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.: AVD111960

Title: Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) A Multicenter Randomized Double-Blind Placebo-Controlled Trial of a Thiazolidinedione or Placebo and of Vitamin D or Placebo In People With Type 2 Diabetes at Risk For Cardiovascular Disease

Rationale: The TIDE study was designed as a long-term cardiovascular (CV) outcomes trial to assess if the addition of a thiazolidinedione (TZD) to the therapeutic regimen of a person with type 2 diabetes mellitus (T2DM) would reduce the risk of CV outcomes and if the addition of vitamin D would reduce total mortality and/or serious cancer in people with T2DM who are at high risk for CV disease.

Phase: IV

Study Period: The first subject was enrolled on 07 May 2009. On 23 September 2010, the Food and Drug Administration (FDA) placed the Thiazolidindione Intervention with vitamin D Evaluation (TIDE) trial on full clinical hold. The study was terminated and the last subject last visit was conducted on 22 November 2010.

Study Design: Multicenter, international, randomized double-blind placebo-controlled trial using a factorial design.

Centres: : A total of 175 centers in 21 countries randomized subjects in this multi-centre study: Canada, Chile, Colombia, Czech Republic, Denmark, Germany, India, Italy, Latvia, Mexico, Netherlands, Norway, Pakistan, Philippines, Romania, Russia, Slovakia, South Africa, Sweden, United Kingdom, United States.

Indication: Type 2 diabetes mellitus.

Treatment: Treatment comprised the addition of once daily TZD or placebo, and vitamin D or placebo to the care of participants with T2DM and other CV risk factors for up to 5.5 years for TZDs and for up to 10 years for vitamin D. Randomization occurred subsequent to a 3-week rosiglitazone (RSG) and vitamin D single-blind run-in to assess compliance and tolerability. These therapies were tested independently using a factorial design and were added to the regimen of participants who were otherwise treated according to standard of care at the discretion of their physician and/or investigator according to the best available clinical evidence. RSG, pioglitazone (PIO), and placebo were allocated in 30:30:40 ratios, respectively. Once randomized, TZD study drug was titrated. It was titrated to 1 tablet daily containing up to 8 mg of RSG or 45 mg of PIO or placebo. For the other factorial arm, Vitamin D and placebo were allocated in a 1:1 ratio. Vitamin D or placebo was given as one 1000 IU tablet daily.

Objectives: This study had 2 objectives. The first was to test the cardiovascular effects of long-term treatment with RSG or PIO when used as part of standard of care compared to similar standard of care without RSG or PIO in subjects with T2DM who have a history of or are at risk for cardiovascular disease. The second was to compare the effects of long-term supplementation of vitamin D on death and cancer. Only results for the TZD factorial portion of the study are presented in this results summary.

Primary Outcome/Efficacy Variable: The composite CV primary outcome for the TZD research questions was the first occurrence of either: CV death, non-fatal MI, non-fatal stroke (confirmed outcomes as per adjudication review). The composite primary outcome for the vitamin D research question was death or serious cancer requiring hospitalization, chemotherapy or surgery.

Secondary Outcome/Efficacy Variable (s):
Secondary and other outcomes were:

- all-cause mortality;
- components of the composite outcomes;
- a composite microvascular outcome comprising retinopathy requiring laser therapy, vitrectomy, a 30% decline in estimated glomerular filtration rate (GFR), or need for renal replacement therapy;
- any hospitalization for congestive heart failure (CHF),
- any hospitalization for shortness of breath;
- any hospitalization for pneumonia;
- any revascularization;
- any hospitalization for unstable, new or worsening angina;
- any fracture;
- any cancer;
- other hospitalization;
- cognitive decline equivalent to a difference of $\geq$ 1.5 units in the Digit Symbol Substitution Test (DSS) score;
- erectile dysfunction (e.g. International Index of Erectile Dysfunction);
- liver function tests;

- quality of life (e.g. EuroQol 5D);
- cognitive function [e.g. Montreal Cognitive Assessment (MoCA)].

