Study No.: AVA105640

Title: A 24-week, double-blind, double-dummy, randomized, parallel group study to investigate the effects of rosiglitazone (extended release tablets), donepezil, and placebo as monotherapy on cognition and overall clinical response in *APOE ε4*-stratified subjects with mild-to-moderate Alzheimer's disease. (REFLECT-1)

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 the pilot study showed significant improvements in cognitive assessments with RSG IR 4mg given for up to 6 months (n=20) relative to placebo (n=10) in subjects with mild AD or amnesic cognitive impairment [Watson, *Am J Geriatr Psychiatry.* 2005;13:950-958]. 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 (od) at 2, 4 and 8mg 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 analyses showed subjects lacking an *Apoliprotein* (*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.

Based on these findings, this Phase III study, AVA105640 was conducted to evaluate the relationship between *APOE ε4* allele status and the effectiveness of 24 weeks of RSG XR monotherapy given od at 2mg or 8mg in treatment of subjects with mild-to-moderate AD. Subjects were randomized to treatment after stratification according to their *APOE ε4* status; i.e., *ε4*-non-carriers (*APOE ε4*-negative) and *ε4*-carriers (*APOE ε4*-positive). Donepezil, the most widely used of the acetylcholinesterase inhibitors in treatment of AD, was used as an active control arm to provide a measure of assay sensitivity.

Phase: III

Study Period: 27 February 2007 to 05 September 2008

Study Design: Double-blind, double-dummy, randomized, placebo-controlled, active-controlled, parallel-group study including a 2-week Screening Phase, 4 week Placebo Run-in Phase, 24-week Double-blind Treatment Phase, and 2-week Post treatment Follow-up Visit. Subjects who completed the Week 24 Visit were eligible to enter an extension study (AVA102677) where they were titrated to open-label, 8mg RSG XR. Subjects who did not enter the extension study had the Follow-up Visit at Week 26.

Centers: 163 centers were initiated and 134 of those centers screened and enrolled at least one subject in the following countries: Austria, Bulgaria, Chile, China, Croatia, Estonia, Germany, Greece, Hungary, Korea, Mexico, New Zealand, Pakistan, Peru, Phillipines, Puerto Rico, Russia, the United Kingdom, and the United States.

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 2:2:2:1 ratio to receive placebo, 2mg RSG XR, 8mg RSG XR, or donepezil (10mg). GlaxoSmithKline (GSK) provided 2mg, 4mg and 8mg tablets or RSG XR and matching RSG XR placebo tablets; and 5mg and 10mg donepezil capsules and matching donepezil placebo capsules.

All study drug was taken od in the evening with or without food. During the 4-week, single-blind, Placebo Run-in Phase, all subjects received 1 placebo tablet matching RSG XR and 1 placebo capsule matching donepezil. During the 24-week, double-dummy, double-blind Treatment Phase, subjects also took 1 tablet plus 1 capsule of study drug. Subjects randomized to placebo or 2mg RSG XR received the assigned dose throughout the 24-week Treatment Phase. Subjects in the 8mg RSG XR and donepezil (10mg) groups received 50% of the assigned dose (i.e., 4mg RSG XR and 5mg donepezil) for the first 4 weeks of treatment, and then were up-titrated to full dose to the end of treatment.

Objectives: The primary objectives were to investigate the effects of od dosing for 24 weeks with RSG XR versus placebo on cognitive function and overall clinical response in subjects with mild-to-moderate AD as a function of *APOE ε4* status; and to estimate the effects of donepezil on cognitive function and overall clinical response in this study population.

Primary Efficacy Endpoints: Change from baseline at Week 24 in AD Assessment Scale – Cognitive (ADAS-Cog) and Clinician Interview-Based Impression of Change Plus (CIBIC+) scores.

Secondary Efficacy Endpoints: The secondary efficacy endpoints were as follows: change from baseline in ADAS-

Cog Total score at Weeks 8 and 16; change from baseline in CIBIC+ score at Weeks 8 and 16; change from baseline in Neuropsychiatric Inventory (NPI) total scores; change from baseline in Disability Assessment for Dementia (DAD) scores; change from baseline in Short-Term Memory Assessment scores (i.e., sum of Items 1 and 7 of ADAS-Cog); change from baseline in European Quality of Life -5 Dimensions Proxy (EQ-5D Proxy) total score; change from baseline in domains of the Resource Utilization in Dementia (RUD) scale; change from baseline in Alzheimer's Carer's Quality of Life Instrument (ACQLI) score; change from baseline in Mini Mental State Examination (MMSE) score; and change from baseline in glycosylated hemoglobin (Hb_{A1c}) at Week 24.

