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Study No.: AVA102675
Title: An open-label extension study of the long-term safety and efficacy of rosiglitazone extended-release (RSG XR) as adjunctive therapy to acetylcholinesterase inhibitors in subjects with mild-to-moderate Alzheimer's disease (REFLECT-4).
Rationale: The Phase III rosiglitazone extended-release program included three double-blind, placebo-controlled studies (two adjunctive therapy studies AVA102670, AVA102672; a monotherapy study (AVA105640) and two open-label extension (OLE) studies (adjunctive therapy study AVA102675, monotherapy study AVA102677) to evaluate long-term safety and efficacy of RSG XR in subjects with mild-to-moderate Alzheimer's disease. These studies collectively were coined the **R**osiglitazone (XR) **EF**ficacy in A**L**zheimer's dis**E**ase **C**linical **T**rials (REFLECT) program. The current study, AVA102675 was an open-label extension study following studies AVA102670 and AVA102672 to evaluate the long-term safety and efficacy of RSG XR in subjects with mild-to-moderate AD.. After results from AVA102672 failed to demonstrate efficacy of RSG XR as adjunctive therapy, GSK terminated this open-label extension study on 30 May 2009.
Phase: III
Study Period: 08Aug2007 – 30May2009
Study Design: A global, Phase III, multicenter, single group, 52-week open-label study of RSG-XR with the option for additional years of open-label treatment, and a 6 week post-treatment followup period in subjects with mild-to-moderate AD who completed the double-blind treatment phase of either parent study: AVA102670 or AVA102672. Subjects were allowed to continue their current dose of AChEI while adding open-label RSG XR as adjunctive therapy. Subjects who completed AVA102670 or AVA102672 attended visits beginning open-label treatment at Week 0 (starting 4mg RSG-XR), and continuing open-label treatment at Week 4 (titrating up to 8mg RSG XR), 8, 12, 16, 24, 36, and 52. Upon completion of the initial 52 weeks, subjects/caregivers could re-consent for additional years of open label treatment, attending visits each year at Week 12, 24, 36, and 52.
Centres: Two hundred sixty seven centres enrolled at least one subject in the following 29 countries: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Czech Republic, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Italy, Korea, Mexico, Netherlands, Philippines, Poland, Portugal, Slovakia, Slovenia, South Africa, Spain, Sweden, United Kingdom, and United States.
Indication: Alzheimer's Disease
Treatment: Subjects received treatment with open-label RSG XR throughout the treatment period as adjunctive therapy to their existing dose of an acetylcholinesterase inhibitor (AChEI) and/or memantine for Alzheimer's disease treatment. Subjects took one tablet of study medication daily in the morning with or without food. All subjects received 4 mg RSG XR once daily for the first 4 weeks of the study. The RSG XR dose was then increased to 8 mg once daily from Week 4 through Week 52. After the first 52 weeks of treatment, subjects could re-consent to continue 8mg RSG XR for subsequent years. However, at any time, after consultation with the Medical Monitor, the dose of RSG XR could be reduced to 2 mg once daily, if the 8 mg dose was not well tolerated by the subject. If the 2mg dose was shown to be ineffective in AVA102670 or AVA102672, the 2mg dose would no longer have been offered as an option in AVA102675, and subjects on 2mg would have been withdrawn from the study.
Objectives: The primary objective was to evaluate the long-term safety and tolerability of RSG XR in subjects with mild-to-moderate AD, on stable doses of acetylcholinesterase inhibitors, who completed either Study AVA102670 or AVA102672. The secondary objective of this study was to explore further the long-term efficacy of RSG XR on cognitive function and overall clinical response in subjects with mild to moderate AD who completed Study AVA102670 or AVA102672.
Primary Outcome: Incidence and severity of adverse events (AEs)
Secondary Outcomes: Secondary safety endpoints were: • Incidence and severity of serious adverse events (SAEs) • Percentage of subjects with AE of oedema • Change from baseline in vital signs • Frequency of vital signs of clinical concern

- Change from baseline in weight
- Change from baseline in non-fasting measures of lipid metabolism (total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides)
- Frequency of clinical chemistry (including lipids) and haematology parameters of clinical concern

In addition special assessments and safety measures were included for subjects exhibiting signs of liver function abnormality, edema or CHF, as well as subjects, who experienced a significant CV event, were enrolled with T2DM, who had a QTc exceeding pre specified criteria during the study, and (after protocol amendment 3) who had creatine phosphokinase (CK) values >ULN or elevated 50 U/L from baseline.