Statistical Methods: Since on September 23, 2010 the FDA placed the TIDE trial on full clinical hold and the study was terminated early prior to full enrollment of subjects, the statistical analyses described in the protocol for the full study are no longer appropriate. All analyses in this results summary are descriptive in nature. Among the secondary endpoints cognitive decline, erectile dysfunction and quality of life were not assessed. Information for liver function tests was obtained from the adverse events data. Information for hypoglycaemia and clinical proteinuria was obtained from outcomes reported by the site. Description of the screening and run-in phases are based on the set of all participants enrolled in the study. All further analyses (primary, secondary and all safety related analyses) are based on the intent-to-treat (ITT) population, which included all randomized participants in the treatment groups to which they were assigned through central randomization.

Study Population: Subjects were enrolled from primary care, diabetes and cardiology clinics if they had T2DM and a glycated hemoglobin (A1C) level ranging from 6.5% to 9.5%, were drug-naïve or taking up to 2 non-insulin glucose-lowering medications, and were at risk of cardiovascular disease on the basis of: a) age at least 50 years with a prior cardiovascular event; b) age at least 55 years with documented arterial stenosis, albuminuria, ankle brachial index >0.9 or left ventricular hypertrophy; or c) age at least 60 years with at least two risk factors (tobacco use, high LDL-cholesterol, dyslipidemia, hypertention or obesity). Key exclusion criteria were a cardiovascular event within 30 days before randomization, prior pulmonary edema, symptomatic heart failure (New York Heart Association class II-IV), known left ventricular ejection fraction below 40%, or use of a loop diuretic, fracture in the prior year, known osteomalacia, or hypercalcemia.

Number of Subjects:	Placebo	PIO	RSG
Planned, N	6400	4800	4800
TZD Randomized, N	541	392	399
Completed study hold visit or final visit, n (%)	533 (98.9)	388 (99.0)	393 (98.7)
Total Number Subjects Withdrawn from or Discontinued Investigational Product (IP), N (%)	214 (39.6)	150 (38.3)	152 (38.1)
Reason for withdrawal/early-permanent discontinuation of IP, n (%)			
Participants with any AE leading to permanent discontinuation of IP	29 (5.4)	23 (5.9)	18 (4.5)
Investigator, change in health status	14 (2.6)	10 (2.6)	9 (2.3)
Subject, change in health status	15 (2.8)	13 (3.3)	9 (2.3)
All other reasons for permanent discontinuation of IP	185 (34.2)	127 (32.4)	134 (33.6)
Demographics, N (ITT)	Placebo 541	PIO 392	RSG 399
Females: Males	220:321	167:225	161:238
Mean Age, years (standard deviation [SD])	66.4 (6.8)	66.3 (6.6)	66.5 (6.4)
Race/Ethnicity, n/N reporting race, (%)	540	392	399
European/Caucasian/White	330 (61.1)	241 (61.5)	255 (63.9)
All Other[1]	210 (38.9)	151 (38.5)	144 (36.1)

1. Includes: South Asian, Black African, Native South American, Other Asian, Native North American, Japanese, Arab/Persian, Native Hawaiian/Australian or Other Asian Pacific, Malays, and Sub-Saharan African

Primary Outcome Results: N (ITT)	Placebo 541	PIO 392	RSG 399
Subjects with Primary Cardiovascular Outcome (MACE), n (%)	5 (0.9)	2 (0.5)	1 (0.3)
CV Death	1 (0.2)	0	0
Non-Fatal MI	2 (0.4)	0	1 (0.3)
Non-Fatal Stroke	2 (0.4)	2 (0.5)	0
Secondary Outcome Variables: N (ITT)	Placebo 541	PIO 392	RSG 399
Any Revascularization, n (%)	6 (1.1)	3 (0.8)	5 (1.3)
Any Hospitalization	31 (5.7)	16 (4.1)	24 (6.0)
Hospitalization for CHF	1 (0.2)	2 (0.5)	0
Hospitalization for Shortness of Breath	0	1 (0.3)	2 (0.5)
Hospitalization for Pneumonia	0	1 (0.3)	0
Hospitalization for Angina	3 (0.6)	1 (0.3)	1 (0.3)