Statistical Methods: The analysis populations were as follows: Randomized, Safety (randomized subjects who took ≥1 dose of study drug); ITT (subjects in the Safety population who also had at least one post-baseline ADAS-Cog or CIBIC+ assessment)

Analyses were performed for 2 subgroups based on *APOE* allele status; *APOE ε4*-neg 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 combined (Full Population).

A hierarchical testing approach was applied to control familywise type I error associated with testing of the primary efficacy endpoints. At the first step in the hierarchy the 8mg RSG XR group was tested against placebo at the 5% level, for APOE E4 negative subjects. If a statistically significant result was obtained then testing continued along two pathways. In one pathway an alpha level of 1% was specified for comparisons of the 8mg RSG XR group against placebo (All except E4/E4 then Full population). In the second pathway an alpha level of 4% was specified for comparisons of the 2mg RSG XR group against placebo (APOE E4 negative, followed by All except E4/E4, and then the Full Population). Progression at each step of the hierarchy required statistically significant results to have been observed for both co-primary endpoints.

Change from baseline in ADAS-Cog and CIBIC+ scores were analyzed using a mixed model for repeated measures (MMRM). Primary inferences were based on the Week 24 treatment differences for the ITT Population.

Inferences for analysis of changes from baseline in DAD, NPI, Short-term Memory, EQ-5D, ACQLI, Caregiver Hours (secondary endpoints) were drawn from treatment differences at Week 24 from the MMRM model for the ITT Population. Change from baseline in MMSE and HbA_{1c} at Week 24 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.

Study Population: Males or non-pregnant and non-lactating females, aged ≥50 and ≤90 years with a clinical diagnosis of probable AD in accordance with National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for at least 3 months; mild-to-moderate AD (i.e., Mini Mental State Examination [MMSE] score of 10 to 23, inclusive at screening), with a Hachinski Ischemia Score ≤4 at screening; with no evidence of any other potential cause of dementia other than AD.

NUMBER OF SUBJECTS:

		Treatment Group			
	Subject Group	**Placebo**	**2mg RSG XR**	**8mg RSG XR**	**Donepezil (10mg)**
Subject Enrollment by *APOE* Genotype (Randomized)					
Planned to randomize, N	*APOE ε4*-negative	81	81	81	40
	APOE ε4-positive	81	81	81	40
Randomized, N	*APOE ε4*-negative	86	85	86	42
	APOE ε4-positive	80	81	79	42
	All Except *ε4/4*	151	147	150	75
	Full Population	166	166	165	84
Subject Disposition (Safety Population)					
Safety Population, n (%)	*APOE ε4*-negative	86 (100)	85 (100)	86 (100)	42 (100)
	All Except *ε4/4*	150 (>99)	147 (100)	150 (100)	74 (99)
	Full Population	165 (100)	166 (100)	165 (100)	83 (99)
Completed Double-blind	*APOE ε4*-negative	65 (76)	71 (84)	66 (77)	27 (64)
Treatment Phase, n (%)	All Except *ε4/4*	117 (78)	119 (81)	114 (76)	48 (65)
	Full Population	131 (79)	135 (81)	127 (77)	55 (66)
Total Withdrawn, n (%)	*APOE ε4*-negative	21 (24)	14 (16)	20 (23)	15 (36)
	All Except *ε4/4*	33 (22)	28 (19)	36 (24)	26 (35)

