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.:** AVA102677

**Title:** An open-label extension study of the long-term safety and efficacy of rosiglitazone extended-release (RSG XR) in subjects with mild-to-moderate Alzheimer's disease (REFLECT-5)

**Rationale:** The Phase III program for rosiglitazone extended-release (RSG XR) in AD included three double-blind, placebo-controlled studies - two adjunctive therapy studies (AVA102670 and AVA102672) and a monotherapy study (AVA105640) - and two open-label extension studies evaluating long-term safety with RSG XR (AVA102675 and AVA102677). Together these studies were referred to as the **R**osiglitazone (XR) **EF**ficacy in a**L**zheimer's dis**E**ase **C**linical **T**rials (REFLECT) program. The current study, AVA102677 (REFLECT-5), was an open-label extension study following parent study AVA105640 to evaluate the long-term safety and efficacy of RSG XR in subjects with mild-to-moderate AD. After results from AVA105640 failed to demonstrate efficacy of RSG XR as monotherapy in AD, GSK terminated this open-label extension study on 12 February 2009.

**Phase:** III

**Study Period:** 01 October 2007 to 12 February 2009

**Study Design:** After informed consent was obtained, enrolment of eligible subjects into AVA102677 (Visit 1) usually occurred at Visit 8 (final treatment visit) of AVA105640. (A delay of up to one month was permissible but only after discussion with and agreement by a Medical Monitor.) Subjects attended visits at Weeks 0, 4, 8, 12, 16, 24, 36, and 52 of open-label treatment. If a subject and caregiver chose to extend treatment beyond the first 52 weeks, following re-consent, patients were allowed to continue and attend visits at 12-, 24-, 36-, and 52-week timepoints every year.

**Centres:** There were 72 centers initiated in 17 countries. A total of 68 of the 72 initiated centers enrolled at least one subject in the following countries: Austria, Bulgaria, Chile, China, Croatia, Estonia, Germany, Greece, Hungary, Korea, Mexico, New Zealand, Peru, Philippines, Russia, the United Kingdom [UK], and the United States [US]).

**Indication:** Alzheimer's Disease

**Treatment:** Subjects received open-label RSG XR throughout the treatment period. Subjects took one tablet of study medication daily in the morning with or without food. All subjects received 4mg once daily RSG XR for the first 4 weeks of the study (the 4mg dose could only be used for the first 4 weeks of the study). The RSG XR dose was then increased to 8mg once daily for the rest of the study. After consultation with the Medical Monitor, the dose of RSG XR could be reduced to 2mg once daily if the 8mg dose was not well tolerated by the subject; in such cases, subjects were not permitted to titrate back to 8mg RSG XR. If the 2mg dose was shown to be ineffective in AVA105640, the 2mg dose would no longer have been offered as an option in AVA102677, and subjects on 2mg would have been withdrawn from the study.

**Objectives:** The primary objective of this study was to evaluate the long-term safety and tolerability of RSG XR in subjects with mild-to-moderate AD who had completed Study AVA105640.
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 AVA105640.

**Primary Outcome/Efficacy Variable:** Incidence and severity of adverse events (AEs)

**Secondary Outcome/Efficacy Variable(s):**
Secondary safety endpoints were:

- Incidence and severity of serious adverse events (SAEs)
- Percentage of subjects with AE of edema
- 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 ε4 status.
- Change from baseline in Clinician Interview-Based Impression of Change Plus Caregiver input (CIBIC+) score as a function of APOE ε4 status
- Change from baseline in Mini Mental State Examination (MMSE) total score as a function of APOE ε4 status.
- Change from baseline in Disability Assessment for Dementia scale (DAD) total score as a function of APOE ε4 status.
- Change from baseline in Neuropsychiatric Inventory (NPI) total score as a function of APOE ε4 status.

Other secondary endpoints were:

- Change from baseline in glycosylated haemoglobin (HbA1c).

For safety endpoints, 'baseline' referred to the AVA102677 baseline assessment, i.e., AVA102677 Visit 1 equals AVA105640 Visit 8. For efficacy endpoints, the term 'baseline' referred to the baseline assessment of the parent study, i.e. AVA105640, Visit 3.

