%)	0	0
Gastroenteritis norovirus	0	1 (<1%)	0

Gastroenteritis rotavirus	0	1 (<1%)	0
Haemorrhagic stroke	1 (<1%)	0	0
Haemorrhoids	1 (<1%)	0	0
Hepatic neoplasm malignant	1 (<1%)	0	0
Hepatitis toxic	1 (<1%)[1]	0	0
Herpes zoster	1 (<1%)	0	0
Hypertensive crisis	1 (<1%)[1]	0	0
Inguinal hernia	0	2 (<1%)	0
Intraductal papilloma of breast	1 (<1%)	0	0
Iron deficiency anaemia	1 (<1%)	1 (<1%)	0
Jaundice	1 (<1%)	0	0
Large intestine perforation	1 (<1%)	0	0
Lateral patellar compression syndrome	1 (<1%)	0	0
Ligament rupture	0	1 (<1%)	0
Loss of consciousness	1 (<1%)[1]	0	0
Lower limb fracture	0	1 (<1%)	0
Meniscus lesion	0	1 (<1%)	0
Metrorrhagia	1 (<1%)	0	0
Muscle spasms	0	1 (<1%)	0
Myocardial infarction	5 (1%)[2]	1 (<1%)	0
Overdose	1 (<1%)	0	0
Pelvic fracture	1 (<1%)	0	0
Platelet count decreased	0	1 (<1%)	0
Prostate cancer	1 (<1%)	0	0
Psychotic disorder due to a general medical condition	0	1 (<1%)	0
Rectal haemorrhage	1 (<1%)	0	0
Renal failure acute	1 (<1%)	0	0
Rib fracture	0	1 (<1%)	0
Sarcoma	1 (<1%)	0	0
Sinusitis	0	1 (<1%)	0
Skin fissures	1 (<1%)	0	0
Skin ulcer	1 (<1%)	0	0
Spinal compression fracture	0	1 (<1%)[1]	0
Suicide attempt	1 (<1%)	0	0
Tachyarrhythmia	0	1 (<1%)	0
Tibia fracture	0	1 (<1%)	0
Transient ischaemic attack	1 (<1%)	0	0
Vertigo	0	1 (<1%)	0
Viral infection	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=496	Full Population N=494	Full Population N=489
Preferred Term	n (%) [related]	n (%) [related]	n (%) [related]
ANY EVENT	12 (2%) [2]	6 (1%) [0]	8 (2%) [1]
Cardiac arrest	2 (<1%)	2 (<1%)	1 (<1%)
Myocardial infarction	3 (<1%)	1 (<1%)	0
Cardiac failure acute	0	0	2 (<1%)[1]
Cardio-respiratory arrest	1 (<1%)[1]	1 (<1%)	0

Cardiac failure congestive	1 (<1%)	0	0
Bronchopneumonia	1 (<1%)	1 (<1%)	0
Pneumonia	0	0	1 (<1%)
Aortic aneurysm	1 (<1%)	1 (<1%)	0
Aortic dissection	1 (<1%)[1]	0	0
Death	0	0	2 (<1%)
Bile duct cancer	0	0	1 (<1%)
Lymphoma	0	0	1 (<1%)
Pulmonary embolism	1 (<1%)	0	0
Respiratory failure	1 (<1%)	0	0
Haemorrhagic stroke	1 (<1%)	0	0
Renal failure acute	1 (<1%)	0	0

Conclusion:

- The first step of the prespecified primary endpoint testing hierarchy was to test 8 mg RSG-XR versus placebo for both the APOE ε4 negative and All Except ε4/ε4 subgroups. There were no statistically significant or clinically relevant treatment differences observed for 8 mg RSG XR in any of the populations.
- Evaluations of the primary endpoints that included comparisons for 2 mg RSG XR versus placebo were exploratory. A small to moderate potential benefit of 2 mg RSG XR was suggested based on ADAS-Cog treatment differences of 1 to 1.3 points and CDR-SB treatment differences of 0.5 points with unadjusted p-values ranging from p=0.002 to p=0.056..
- 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.