	Full Population	34 (21)	31 (19)	38 (23)	28 (34)
Withdrawn due to	*APOE ε4*-negative	8 (9)	3 (4)	7 (8)	5 (12)
Adverse Events, n (%)	All Except *ε4/4*	9 (6)	6 (4)	9 (6)	10 (14)
	Full Population	10 (6)	8 (5)	10 (6)	11 (13)
Withdrawn for other	*APOE ε4*-negative	13 (15)	11 (12)	13 (15)	10 (24)
reasons, n (%)	All Except *ε4/4*	14 (16)	22 (15)	25 (18)	16 (21)
	Full Population	24 (15)	23 (14)	28 (17)	17 (21)
DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS (ITT Population)					
		Treatment Group			
	Subject Group	**Placebo**	**2mg RSG XR**	**8mg RSG XR**	**Donepezil (10mg)**
N	*APOE ε4*-negative	82	84	80	38
	All Except *ε4/4*	144	144	142	68
	Full Population	159	162	156	76
Mean (SD) age, years	*APOE ε4*-negative	72.7 (9.14)	73.3 (7.84)	73.2 (9.01)	72.9 (7.89)
	All Except *ε4/4*	72.9 (8.63)	72.0 (8.09)	72.9 (8.73)	73.4 (7.88)
	Full Population	72.5 8.56)	71.7 (7.91)	72.6 (8.63)	72.9 (7.97)
% Female: % Male	*APOE ε4*-negative	54:46	62:38	68:33	66:34
	All Except *ε4/4*	60:40	63:37	65:35	66:34
	Full Population	60:40	64:36	65:35	63:37
% White	*APOE ε4*-negative	74	67	74	84
	All Except *ε4/4*	76	67	73	75
	Full Population	77	67	72	75
Mean (SD) time since	*APOE ε4*-negative	1.75 (2.052)	1.67 (1.493)	1.30 (1.209)	1.52 (1.783)
diagnosis, years	All Except *ε4/4*	1.66 (1.811)	1.57 (1.362)	1.55 (2.126)	1.43 (1.518)
	Full Population	1.62 (1.756)	1.62 (1.739)	1.66 (2.155)	1.47 (1.530)
% with significant	*APOE ε4*-negative	52	64	53	55
worsening in past	All Except *ε4/4*	56	59	54	56
6 months	Full Population	55	56	54	58
Mean (SD) ADAS-Cog	*APOE ε4*-negative	24.5 (10.40)	26.2 (10.44)	24.9 (10.73)	23.3 (10.29)
Total Score at Baseline	All Except *ε4/4*	25.0 (10.26)	26.3 (10.30)	25.8 (11.40)	24.9 (9.68)
[Range: 0 to 70 with higher scores implying worse cognition]	Full Population	25.0 (10.04)	26.7 (10.14)	25.4 (11.54)	24.5 (9.52)
Mean (SD) MMSE	*APOE ε4*-negative	20.0 (4.10)	19.2 (3.95)	19.4 (4.47)	20.0 (4.14)
Score at Baseline	All Except *ε4/4*	19.7 (3.92)	18.9 (3.91)	19.2 (4.68)	19.6 (3.93)
[Range: 0 to 30 with lower scores implying worse cognition]	Full Population	19.6 (4.04)	18.9 (3.98)	19.1 (4.64)	19.4 (4.01)

EFFICACY AND HEALTH OUTCOMES RESULTS:

Co-Primary Efficacy Analyses

					Treatment Comparison		
Subject Group	**Treatment Group**	**n**	**LSM**	**SE**	**Difference**	**(95% CI)**	**p-value**
ADAS-Cog Total Scores: Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population) [ADAS-Cog Total scores range from 0 to 70 with increasing scores implying worse cognition. Positive changes from 0 to 24 weeks imply cognitive decline from baseline.]							
APOE ε4-negative	Placebo	63	1.6	0.78	---	---	---
	2mg RSG XR	69	−0.2	0.67	−1.8	(−3.8, 0.2)	0.074
	8mg RSG XR	65	0.6	0.67	−1.0	(−3.0, 1.0)	0.338
	Donepezil	28	0.9	1.16	−0.7	(−3.5, 2.1)	0.602
All Except *ε4/4*	Placebo	117	1.5	0.58	---	---	---
	2mg RSG XR	115	0.3	0.54	−1.2	(−2.7, 0.4)	0.131
	8mg RSG XR	112	0.7	0.57	−0.8	(−2.4, 0.8)	0.315