All Death	4 (0.7)	1 (0.3)	1 (0.3)
Any Cancer	3 (0.6)	4 (1.0)	0
Composite Microvascular Outcome	21 (3.9)	8 (2.0)	9 (2.3)
Rentinopathy Requiring Laser Therapy	1 (0.2)	0	0
Decline in eGFR >=30%	20 (3.7)	8 (2.0)	9 (2.3)
Vitrectomy	0	0	0
Renal Replacement Therapy	0	0	0
Severe Hypoglycemia	0	2 (0.5)	1 (0.3)
Clinical Proteinuria	1 (0.2)	0	0
Fracture	2 (0.4)	2 (0.5)	3 (0.8)
Hepatic enzyme increased/Liver function test abnormal	1 (0.2)	0	1 (0.3)

Safety Results: On-therapy AEs were defined as changes in health status that required IP modification or discontinuation (including temporary withholding). This ensured that only those events the investigator thought were associated with IP were considered an adverse event. AEs were collected from the start of IP administration until the final study visit. Due to low overall and treatment group frequencies all AEs (serious and non-serious) are listed. Serious AEs were collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) were recorded from the time a subject consented to participate in the study up to and including any follow up contact. The occurrence of an endpoint or a hospitalization was noted at each follow-up visit. Information on specific outcomes such as myocardial infarction, stroke, death, and revascularization as well as information on any hospitalization was collected on specific endpoint forms. According to the protocol, primary, secondary and other study outcomes were not to be reported as SAEs; however, some SAEs reported by investigators may also have been reported as outcome events. They were reported to the Independent Data Monitoring Committee (IDMC) on a regular basis, who reviewed open analyses of emerging event rates for all of these outcomes as well as safety data in active and placebo groups during their meetings.

All Adverse Events (Serious and Non-Serious) On-Therapy AE Preferred Term	Placebo N=541	PIO N=392	RSG N=399
Subjects with any AE (Serious and Non-serious AEs), n (%)	41 (7.6)	37 (9.4)	23 (5.8)
Oedema peripheral	4 (0.7)	8 (2.0)	1 (0.3)
Oedema	2 (0.4)	5 (1.3)	1 (0.3)
Dyspnoea	1 (0.2)	3 (0.8)	4 (1.0)
Diarrhoea	2 (0.4)	3 (0.8)	1 (0.3)
Cardiac failure	3 (0.6)	2 (0.5)	0
Hypoglycaemia	1 (0.2)	3 (0.8)	1 (0.3)
Constipation	0	3 (0.8)	1 (0.3)
Nausea	2 (0.4)	2 (0.5)	0
Malaise	1 (0.2)	3 (0.8)	0
Weight increased	0	2 (0.5)	2 (0.5)
Dyspepsia	1 (0.2)	2 (0.5)	0
Chest pain	1 (0.2)	0	2 (0.5)
Myocardial infarction	1 (0.2)	0	1 (0.3)
Abdominal discomfort	1 (0.2)	0	1 (0.3)
Abdominal distension	0	0	2 (0.5)
Abdominal pain	1 (0.2)	1 (0.3)	0
Abdominal pain upper	0	2 (0.5)	0
Crohn's disease	1 (0.2)	1 (0.3)	0
Fatigue	0	2 (0.5)	0
Myalgia	0	2 (0.5)	0
Renal cancer	0	2 (0.5)	0
Cerebrovascular accident	1 (0.2)	1 (0.3)	0
Dizziness	0	2 (0.5)	0
Hydronephrosis	2 (0.4)	0	0
Angina pectoris	0	1 (0.3)	0
Palpitations	0	0	1 (0.3)
Right ventricular failure	1 (0.2)	0	0