**Statistical Methods:** The sample size was determined by the number of subjects who wished to continue after the end of AVA105640. It was assumed that approximately 383 subjects would enter the study, resulting in 287 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-randomised, self selected population of subjects and no control treatment 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 8 of parent study AVA105640 without safety/tolerability issues were offered open-label extension treatment in AVA102677. At Visit 8 of AVA105640, a subject was eligible to continue open-label treatment in AVA102677 if, in the opinion of the subject /carer and of the investigator, it could be beneficial for the subject to continue to receive RSG XR and both subject and carer re-consented to continued treatment. 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 considered for enrolment had a QTc (either QTc B (Bazett's correction) or QTc F (Fridericia's correction)) <450msec at Visit 1, with the exception of subjects with bundle branch block (for whom either QTc B or QTc F was required to be <480msec). (Note: This inclusion criterion only applied to subjects who needed to meet QTc entry criteria in AVA105640 after its protocol was amended; however, QT withdrawal criteria still applied to all subjects.) Subjects were not taking any acetylcholinesterase inhibitor (AChEI) drug at Visit 1 of AVA102677, in accordance with the study design for AVA105640. In accordance with approved prescribing information, the investigator's medical judgement and recommendation, subjects were permitted to begin dosing with an AChEI and/or memantine as adjunctive therapy only after the RSG XR titration period had been evaluated (i.e. from Visit 3 / Week 8 onwards).

| | **8 mg RSG XR** |
|---|---|
| Number of Subjects: | All Subjects Population |
| Enrolled, N | 331 |
| Completed*, n (%)<br>(*Includes subjects who completed 52 weeks of treatment in AVA102677 and chose not to continue beyond 52 weeks.) | 26 (8) |
| Still in the Study at Termination, n (%) | 206 (62) |
| Total Number Subjects Withdrawn, N (%) | 97 (29) |
| Withdrawn due to Adverse Events, n (%) | 28 (8) |
| Withdrawn for other reasons, n (%) | 69 (21) |
| Missing | 2 (<1) |
| | |
| **Demographics** | **8 mg RSG XR** |
| N (All Subjects) | 311 |
| % Females: % Males | 62: 38 |
| Mean Age, years (SD) | 72.8 (7.95) |
| White, n (%)<br>Asian, n (%) | 242 (73)<br>85 (26) |
| | |

**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 (10 most frequent AEs in the treatment group)** | |
| Subjects with any AE(s), n(%) | |
| Treatment Group<br>Preferred Term | 8 mg RSG XR<br>N=311 |
| ANY EVENT | 125 (38) |
| Edema peripheral | 42 (13) |
| Anemia | 9 (3) |
| Headache | 9 (3) |
| Dizziness | 8 (2) |
| Nasopharyngitis | 6 (2) |
| Cough | 5 (2) |
| Dyslipidaemia | 5 (2) |
| Hyperlipidaemia | 5 (2) |
| Face edema | 4 (1) |
| Urinary tract infection | 4 (1) |
| Blood creatine phosphokinase increased | 4 (1) |
| Nausea | 4 (1) |
| **Serious Adverse Events - On-Therapy**<br>**n (%) [n considered by the investigator to be related to study medication]** | |
| Subjects with non-fatal SAEs, n (%) [related] | |
| Treatment Group<br><br>Preferred Term | 8 mg RSG XR<br>N=311<br>n (%) [related] |
| ANY EVENT | 8 (2) |
| Atrioventricular block complete | 1 (<1) |
| Coronary aretery disease | 1 (<1) |
| Constipation | 1 (<1) |
| Urinary tract infection | 1 (<1) |
| Fracture | 1 (<1) |
| Blood pressure increased | 1 (<1) |
| Dehydration | 1 (<1) |
| Hypoglycemia | 1 (<1) [1] |
| Pathological fracture | 1 (<1) |
| Facial palsy | 1 (<1) |
| Dyspnea | 1 (<1) |
| | |
| Subjects with fatal SAEs, n (%) [related] | |
| Treatment Group<br><br>Preferred Term | 8 mg RSG XR<br>N=311<br>n (%) [related] |
| ANY EVENT | 3 (<1%) |
| Carbon monoxide poisoning | 1 (<1%) |
| Circulatory collapse | 1 (<1%) [1] |
| Death | 1 (<1%) |
| **Vital Signs of Potential Clinical Concern Anytime On-Treatment** | |
| **Treatment Group** | **8mg RSG XR**<br>**N=331** |
| **Systolic Blood Pressure** | |
| Baseline, n | 52 |
| >140 or <90 mmHg, n (%) | 10 (19) |
| Anytime on-treatment, n | 319 |
| ≥40mmHg increase, n (%) | 8 (3) |
| ≥30mmHg decrease, n (%) | 22 (7) |