	Donepezil	49	−0.1	0.79	−1.6	(−3.5, 0.3)	0.105
Full Population	Placebo	131	2.0	0.56	---	---	---
	2mg RSG XR	130	1.2	0.53	−0.8	(−2.2, 0.6)	0.272
	8mg RSG XR	125	1.2	0.55	−0.8	(−2.2, 0.7)	0.297
	Donepezil	56	0.6	0.74	−1.3	(−3.1, 0.4)	0.131
CIBIC+ Scores at Week 24 (Repeated Measures Analysis) (ITT Population) [The 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; and 7 = marked worsening.]							
APOE ε4-negative	Placebo	63	4.2	0.14	---	---	---
	2mg RSG XR	71	4.2	0.12	0.1	(−0.3, 0.4)	0.663
	8mg RSG XR	66	4.1	0.11	0.0	(−0.4, 0.3)	0.891
	Donepezil	28	3.9	0.22	−0.2	(−0.7, 0.3)	0.414
All Except *ε4/4*	Placebo	117	4.3	0.10	---	---	---
	2mg RSG XR	117	4.3	0.10	0.0	(−0.3, 0.3)	0.913
	8mg RSG XR	114	4.1	0.10	−0.1	(−0.4, 0.1)	0.276
	Donepezil	49	3.8	0.17	−0.5	(−0.8, −0.1)	0.025
Full Population	Placebo	131	4.3	0.09	---	---	---
	2mg RSG XR	133	4.3	0.09	0.0	(−0.2, 0.3)	0.939
	8mg RSG XR	127	4.2	0.10	−0.1	(−0.4, 0.1)	0.307
	Donepezil	56	3.8	0.16	−0.5	(−0.8, −0.1)	0.009
Secondary Endpoints							
					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	78	0.6	0.58	---	---	
	2mg RSG XR	79	−1.6	0.55	−2.2	(−3.7, −0.6)	
	8mg RSG XR	75	−0.3	0.55	−0.9	(−2.4, 0.7)	
	Donepezil	35	−0.7	0.76	−1.2	(−3.1, 0.7)	
All Except *ε4/4*	Placebo	138	0.1	0.41	---	---	
	2mg RSG XR	138	−1.2	0.44	−1.3	(−2.4, −0.1)	
	8mg RSG XR	134	−0.1	0.41	−0.2	(−1.3, 0.9)	
	Donepezil	60	−0.7	0.60	−0.8	(−2.2, 0.6)	
Full Population	Placebo	153	0.4	0.42	---	---	
	2mg RSG XR	155	−0.5	0.45	−0.9	(−2.0, 0.2)	
	8mg RSG XR	147	0.5	0.43	0.1	(−0.9, 1.2)	
	Donepezil	67	−0.3	0.63	−0.7	(−2.1, 0.7)	
Change from Baseline at Week 16 (Repeated Measures Analysis) (ITT Population)							
APOE ε4-negative	Placebo	71	0.5	0.63	---	---	
	2mg RSG XR	76	−0.6	0.62	−1.0	(−2.7, 0.7)	
	8mg RSG XR	67	0.7	0.56	0.2	(−1.5, 1.8)	
	Donepezil	32	−1.4	1.15	−1.9	(−4.5, 0.8)	
All Except *ε4/4*	Placebo	128	0.2	0.46	---	---	
	2mg RSG XR	130	−0.2	0.49	−0.3	(−1.6, 1.0)	
	8mg RSG XR	119	0.6	0.44	0.5	(−0.7, 1.7)	
	Donepezil	55	−1.3	0.81	−1.5	(−3.3, 0.4)	
Full Population	Placebo	143	0.5	0.46	---	---	
	2mg RSG XR	145	0.6	0.49	0.1	(−1.1, 1.3)	
	8mg RSG XR	132	1.3	0.45	0.8	(−0.3, 2.0)	
	Donepezil	62	−1.1	0.80	−1.6	(−3.4, 0.2)	
CIBIC+ Scores:							
At Week 8 (Repeated Measures Analysis) (ITT Population)							
APOE ε4-negative	Placebo	77	4.1	0.09	---	---	

	2mg RSG XR	80	3.9	0.09	−0.1	(−0.4, 0.1)
	8mg RSG XR	76	4.0	0.09	0.0	(−0.3, 0.2)
	Donepezil	35	3.7	0.15	−0.4	(−0.8, −0.1)
All Except *ε4/4*	Placebo	135	4.1	0.07	---	---
	2mg RSG XR	138	3.9	0.08	−0.2	(−0.4, 0.0)
	8mg RSG XR	134	4.0	0.07	0.0	(−0.2, 0.2)
	Donepezil	60	3.9	0.11	−0.2	(−0.4, 0.1)
Full Population	Placebo	150	4.1	0.07	---	---
	2mg RSG XR	156	3.9	0.08	−0.1	(−0.3, 0.0)
	8mg RSG XR	147	4.1	0.08	0.0	(−0.2, 0.2)
	Donepezil	67	3.9	0.12	−0.2	(−0.5, 0.0)
At Week 16 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	71	4.0	0.11	---	---
	2mg RSG XR	75	4.0	0.10	−0.1	(−0.3, 0.2)
	8mg RSG XR	64	4.1	0.10	0.0	(−0.3, 0.3)
	Donepezil	32	3.7	0.18	−0.3	(−0.8, 0.1)
All Except *ε4/4*	Placebo	129	4.1	0.08	---	---
	2mg RSG XR	129	4.0	0.08	−0.2	(−0.4, 0.1)
	8mg RSG XR	115	4.1	0.09	0.0	(−0.3, 0.2)
	Donepezil	54	3.8	0.14	−0.4	(−0.7, −0.1)
Full Population	Placebo	144	4.2	0.08	---	---
	2mg RSG XR	145	4.0	0.08	−0.2	(−0.4, 0.0)
	8mg RSG XR	127	4.1	0.09	−0.1	(−0.3, 0.1)
	Donepezil	61	3.8	0.14	−0.4	(−0.7, −0.1)
NPI Scores: Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population) [NPI Total scores range from 0 (no burden) to 120 (maximum burden) with increasing scores associated with increasing neuropsychiatric disturbance. A positive change from baseline implies increased neuropsychiatric symptoms relative to baseline.]						
APOE ε4-negative	Placebo	63	2.4	1.73	---	---
	2mg RSG XR	71	0.6	0.77	−1.8	(−5.5, 1.9)
	8mg RSG XR	66	1.1	1.48	−1.3	(−5.8, 3.2)
	Donepezil (10mg)	27	0.7	1.72	−1.8	(−6.6, 3.1)
All Except *ε4/4*	Placebo	115	1.5	1.12	---	---
	2mg RSG XR	117	1.6	0.79	0.1	(−2.6, 2.7)
	8mg RSG XR	114	0.6	1.03	−1.0	(−3.9, 2.0)
	Donepezil (10mg)	48	−0.4	1.12	−1.9	(−5.0, 1.2)
Full Population	Placebo	129	1.2	1.04	---	---
	2mg RSG XR	133	1.6	0.74	0.3	(−2.1, 2.7)
	8mg RSG XR	127	1.1	1.01	−0.1	(−2.9, 2.7)
	Donepezil (10mg)	55	−0.6	1.12	−1.9	(−4.8, 1.1)
DAD Scores: Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population) [The DAD scale assesses the ability of a subject to execute basic and instrumental 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. A positive change from baseline in these scores indicates improvement in the subject's condition.]						
APOE ε4-negative	Placebo	63	−3.9	1.42	---	---
	2mg RSG XR	71	−2.5	1.82	1.4	(−3.1, 5.9)
	8mg RSG XR	66	−2.9	1.66	1.1	(−3.2, 5.4)
	Donepezil (10mg)	27	−1.1	2.72	2.8	(−3.4, 9.0)
All Except *ε4/4*	Placebo	115	−3.4	0.99	---	---
	2mg RSG XR	117	−2.2	1.31	1.2	(−2.0, 4.4)
	8mg RSG XR	114	−3.2	1.23	0.2	(−2.9, 3.3)
	Donepezil (10mg)	48	0.3	1.75	3.7	(−0.3, 7.7)
Full Population	Placebo	129	−3.7	0.97	---	---
	2mg RSG XR	133	−2.4	1.21	1.3	(−1.6, 4.2)
	8mg RSG XR	127	−3.8	1.19	−0.1	(−3.0, 2.8)
	Donepezil (10mg)	55	−0.2	1.81	3.6	(−0.4, 7.5)