The efficacy endpoints were:
- Change from baseline in Alzheimer's Disease Assessment Scale – cognitive (ADAS Cog) total score as a function of APOE 4 status.
- Change from baseline in Clinical Dementia Rating scale – Sum of Boxes (CDR-SB) score as a function of APOE 4 status
- Change from baseline in Mini Mental State Examination (MMSE) total score as a function of APOE 4 status.
- Change from baseline in Disability Assessment for Dementia scale (DAD) total score as a function of APOE 4 status.
- Change from baseline in Neuropsychiatric Inventory (NPI) total score as a function of APOE 4 status.

Other secondary endpoints were:
- Change from baseline in glycosylated haemoglobin (HbA1c).

For safety endpoints, 'baseline' referred to the AVA102675 baseline assessment, i.e., AVA102675 Visit 1 equals AVA102670 or AVA102672 Visit 10. For efficacy endpoints, the term 'baseline' referred to the baseline assessment of the parent study, i.e. AVA102670, Visit 3.

Statistical Methods: The sample size was determined by the number of subjects who wished to continue after the end of AVA102670 and AVA102672. It was assumed that approximately 1800 subjects (900 from each parent study) would enter the study, resulting in 1350 subjects completing the first 52 weeks of the study. No formal hypothesis testing was performed on the data from this study since it was primarily a safety study with a non-randomized, self selected population of subjects and no control group. The primary population for the safety and efficacy analyses were those subjects who took at least one dose of study medication. Data were summarized with descriptive statistics (percentages, means, and standard deviations).

Study Population: Male or non-pregnant, non-lactating female subjects who successfully completed Visit 10 of AVA102670 or AVA102672 without safety/tolerability issues. In addition, subjects who completed the AVA102670 or AVA102672 double-blind treatment phase could still be eligible for entry if they withdrew during the last 6 weeks of AVA102670 or AVA102672 due to any reason other than safety. Subjects 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 medication, and report on subject's status. Subjects had a QTc [either QTc B (Bazett's correction) or QTc F (Fridericia's correction)] of <450 msec at Visit 1, with the exception of subjects with bundle branch block (for whom either QTc B or QTc F was <480 msec). This inclusion criterion only applied to subjects who needed to meet QTc entry criteria in AVA102670 or AVA102672; however, QT withdrawal criteria still applied to all subjects.

	RSG XR
Number of Subjects:	All Subjects Population
Enrolled, N	1461
Completed, n (%)	97 (7)
Total Number Subjects Withdrawn, N (%)	390 (27)
Withdrawn due to Adverse Events n (%)	116 (8)
Withdrawn due to Lack of Efficacy n (%)	116 (8)
Withdrawn for other reasons n (%)	274 (19)
Demographics	
N (ITT)	1461
Females: Males	843: 618

Mean Age, years (SD)	73.9 (7.96)
White, n (%)	1396 (96)
Primary 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 (with incidence >2%)	
Subjects with any AE(s), n(%)	
Subject Group Preferred Term	**RSG XR** **N=1461**
ANY EVENT	724 (50)
Edema Peripheral	130 (9)
Fall	46 (30)
Nasopharyngitis	38 (3)
Anemia	37 (3)
Weight Increased	33 (2)
Dizziness	28 (2)
Agitation	24 (2)
Arthralgia	23 (2)
Diarrhea	23 (2)
Hypercholesterolemia	23 (2)
Back Pain	22 (2)
Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**	
Subjects with non-fatal SAEs, n (%) (those reported in more than one subject)	
Preferred Term	**RSG XR** **N=1461** **N (%) [related]**
ANY EVENT	59 (4)

Anemia	5 (<1)
Pneumonia	5 (<1)
Fall	4 (<1)
Cerebrovascular accident	4 (<1)
Syncope	4 (<1)
Femur fracture	3 (<1)
Myocardial infarction	3 (<1)
Aggression	3 (<1)
Spinal compression fracture	3 (<1)
Dementia	3 (<1)
Humerus fracture	2 (<1)
Skin laceration	2 (<1)
Dementia Alzheimer's type	2 (<1)
Transient ischemic attack	2 (<1)
Acute myocardial infarction	2 (<1)
Atrial fibrillation	2 (<1)
Bronchopneumonia	2 (<1)
Urinary tract infection	2 (<1)
Breast cancer	2 (<1)
Delirium	2 (<1)
Osteoarthritis	2 (<1)
Subjects with fatal SAEs, n (%)	
ANY EVENT	20 (1)