Tachycardia	0	0	1 (0.3)
Ventricular tachycardia	0	0	1 (0.3)
Vertigo	1 (0.2)	0	0
Vision blurred	0	0	1 (0.3)
Dry mouth	0	1 (0.3)	0
Dysphagia	0	1 (0.3)	0
Flatulence	0	0	1 (0.3)
Peptic ulcer	0	1 (0.3)	0
Vomiting	0	0	1 (0.3)
Asthenia	1 (0.2)	0	0
Drug intolerance	0	1 (0.3)	0
Multi-organ failure	1 (0.2)	0	0
Swelling	1 (0.2)	0	0
Temperature intolerance	0	1 (0.3)	0
Cholecystitis acute	0	0	1 (0.3)
Chronic sinusitis	1 (0.2)	0	0
Urinary tract infection	0	0	1 (0.3)
Cardiac stress test abnormal	1 (0.2)	0	0
Catheterisation cardiac	0	0	1 (0.3)
Echocardiogram abnormal	1 (0.2)	0	0
Ejection fraction abnormal	1 (0.2)	0	0
Ejection fraction decreased	1 (0.2)	0	0
Electrocardiogram abnormal	1 (0.2)	0	0
Electrocardiogram change	1 (0.2)	0	0
Glycosylated haemoglobin increased	0	0	1 (0.3)
Hepatic enzyme increased	0	0	1 (0.3)
Liver function test abnormal	1 (0.2)	0	0
Decreased appetite	1 (0.2)	0	0
Diabetes mellitus inadequate control	1 (0.2)	0	0
Fluid overload	0	0	1 (0.3)
Fluid retention	0	0	1 (0.3)
Joint swelling	0	0	1 (0.3)
Muscle spasms	0	1 (0.3)	0
Musculoskeletal pain	1 (0.2)	0	0
Osteoarthritis	0	0	1 (0.3)
Osteoporosis	0	1 (0.3)	0
Pain in extremity	0	0	1 (0.3)
Meningioma	1 (0.2)	0	0
Neoplasm malignant	1 (0.2)	0	0
Syncope	1 (0.2)	0	0
Bladder obstruction	1 (0.2)	0	0
Chromaturia	0	1 (0.3)	0
Benign prostatic hyperplasia	0	1 (0.3)	0
Bronchial disorder	0	1 (0.3)	0
Chronic obstructive pulmonary disease	0	1 (0.3)	0
Sinus disorder	0	1 (0.3)	0
Erythema	1 (0.2)	0	0
Hyperhidrosis	1 (0.2)	0	0
Pruritus allergic	1 (0.2)	0	0
Rash pruritic	0	1 (0.3)	0
Skin discolouration	0	0	1 (0.3)
Angioplasty	1 (0.2)	0	0
Aortic aneurysm repair	1 (0.2)	0	0
Cardiac pacemaker insertion	0	0	1 (0.3)
Hospitalisation	1 (0.2)	0	0
Surgery	1 (0.2)	0	0

Aortic aneurysm	1 (0.2)	0	0
Fatal Events: Cause of death is listed as reported by the investigator.			
Fatal Events/Reported Cause of Death	Placebo N=541	PIO N=392	RSG N=399
Subjects with Fatal Event	4 (0.7)	1 (0.3)	1 (0.3)
Other cardiovascular/multiple organ failure [also reported as SAE]	1 (0.2)	0	0
Infection	1 (0.2)	0	0
Stroke	1 (0.2)	0	0
Cancer	1(0.2)	0	0
Pulmonary	0	1 (0.3)	0
Pneumonia	0	0	1(0.3)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication].			
All On-Therapy SAEs (Ordered by overall decreasing frequency) SAE Preferred Term	Placebo N=541	PIO N=392	RSG N=399
Subjects with Any SAE, n (%) [related]	7 (1.3)	5 (1.3)	2 (0.5)
Hypoglycaemia	0	1 (0.3)	1 (0.3)
Angioplasty	1 (0.2)	0	0
Aortic aneurysm	1 (0.2)	0	0
Aortic aneurysm repair	1 (0.2)	0	0
Benign prostatic hyperplasia	0	1 (0.3)	0
Bronchial disorder	0	1 (0.3)	0
Chronic obstructive pulmonary disease	0	1 (0.3)	0
Chronic sinusitis	1 (0.2)	0	0
Cholecystitis acute	0	0	1 (0.3)
Hydronephrosis	1 (0.2) [1*]	0	0
Intestinal prolapse	1 (0.2)	0	0
Multi-organ failure	1 (0.2)	0	0
Pruritus allergic	1 (0.2) [1]	0	0
Renal cancer	0	1 (0.3)	0
*relation to IP reported as unknown			
Conclusion: See Publication Below			
Publication: Punthakee Z, Bosch J, and Dagenais G et al. Design, history and results of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) randomised controlled trial. *Diabetologia*. 2012 Jan;55(1):36-45.			