Short-term Memory Assessment Scores: Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population) [The Short-term Memory Assessment score was the sum of the scores for Question 1 (Word Recall) and Question 7 (Word Recognition) of the ADAS-Cog scale. Negative changes from baseline indicate improvement in symptoms.]						
APOE ε4-negative	Placebo	63	0.7	0.38	---	---
	2mg RSG XR	70	−0.4	0.37	−1.1	(−2.2, -0.1)
	8mg RSG XR	63	0.5	0.38	−0.2	(−1.2, 0.9)
	Donepezil (10mg)	28	0.6	0.63	−0.1	(−1.6, 1.4)
All Except *ε4/4*	Placebo	117	0.5	0.28	---	---
	2mg RSG XR	115	−0.1	0.31	−0.6	(−1.4, 0.2)
	8mg RSG XR	110	0.4	0.29	−0.1	(−0.8, 0.7)
	Donepezil (10mg)	49	−0.1	0.47	−0.6	(−1.7, 0.5)
Full Population	Placebo	131	0.7	0.27	---	---
	2mg RSG XR	128	0.3	0.30	−0.4	(−1.1, 0.3)
	8mg RSG XR	123	0.6	0.29	−0.1	(−0.8, 0.6)
	Donepezil (10mg)	56	0.2	0.43	−0.5	(−1.5, 0.5)
MMSE Scores: Change from Baseline at Week 24 (ANCOVA) (ITT Population) [The MMSE cursorily 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	63	−0.2	0.36	---	---
	2mg RSG XR	71	−0.4	0.34	−0.2	(−1.2, 0.7)
	8mg RSG XR	66	−0.5	0.35	−0.3	(−1.2, 0.7)
	Donepezil (10mg)	28	0.5	0.52	0.7	(−0.5, 1.9)
All Except *ε4/4*	Placebo	117	−0.3	0.26	---	---
	2mg RSG XR	117	−0.1	0.27	0.3	(−0.5, 1.0)
	8mg RSG XR	114	−0.3	0.28	0.1	(−0.7, 0.8)
	Donepezil (10mg)	49	0.8	0.40	1.1	(0.1, 2.0)
Full Population	Placebo	131	−0.5	0.27	---	---
	2mg RSG XR	133	−0.6	0.27	0.0	(−0.7, 0.6)
	8mg RSG XR	127	−0.7	0.28	−0.1	(−0.8, 0.6)
	Donepezil (10mg)	56	0.4	0.38	1.0	(0.1, 1.8)
HbA_{1c} (%): Change from Baseline at Week 24 (ANCOVA) (ITT Population)						
APOE ε4-negative	Placebo	58	0.1	0.07	---	---
	2mg RSG XR	65	0.3	0.06	0.2	(0.0, 0.4)
	8mg RSG XR	60	0.2	0.07	0.1	(−0.1, 0.3)
	Donepezil (10mg)	26	0.1	0.10	0.0	(−0.2, 0.3)
All Except *ε4/4*	Placebo	108	0.1	0.05	---	---
	2mg RSG XR	105	0.2	0.05	0.1	(−0.0, 0.3)
	8mg RSG XR	105	0.1	0.05	0.0	(−0.1, 0.1)
	Donepezil (10mg)	45	0.1	0.07	0.0	(−0.1, 0.2)
Full Population	Placebo	123	0.1	0.05	---	---
	2mg RSG XR	120	0.2	0.05	0.1	(−0.0, 0.2)
	8mg RSG XR	117	0.1	0.05	0.0	(−0.1, 0.1)
	Donepezil (10mg)	52	0.1	0.07	0.0	(−0.1, 0.2)
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 24 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	62	−0.3	1.93	---	---
	2mg RSG XR	71	−0.4	1.90	−0.1	(−5.3, 5.1)
	8mg RSG XR	66	−0.7	2.19	−0.5	(−6.1, 5.2)
	Donepezil (10mg)	27	2.5	3.30	2.8	(−4.9, 10.6)
All Except *ε4/4*	Placebo	114	0.9	1.50	---	---
	2mg RSG XR	116	−0.2	1.52	−1.1	(−5.2, 3.0)