Cerebral hemorrhage	1 (<1)
Cerebrovascular accident	1 (<1)
Cerebrovascular disorder	1 (<1)
Coma	1 (<1)
Dementia Alzheimer's type	1 (<1)
Subarachnoid hemorrhage	1 (<1)
Acute myocardial infarction	1 (<1)
Cardiac arrest	1 (<1)
Cardiac failure	1 (<1)
Cardiorespiratory arrest	1 (<1)
Myocardial infarction	1 (<1)
Death	1 (<1)
Multi-organ failure	1 (<1)
Sudden death	1 (<1)
Bronchopneumonia	1 (<1)
Pneumonia	1 (<1)
Urinary tract infection	1 (<1)
Ovarian cancer	1 (<1)
Prostate cancer	1 (<1)
Pneumonia aspiration	1 (<1)
Pulmonary embolism	1 (<1)
Head injury	1 (<1)
Circulatory collapse	1 (<1)
Vital Signs of Potential Clinical Concern Anytime On-Treatment	
Treatment Group	**RSG XR N=1461**
Systolic blood pressure	
Baseline, n >140 or <90 mmHg, n (%)	1461 310 (21)
Anytime on-treatment, n ≥40mmHg increase, n (%) ≥30mmHg decrease, n (%)	1409 33 (2) 179 (13)
Diastolic blood pressure	
Baseline, n >90 or <50, n (%)	1461 52 (4)
Anytime on-treatment,n ≥30mmHg increase, n (%) ≥20mmHg decrease, n (%)	1409 20 (1) 211 (15)
Heart rate	
Baseline, n >100 or <50bpm, n (%)	1461 29 (2)
Anytime on-treatment, n ≥30bpm increase ≥30bpm decrease	1409 25 (2) 14 (<1)
Vital Signs: Change from Baseline (blood pressure in mmHg, heart rate in beats/min)	

AVA102675 Study Visit	n	Systolic Blood Pressure Mean (SD)	Diastolic Blood Pressure Mean (SD)	Heart Rate Mean (SD)
Week 0 (Baseline)	1461	131.0 (15.04)	75.1 (9.26)	67.6 (9.92)
Change to:				
Week 4	1395	-1.4 (14.10)	-1.4 (9.41)	1.0 (8.95)
Week 8	1274	-2.4 (14.73)	-2.0 (9.53)	1.8 (9.60)
Week 12	1146	-2.7 (14.73)	-2.1 (9.74)	1.6 (9.77)
Week 16	1061	-3.7 (15.02)	-2.4 (9.62)	1.6 (9.66)
Week 24	892	-2.1 (15.51)	-2.4 (9.48)	0.9 (9.99)
Week 36	666	-1.4 (15.14)	-2.0 (9.85)	1.3 (9.86)
Week 52	251	-1.7 (16.18)	-3.6 (9.94)	0.7 (8.54)
Year 2 Week 12	15	-2.2 (13.78)	-6.3 (6.72)	1.0 (8.02)
Follow-up	1280	-1.8 (15.60)	-0.9 (10.23)	0.9 (10.03)

Weight: Change from baseline (kg)

AVA102675 Study Visit	n	Mean (SD)
Week 0 (Baseline)	1461	69.7 (13.59)
Change to:		
Week 4	1391	0.3 (2.04)
Week 8	1263	0.6 (2.45)
Week 12	1139	0.6 (2.43)
Week 16	1057	0.7 (3.53)
Week 24	889	0.6 (2.95)
Week 36	666	1.0 (4.08)
Week 52	251	1.2 (3.82)
Year 2 Week 12	15	1.4 (2.52)
Follow-up	1268	0.5 (3.15)

Clinical Chemistry Parameters of Potential Clinical Concern (PCC) [Parameters where greater than 1% of subjects had a value that was either high and of PCC or low and of PCC at any time on-treatment are listed.]

Parameter	Frequency Numbers of subjects (%)
High values of PCC	
Aldolase	16/464 (3)
BUN/creatinine ratio	87/1385 (6)
Cholesterol	175/1385 (13)
Creatine kinase	131/1385 (9)
Creatinine	27/1385 (2)
Glucose	100/1385 (7)
LDL cholesterol calculation	469/1368 (34)
Potassium	17/1384 (1)
Troponin I	13/426 (3)
Urea	97/1385 (7)
Low values of PCC	
Aldolase	78/464 (17)
Glucose	40/1385 (3)

Hematology Parameters of Potential Clinical Concern (PCC) [Parameters where greater than 1% of subjects had a value that was either high and of PCC or low and of PCC at any time on-treatment are listed.]

