Clinical Study Report Synopsis

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SAVOR

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus

A Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate the Effect of Saxagliptin on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischaemic Stroke in Patients with Type 2 Diabetes

Study dates: First subject enrolled: 10 May 2010
Last subject last visit: 16 May 2013

Phase of development: Therapeutic use (4)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Publications

Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369(14):1317-26.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	Determine, as a superiority assessment, whether treatment with saxagliptin compared with placebo when added to current background therapy will result in a reduction in the composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke in subjects with T2DM.	Time to first event for the composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke
Primary	Safety	Establish that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke observed with saxagliptin to that observed in the placebo group is less than 1.3.	Time to first event for the composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke
Secondary	Efficacy	Determine whether treatment with saxagliptin compared with placebo when added to current background therapy in subjects with T2DM will result in a reduction of the composite endpoint of CV death, non-fatal MI, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris, or hospitalisation for coronary revascularisation.	Time to first event for the composite endpoint of CV death, non-fatal MI, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris, or hospitalisation for coronary revascularisation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	Determine whether treatment with saxagliptin compared to placebo when added to current background therapy in subjects with T2DM would result in a reduction of all-cause mortality.	Time to all-cause mortality
Secondary	Safety	Safety and tolerability evaluated by assessment of overall AEs and AEOSI including assessment of the long-term effects of saxagliptin on decrease in lymphocyte counts, decrease in thrombocyte counts, severe infections[a], hypersensitivity reactions, liver abnormalities, bone fractures, pancreatitis, skin reactions, and renal abnormalities.	Incidence of overall AEs and AEOSI
Other	Efficacy	Determine whether treatment with saxagliptin compared with placebo when added to current background therapy in subjects with T2DM will result in a reduction of:	
		• Need for increase in dose or addition of new antidiabetic medication	Time to first event of addition of new antidiabetic medication or ≥1-step increase in dose for an oral antidiabetic drug or ≥25% increase in insulin dose which lasts for ≥3 months
		• Initiation of insulin therapy in subjects not receiving insulin therapy at baseline	Time to first event of start of insulin regimen which lasts for ≥3 months
		• Hospitalisation for hypoglycaemia	Time to first event of hospitalisation for hypoglycaemia
Other	Efficacy	• The individual components of the primary endpoint	Time to first event of CV death, non-fatal MI, or non-fatal ischaemic stroke
		• The individual additional components of the secondary efficacy endpoint	Time to first event of hospitalisation for heart failure, unstable angina pectoris, or coronary revascularisation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		• The primary composite endpoint (CV death, non-fatal MI, or non-fatal ischaemic stroke) during the first year of follow-up and after the first year	Time to first event of the primary composite endpoint (CV death, non-fatal MI, or non-fatal ischaemic stroke) occurring during the first year of follow-up and after the first year
		• Retinal laser treatment due to development of and/or deterioration in diabetic retinopathy	Time to first event of documented laser treatment due to the development of and/or deterioration in diabetic retinopathy
Other	Efficacy	• New and/or progression of diabetic nephropathy	Diabetic renal disease progression (diabetic nephropathy) as assessed by any of the following: • Change from baseline of the microalbumin/creatinine ratio • Categorical change from baseline in albuminuria (normoalbuminuria, microalbuminuria, and/or macroalbuminuria) • Doubling of serum creatinine levels (time to first event) • Initiation of chronic dialysis and/or renal transplant and/or a serum creatinine >6.0 mg/dL (530 µmol/L) (time to first event)
		• The composite endpoint of death, doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or a serum creatinine >6.0 mg/dL (530 µmol/L)	Time to first event of the composite endpoint of death, doubling of serum creatinine, initiation of chronic dialysis, renal transplant, or a serum creatinine >6.0 mg/dL (530 µmol/L)
Other	Safety	Safety and tolerability evaluated by assessment of:	
		• Hypoglycaemic events, cancers, peripheral oedema	Incidence of hypoglycaemic events, cancers[b], and peripheral oedema