	8mg RSG XR	113	0.9	1.71	0.0	(−4.4, 4.3)
	Donepezil (10mg)	48	2.2	2.57	1.2	(−4.6, 7.1)
Full Population	Placebo	128	1.9	1.56	---	---
	2mg RSG XR	130	−0.7	1.52	−2.6	(−6.6, 1.4)
	8mg RSG XR	126	0.2	1.71	−1.7	(−5.9, 2.6)
	Donepezil (10mg)	55	1.5	2.40	−0.4	(−5.8, 5.1)
Utility Score: Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	69	−0.01	0.026	---	---
	2mg RSG XR	78	0.02	0.020	0.03	(−0.03, 0.09)
	8mg RSG XR	70	−0.01	0.027	0.00	(−0.07, 0.07)
	Donepezil (10mg)	33	0.04	0.022	0.05	(−0.02, 0.12)
All Except *ε4/4*	Placebo	114	−0.01	0.018	---	---
	2mg RSG XR	116	0.02	0.015	0.03	(−0.01, 0.08)
	8mg RSG XR	112	0.00	0.018	0.01	(−0.04, 0.06)
	Donepezil (10mg)	48	0.02	0.016	0.03	(−0.01, 0.08)
Full Population	Placebo	128	−0.02	0.017	---	---
	2mg RSG XR	130	0.00	0.016	0.03	(−0.01, 0.07)
	8mg RSG XR	125	0.01	0.016	0.04	(−0.01, 0.08)
	Donepezil (10mg)	55	0.01	0.021	0.03	(−0.02, 0.09)
ACQLI Total Score: Change from Baseline at Week 24 (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	62	0.5	0.64	---	---
	2mg RSG XR	70	−0.6	0.60	−1.1	(−2.8, 0.6)
	8mg RSG XR	65	0.4	0.80	−0.1	(−2.1, 1.9)
	Donepezil (10mg)	27	−1.4	0.65	−1.9	(−3.7, −0.1)
All Except *ε4/4*	Placebo	114	0.4	0.45	---	---
	2mg RSG XR	116	−0.5	0.50	−0.9	(−2.1, 0.4)
	8mg RSG XR	113	−0.4	0.53	−0.8	(−2.1, 0.6)
	Donepezil (10mg)	47	−0.2	0.76	−0.6	(−2.4, 1.1)
Full Population	Placebo	128	0.6	0.45	---	---
	2mg RSG XR	132	−0.2	0.49	−0.8	(−2.0, 0.4)
	8mg RSG XR	126	0.0	0.54	−0.6	(−1.9, 0.7)
	Donepezil (10mg)	54	−0.0	0.69	−0.6	(−2.2, 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 24 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	62	17.5	13.89	---	---
	2mg RSG XR	71	−12.1	4.82	−29.6	(−58.5, −0.6)
	8mg RSG XR	66	3.6	10.81	−13.9	(−48.5, 20.7)
	Donepezil (10mg)	27	−9.4	7.61	−26.9	(−58.2, 4.4)
All Except *ε4/4*	Placebo	114	21.8	11.07	---	---
	2mg RSG XR	117	−9.0	3.58	−30.8	(−53.6, −8.0)
	8mg RSG XR	114	4.8	6.55	−17.0	(−42.2, 8.2)
	Donepezil (10mg)	48	−4.2	5.42	−26.0	(−50.2, −1.8)
Full Population	Placebo	128	20.2	9.93	---	---
	2mg RSG XR	133	−3.7	4.58	−23.9	(−44.9, −3.0)
	8mg RSG XR	127	6.4	6.25	−13.7	(−36.3, 8.8)
	Donepezil (10mg)	55	−3.0	5.09	−23.2	(−44.7, −1.7)
Caregiver Hours Spent on Instrumental Activities:from RUD: Change from Baseline at Week 24 (Repeated Measures Analysis) (ITT Population)						
APOE ε4-negative	Placebo	62	18.3	11.57	---	---