| **Diastolic Blood Pressure** | |
|---|---|
| Baseline, n | 52 |
| >90 or <50, n (%) | 1 (2) |
| Anytime on-treatment, n | 319 |
| ≥30mmHg increase, n (%) | 2 (<1) |
| ≥20mmHg decrease, n (%) | 31 (10) |
| **Heart Rate** | |
| Baseline, n | 52 |
| >100 or <50bpm, n (%) | 0 (0) |
| Anytime on-treatment, n | 319 |
| ≥30bpm increase | 2 (<1) |
| ≥30bpm decrease | 0 (0) |

**Vital Signs: Change from Baseline** (blood pressure in mmHg, heart rate in beats/min)

| AVA102677 Study Visit | n | Systolic Blood Pressure Mean (SD) | Diastolic Blood Pressure Mean (SD) | Heart Rate Mean (SD) |
|---|---|---|---|---|
| Week 0 (Baseline) | 330 | 128.6 (14.38) | 75.8 (8.40) | 68.9 (8.99) |
| Change to: | | | | |
| Week 4 | 318 | -0.2 (11.61) | -0.8 (7.59) | 1.1 (7.19) |
| Week 8 | 294 | -1.1 (11.83) | -2.1 (8.52) | 1.8 (7.44) |
| Week 12 | 281 | -0.7 (13.80) | -2.0 (8.74) | 2.2 (8.70) |
| Week 16 | 271 | -1.3 (13.66) | -2.2 (9.00) | 1.2 (7.89) |
| Week 24 | 231 | -1.2 (13.30) | -2.1 (8.53) | 1.0 (7.87) |
| Week 36 | 134 | -3.0 (15.37) | -3.0 (9.11) | 1.7 (7.60) |
| Week 52 | 37 | 0.3 (12.85) | -1.4 (8.26) | -0.8 (8.87) |

**Weight: Change from Baseline** (kg)

| AVA102677 Study Visit | n | Mean (SD) |
|---|---|---|
| Week 0 (Baseline) | 330 | 67.1 (12.72) |
| Change to: | | |
| Week 4 | 318 | 0.2 (1.57) |
| Week 8 | 293 | 0.4 (2.42) |
| Week 12 | 281 | 0.5 (2.06) |
| Week 16 | 271 | 0.5 (2.59) |
| Week 24 | 231 | 0.6 (2.80) |
| Week 36 | 134 | 0.5 (3.60) |
| Week 52 | 37 | 0.0 (3.75) |

**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 | 3/56 (5) |
| BUN/creatinine ratio | 18/309 (6) |
| Cholesterol | 52/309 (17) |
| Creatine kinase | 32/309 (10) |
| Glucose | 19/309 (6) |
| LDL cholesterol calculation | 135/307 (44) |
| Troponin I | 2/47 (4) |
| Urea | 19/309 (6) |
| **Low values of PCC** | |
| Aldolase | 7/56 (13) |
| Glucose | 5/309 (2) |

**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** | |
| Red cell distribution width | 30/308 (10) |
| **Low values of PCC** | |
| Hemoglobin | 20/308 (6) |
| Lymphocytes | 5/308 (2) |
| Lymphocytes % | 5/308 (2) |
| Monocytes | 17/308 (6) |
| Segmented neutrophils | 14/308 (5) |
| Segmented neutrophils % | 6/308 (2) |
| Total neutrophils | 14/308 (5) |
| Total neutrophils % | 6/308 (2) |
| White blood cell count | 9/308 (3) |

**Lipid Measures: Change from Baseline** (mmol/L)

| AVA102677 Study Visit | n | Cholesterol Mean (SD) | HDL Mean (SD) | LDL Mean (SD) | Triglycerides Mean (SD) |
|---|---|---|---|---|---|
| Week 0 (Baseline) | 319 | 5.90 (1.222) | 1.50 (0.384) | 3.62 (1.108) | 1.71 (0.836) |
| Change to: | | | | | |
| Week 4 | 288 | 0.11 (0.734) | -0.04 (0.222) | 0.09 (0.669) | 0.08 (0.692) |
| Week 16 | 254 | 0.20 (0.971) | -0.03 (0.260) | 0.21 (0.915) | 0.03 (0.836) |
| Week 36 | 142 | 0.14 (1.066) | -0.07 (0.271) | 0.16 (0.948) | 0.05 (0.877) |
| Week 52 | 35 | 0.33 (1.245) | -0.02 (0.342) | 0.39 (1.035) | -0.18 (1.057) |