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		• Laboratory tests	Change from baseline and incidence of MAs in haematology and serum chemistry parameters
		• Pulse, BP, waist circumference, and body weight	Change from baseline in pulse, BP, body weight, and waist circumference
Exploratory[c]	Efficacy	Collection of standard parameters used to assess glycaemic control.	Change from baseline in HbA1c, FPG, and HOMA2-β and achievement of HbA1c ≤6.5% and <7%
Additional	HEOR	Health economic data (hospitalisation information)	Hospitalisation information including dates of admission and discharge
		Patient reported outcome of health-related quality of life data	The EQ-5D questionnaire (descriptive and EQ-VAS) measured at baseline, annually, and after any MACE had occurred

[a] Including opportunistic infections.
[b] A separate analysis of pancreatic cancer was also performed. The results of the planned analysis for all cancers and the added analysis for pancreatic cancer are discussed as AEOSI.
[c] Exploratory objectives also included future biological research and future genetic research; consent to participate was optional. These research studies are not addressed in the CSR.

AE Adverse event; AEOSI Adverse event of special interest; BP Blood pressure; CI Confidence interval; CSP Clinical study protocol; CSR Clinical study report; CV Cardiovascular; EQ-5D EuroQol-5 Dimension (quality of life health status questionnaire); EQ-VAS EuroQol visual analogue scale; FPG Fasting plasma glucose; HbA1c Glycosylated haemoglobin; HEOR Health economics outcome research; HOMA2-β Homeostasis model assessment beta cell function; MA Marked abnormality; MACE Major adverse cardiovascular event; MI Myocardial infarction; SAP Statistical analysis plan; T2DM Type 2 diabetes mellitus.

Study design

This was a multicentre, randomised, double-blind, placebo-controlled Phase 4 study to definitively exclude unacceptable cardiovascular (CV) risk with saxagliptin treatment and to evaluate whether treatment with saxagliptin when added to current background therapy could reduce the composite endpoint of CV death, non-fatal myocardial infarction (MI), or non-fatal ischaemic stroke in subjects with type 2 diabetes mellitus (T2DM) at high risk for CV disease (CVD).

Subjects meeting all inclusion criteria and with no exclusion criteria were randomised in a 1:1 ratio to receive either saxagliptin or placebo once daily. Subjects were eligible, at the investigator's discretion and based on local treatment guidelines, for adjustments in their diabetes treatment. This included discontinuing or changing the dose of their concomitant diabetes medication as well as adding other diabetes medications (except for other dipeptidyl peptidase-4 [DPP4] inhibitors or glucagon-like peptide 1 [GLP-1] mimetics) to achieve or maintain glycaemic control. All subjects were to be treated in accordance with regional standards of care for CV risk factors (eg, hypertension, dyslipidaemia) and glycosylated haemoglobin (HbA1c).

During the randomised treatment period, dietary and lifestyle modifications were reinforced. Subjects returned to the study site every 6 months for assessment of events related to the objectives of the study, tolerability and safety (including adverse events of special interest [AEOSI]), assessment of treatment compliance, and provision of study drug. In addition, phone contacts were performed at 3-month intervals between regular visits. Within 8 weeks following the decision of the Executive Committee to close the study, all investigators were to complete an End of Treatment (EoT)/Closing visit for subjects still being treated with ivestigational product (IP), or a Closing visit to capture any adverse events (AEs) and clinical events for subjects who had prematurely discontinued the IP (ie, subjects who had completed the EoT visit in connection with the discontinuation of IP and subsequently attended the scheduled visits to capture any clinical events).

All randomised subjects, whether taking randomised IP or not, were to be followed up at the close of the study (ie, after the fixed calendar end-of-study date), at a minimum, for AEs, CV events, and survival. Deaths based on publicly available sources in cases where subjects withdrew consent were adjudicated and included in the primary and secondary analyses and in the analysis of CV death (other efficacy endpoint).