	2mg RSG XR	71	3.4	6.12	−14.9	(−40.7, 10.8)
	8mg RSG XR	66	9.1	11.55	−9.2	(−41.3, 22.8)
	Donepezil (10mg)	38	−9.8	11.15	−28.1	(−59.8, 3.7)
All Except *ε4/4*	Placebo	114	21.1	7.54	---	---
	2mg RSG XR	117	8.5	4.97	−12.6	(−30.0, 4.8)
	8mg RSG XR	114	23.8	10.53	2.7	(−22.5, 27.9)
	Donepezil (10mg)	48	3.4	7.69	−17.7	(−38.7, 3.3)
Full Population	Placebo	128	19.8	7.07	---	---
	2mg RSG XR	133	7.8	4.68	−12.0	(−27.8, 3.6)
	8mg RSG XR	127	21.7	9.73	1.8	(−21.0, 24.7)
	Donepezil (10mg)	55	3.0	7.02	−16.8	(−35.6, 1.9)

SAFETY RESULTS:

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-Treatment, number and % of subjects with event

Treatment Group	Placebo		2mg RSG XR		8mg RSG XR		Donepezil (10mg)	
Subject Group	Full	*APOE ε4*−neg	Full	*APOE ε4*−neg	Full	*APOE ε4*−neg	Full	*APOE ε4*−neg
Preferred Term	N=165	N=86	N=166	N=85	N=165	N=86	N=83	N=42
Subject with any AE	62 (38)	27 (31)	60 (36)	30 (35)	69 (42)	36 (42)	42 (51)	19 (45)
Edema peripheral	9 (5)	4 (5)	6 (4)	2 (2)	24 (15)	11 (13)	3 (4)	2 (5)
Diarrhea	1 (<1)	0	2 (1)	1 (1)	4 (2)	3 (3)	4 (5)	1 (2)
Nasopharyngitis	4 (2)	1 (1)	11 (7)	6 (7)	4 (2)	2 (2)	1 (1)	0
Headache	0	0	2 (1)	1 (1)	2 (1)	1 (1)	7 (8)	7 (17)
Hyperlipidemia	1 (<1)	0	9 (5)	3 (4)	1 (<1)	0	2 (2)	3 (1)
Nausea	0	0	1 (<1)	0	1 (<1)	1 (1)	4 (5)	3 (7)
Gastroesophageal reflux	1 (<1)	1 (1)	0	0	0	0	2 (2)	2 (5)
Insomnia	1 (<1)	0	0	0	0	0	3 (4)	2 (5)

Serious Adverse Events (SAEs) - On-Treatment

SAEs are summarized below first for any SAE (fatal and nonfatal events) followed by fatal SAEs only. The summaries are given a**s** n (%) of subjects with event with number of events considered by the investigator to be related to study drug in brackets (i.e., n (%) [n]).

Summary for Any SAE (fatal or nonfatal)

Treatment Group	Placebo		2mg RSG XR		8mg RSG XR		Donepezil (10mg)	
Subject Group	Full	*APOE ε4*−neg	Full	*APOE ε4*−neg	Full	*APOE ε4*−neg	Full	*APOE ε4*−neg
	N=165	N=86	N=166	N=85	N=165	N=86	N=83	N=42
Preferred Term	**n (%) [related]**							
Any SAE (fatal or nonfatal)	**10 (6) [2]**	**5 (6) [1]**	**7 (4) [2]**	**4 (5) [2]**	**8 (5) [3]**	**3 (3) [1]**	**6 (7) [2]**	**2 (5) [1]**
Anemia	0	0	0	0	1 (<1) 1]	1 (1) [1]	0	0
Arrhythmia supraventricular	0	0	0	0	1 (<1) [1]	0	0	0
Aspiration	0	0	0	0	1 (<1) [0]	1 (1) [0]	0	0
Dehydration	0	0	0	0	1 (<1) [0]	0	0	0
Iron deficiency anemia	0	0	0	0	1 (<1) [0]	0	0	0
Orthostatic hypotension	0	0	0	0	1 (<1) [0]	1 (1) [0]	0	0
Phlebitis	0	0	0	0	1 (<1) [0]	0	0	0
Respiratory failure	0	0	0	0	1 (<1) [0]	1 (1) [0]	0	0
Thrombophlebitis	0	0	0	0	1 (<1) [1]	0	0	0