**Efficacy Results:**

| AVA102677 (open-label) Study Visit | Study Visit Timing Relative to AVA105640 (Double-Blind) Study Baseline | N | Mean (SD) |
|---|---|---|---|
| **ADAS-Cog Total Scores: Change from baseline at Weeks 24 and 52** [ADAS-Cog Total scores range from 0 to 70 with increasing scores implying worse cognition. Positive changes from Week 0 indicate cognitive decline from baseline.] | | | |
| Week 0 (Baseline) | Week 24 | 330 | 25.0 (11.42) |
| (Change to) Week 24 | Week 48 | 243 | 1.9 (5.23) |
| (Change to) Week 52 | Week 76 | 58 | 2.5 (5.69) |
| **CIBIC+ Scores: Change from Baseline at Weeks 24 and 52** [The CIBIC+ is scored on a 7-point scale to determine global clinical change from baseline of the parent study AVA105640: 1 = marked improvement; 2 = moderate improvement; 3 = minimal improvement; 4 = no change; 5 = minimal worsening; 6 = moderate worsening; and 7 = marked worsening.] | | | |
| Week 0 (Baseline) | Week 24 | 328 | 4.0 (1.08) |
| Week 24 | Week 48 | 241 | 4.3 (1.05) |
| Week 52 | Week 76 | 60 | 4.5 (1.10) |
| **MMSE Total Scores: Change from Baseline at Weeks 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.] | | | |
| Week 0 (Baseline) | Week 24 | 331 | 19.4 (4.94) |
| (Change to) Week 24 | Week 48 | 203 | -0.7 (2.65) |
| (Change to) Week 52 | Week 76 | 19 | -1.6 (2.85) |
| **DAD Percentage Scores: Change from Baseline at Weeks 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.] | | | |
| Week 0 (Baseline) | Week 24 | 331 | 69.7 (22.91) |
| (Change to) Week 24 | Week 48 | 203 | -3.2 (10.23) |
| (Change to) Week 52 | Week 76 | 19 | -5.2 (18.21) |

| | | | |
|---|---|---|---|
| **NPI Total Scores: Change from Baseline at Weeks 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.] | | | |
| Week 0 (Baseline) | Week 24 | 331 | 9.3 (13.61) |
| (Change to) Week 24 | Week 48 | 203 | 1.1 (7.07) |
| (Change to) Week 52 | Week 76 | 19 | 2.1 (9.55) |
| **HbA1c (%): Change from Baseline at Weeks 24 and 52** | | | |
| Week 0 (Baseline) | Week 24 | 307 | 6.00 (0.542) |
| (Change to) Week 24 | Week 48 | 65 | 0.08 (0.512) |
| (Change to) Week 52 | Week 76 | 29 | 0.09 (0.377) |

**Conclusions:**

- Overall, the long-term safety and tolerability profile for RSG XR observed over 52 weeks of treatment with 8mg RSG XR, in this study, was consistent with the known safety profile noted with RSG immediate release 8mg tablets in patients with Type 2 diabetes mellitus (T2DM).
- Edema was the most common AE overall, the most common drug-related AE, and the most common AE leading to discontinuation of the study.
- The majority of the AEs were mild-moderate in severity at maximum intensity, and severe on-treatment AEs were reported infrequently.
- Three subjects died in AVA102677; all had fatal SAEs during the Follow-Up period approximately 30 days after stopping study medication. Only one of the three fatal SAEs was considered possibly related to RSG treatment, an event of circulatory collapse that was later changed to acute cardiovascular failure.
- No specific concerns regarding cardiovascular or bone safety were noted; rates of events for myocardial ischemia and fractures were low (<1% and 2%, respectively).
- 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 noted for hemoglobin, hematocrit, platelet count, RBC count, and WBC count, and an increase noted for RDW.
- Mean cholesterol, CK, LDL cholesterol, LDH, BUN/creatinine ratio, and urea increased over time relative to open-label baseline.
- With respect to mean values, cognitive decline and slight worsening of the global function measured by CIBIC+ were evident during the open label treatment phase of AVA102677. Differences in results were not noted for any efficacy endpoint based on APOE ε4 status.
- Due to the non-randomised 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.