Parameter	Frequency Numbers of subjects (%)
High values of PCC	
RDW	158/1385 (11)
Low values of PCC	
Hemoglobin	74/1385 (5)
Lymphocytes	21/1384 (2)
Monocytes	34/1384 (2)
Segmented neutrophils	15/1384 (1)
Total neutrophils	15/1384 (1)
White blood cell count	22/1384 (2)

Lipid Measures: Change from Baseline (mmol/L)

AVA102675 Study Visit	n	Cholesterol Mean (SD)	HDL Mean (SD)	LDL Mean (SD)	Triglycerides Mean (SD)
Week 0 (Baseline)	1425	5.68 (1.205)	1.52 (0.435)	3.33 (1.086)	1.85 (0.975)
Change to:					
Week 4	1313	0.08 (0.683)	0.01 (0.201)	0.06 (0.621)	0.00 (0.785)
Week 16	1038	0.20 (0.867)	-0.01 (0.243)	0.21 (0.778)	-0.03 (0.805)
Week 36	639	0.25 (0.965)	-0.03 (0.249)	0.28 (0.886)	-0.06 (0.805)
Week 52	234	0.17 (1.144)	-0.04 (0.251)	0.23 (1.056)	-0.09 (0.852)

Efficacy Results

Timepoint	N	Mean (SD)
Change from baseline in ADAS-Cog Total Scores at Week 24 and 52 (ADAS-Cog Total scores range from 0 to 70 with increasing scores implying worse cognition. Positive changes from 0 to 24 weeks and 0 to 52 weeks indicate cognitive decline from baseline.)		
Baseline (Week 0)	1439	26.8 (12.57)
Change to Week 24	973	2.5 (5.51)
Change to Week 52	308	5.1 (6.82)
Change from baseline in CDR-SB Total scores at Week 24 and 52 (CDR-SB scores range from 0 to 18 with		

increasing scores indicating severity of impairment.)		
Baseline (Week 0)	1461	7.9 (4.24)
Change to Week 24	988	0.7 (1.84)
Change to Week 52	313	1.6 (2.26)
Change from baseline in MMSE scores at Week 24 and 52 [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.]		
Baseline (Week 0)	1459	18.3 (5.99)
Change to Week 24	833	-1.2 (2.84)
Change to Week 52	184	-2.3 (3.39)
Change from baseline in DAD percentage scores at Week 24 and 52 [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.]		
Baseline (Week 0)	1461	64.2 (25.32)
Change to Week 24	837	-5.6 (12.36)
Change to Week 52	183	-10.8 (15.07)
Change from baseline in NPI scores at Week 24 and 52 [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.]		
Baseline (Week 0)	1461	9.4 (12.08)
Change to Week 24	835	1.4 (7.87)
Change to Week 52	183	3.2 (10.90)
Change from baseline in HbA_{1c} at Week 24 and 52		
Baseline (Week 0)	1425	5.92 (0.497)
Change to Week 24	189	-0.08 (0.382)
Change to Week 52	219	-0.01 (0.340)

Conclusions:

- Overall, the long term safety and tolerability profile of RSG XR observed over 52 weeks of treatment with 8 mg RSG XR, in this study, was consistent with the known safety profile of RSG immediate release 8mg tablets in patients with Type 2 diabetes mellitus (T2DM).
- Peripheral edema was the most common drug-related AE and the most common AE overall.
- The majority of the AEs were mild-moderate in severity at maximum intensity, and severe on-treatment AEs were reported infrequently.
- Twenty subjects died during AVA102675. These fatal SAEs were not considered by the investigators as possibly related to RSG XR treatment.
- No specific concerns regarding cardiovascular or bone safety were noted; rates of events for myocardial infarction and fractures were low (<1% and 2%, respectively).
- Both the mean systolic and mean diastolic BP values decreased over time, up to 3 mmHg and 2 mmHg, respectively. Mean HR values increased slightly over time, by approximately 1 to 2 beats/min.
- There were no major differences between *APOE ε4* -negative and *APOE ε4* -positive subjects in the overall incidence of SAEs or AEs including AEs of special interest during the study.
- Hematology values consistent with hemodilution were observed with slight mean declines through Week 36 in: hemoglobin, hematocrit, lymphocytes, platelet count, red blood cell (RBC) count, segmented neutrophils, segmented neutrophils %, total neutrophils, total neutrophils %, and white blood cell (WBC) count. An increase was noted for RDW through Week 36.
- Mean cholesterol, CK, LDL cholesterol calculation, lactate dehydrogenase (LDH), and urea increased over time relative to open-label baseline.
- With respect to mean values, cognitive decline measured by ADAS-Cog, and slight worsening of the global function measured by CDR-SB were evident during study AVA102675. Minimal differences were observed between *APOE ε4* -negative and *APOE ε4* -positive subjects.
- Due to the non-randomized study design, efficacy results are descriptive, and can only be considered exploratory. They should be interpreted with caution, and are not intended to guide clinical management of patients with Alzheimer's disease.

Publications: None at the time of this report