Accidental overdose	0	0	1 (<1) [0]	1 (1)	0	0	0	0
Acute myocardial infarction[1]	0	0	0	0	0	0	1 (1) [1]	0
Aortic valve stenosis	0	0	0	0	0	0	1 (1) [1]	1 (2) [1]
Arthralgia	0	0	1 (<1) [0]	1 (1)	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	1 (1) [0]	0
Bradycardia	0	0	0	0	0	0	1 (1) [0]	0
Cardiac failure	1 (<1) [0]	0	0	0	0	0	0	0
Cardiac failure congestive	0	0	1 (<1) [1]	1 (1) [1]	0	0	0	0
Cerebral hemorrhage	1 (<1) [0]	1 (1) [0]	0	0	0	0	0	0
Cholecystitis acute	0	0	1 (<1) [0]	0	0	0	0	0
Cholelithiasis	1 (<1) [0]	1 (1) [0]	0	0	0	0	0	0
Contusion	1 (<1) [0]	1 (1) [0]	0	0	0	0	0	0
Diarrhea	0	0	1 (<1) [0]	0	0	0	0	0
Discomfort	0	0	0	0	0	0	1 (1) [0]	0
Disorientation	1 (<1) [0]	0	0	0	0	0	0	0
Fall	0	0	1 (<1) [0]	1 (1)	0	0	0	0
Gastrointestinal ulcer hemorrhage	0	0	0	0	0	0	1 (1) [0]	0
Hip fracture	1 (<1) [1]	0	1 (<1) [0]	1 (1)	0	0	0	0
Humerus fracture	1 (<1) [1]	1 (1) [1]	0	0	0	0	0	0
Lung neoplasm	1 (<1) [0]	0	0	0	0	0	0	0
Myocardial infarction[1]	0	0	1 (<1) [1]	1 (1) [1]	0	0	0	0
Pain	0	0	1 (<1) 1]	1 (1) [1]	0	0	0	0
Pneumonia	0	0	0	0	0	0	1 (1) [0]	1 (2) [0]
Presyncope	1 (<1) [0]	0	0	0	0	0	0	0
Subdural hematoma	0	0	1 (<1) [0]	0	0	0	0	0
Syncope	1 (<1) [0]	1 (1) [0]	1 (<1) [0]	1 (1)	0	0	0	0
Transient ischemic attack	0	0	0	0	0	0	1 (1) [0]	0
Tremor	0	0	1 (<1) [1]	1 (1) [1]	0	0	0	0

1. Note: Both these events were myocardial infarction but each coded to the different preferred term.

Summary for Any Fatal SAEs								
Treatment Group	**Placebo**		**2mg RSG XR**		**8mg RSG XR**		**Donepezil (10mg)**	
Subject Group	**Full N=165**	***APOE ε4*−neg N=86**	**Full N=166**	***APOE ε4*−neg N=85**	**Full N=165**	***APOE ε4*−neg N=86**	**Full N=83**	***APOE ε4*−neg N=42**
Preferred Term	**n (%) [related]**							
Any SAE (fatal)	**1 (<1) [0]**	**0**	**0**	**0**	**1 (<1) 0]**	**1 (1) [0]**	**0**	**0**
Cardiac failure	1 (<1) [0]	0	0	0	0	0	0	0
Aspiration	0	0	0	0	1 (<1) [0]	1 (1) [0]	0	0
Respiratory failure	0	0	0	0	1 (<1) [0]	1 (1) [0]	0	0
Conclusions:								

• The study failed to detect significant efficacy with 2mg or 8mg RSG XR on either co primary efficacy endpoint (change from baseline at Week 24 in ADAS-Cog Total and CIBIC+ scores) in *APOE ε4*-neg subjects, All Except *ε4/4* subjects, or the Full Population. • The study also failed to detect significant efficacy with donepezil (10mg) relative to placebo on change in ADAS-Cog Total scores in any pre specified subject group; however, a significant effect was seen on change in CIBIC+ scores for the Full Population. The latter demonstrated a degree of assay sensitivity in the study. • Overall, the safety profile for RSG XR, during up to 24 weeks of treatment at 2mg and 8mg, was consistent with the safety and tolerability profile for RSG immediate-release (IR) in type 2 diabetes mellitus.
Publications: None at the time of this report.