All deaths, primary efficacy and safety CV endpoints, secondary CV endpoints, and events of pancreatitis were adjudicated by an independent, blinded Clinical Event adjudication Committee.

Target subject population and sample size

A total of 16500 subjects with documented T2DM (HbA1c >6.5% and <12%) and with either a history of CVD or multiple risk factors (MRF) for vascular disease were planned to be randomised from sites throughout the world (at least 30% in North America, approximately 30% in Europe, and the remainder in South America, Asia, Australia, and South Africa). Both subjects with and without baseline use of glucose-lowering medication including oral antidiabetics and/or insulin (with the exception of other open-label DPP4 inhibitors or GLP-1 mimetics) were enrolled. Randomisation was stratified by CV risk category (established CVD; MRF without established CVD) and by baseline renal impairment category based on estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease formula (normal-mild [eGFR >50 mL/min]; moderate [eGFR ≥30 and ≤50 mL/min]; severe [eGFR <30 mL/min]).

The study required 1040 primary endpoint events in order to provide 85% power to test for superiority of saxagliptin versus placebo at the 2.45% 1-sided level assuming a 17% reduction in risk in the saxagliptin group. This provided at least 98% power to test the following hypothesis at the 2.45% 1-sided level:

$$H_{01}: \text{HR [saxagliptin:placebo]} \geq 1.30 \text{ vs } H_{11}: \text{HR [saxagliptin:placebo]} < 1.30.$$

Thus, it was estimated that a total sample size of 16500 randomised subjects would yield the necessary number of primary endpoint events based on the following assumptions: an annual event rate of 2.1% during treatment with placebo, an accrual period of approximately 15 months, an additional follow-up period of approximately 3 years, and an annual rate of study discontinuation of 2.8%.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Saxagliptin (5 mg in subjects with normal renal function or mild renal impairment and 2.5 mg in subjects with moderate or severe renal impairment) or placebo administered orally once daily. Batch numbers: 9M37650, 9D45693, 9M37227, 0E62038, 9M37648, 0E62037, 1C75255, 1C75251, 1C75252 (saxagliptin 5-mg tablets); 0E61881, 0E9003Z, 7L30712, 1C75250, 2D69604 (saxagliptin 2.5-mg tablets); 9D45538, 0E62039, 0B56792, 0A62087, 0B56793, 1C75260, 0A59845, 9L9031Z, 1C75267, 1C75265 (placebo tablets).

Duration of treatment

The duration of the study was dependent on the accrual of the predetermined number of CV events with an anticipated duration of approximately 4 to 5 years, including an anticipated enrolment period of 1 to 2 years and follow-up period of 3 years. When 50% of the total number of primary endpoint events were accrued (ie, at 520 events), the only interim analysis for superiority was performed. The Executive Committee monitored the accrual of the aggregate number of primary endpoint events and once the target number of primary CV events was recorded (n=1040), the Executive Committee declared the study closing date (15 January 2013) and notified all study sites to begin to perform all final study visits.

Statistical methods

The primary analysis was performed on the Intention-to-treat (ITT) population (all randomised subjects) and compared the time from randomisation to the first occurrence of any event in the primary composite endpoint (CV death, non-fatal MI, or non-fatal ischaemic stroke) between treatments using the Cox proportional hazards model stratified by baseline CV risk group and baseline renal function category, with treatment as a model term. For the final analysis, hazard ratios (HRs) and 2-sided 95.1% confidence intervals (CIs) were reported. The primary non-inferiority and superiority hypotheses were tested at the significance level of 2.45% (1-sided) in order to account for the planned interim analysis. P-values were based on likelihood ratio tests and CIs were based on profile likelihood. The non-inferiority analysis sought to establish the CV safety of saxagliptin by demonstrating that the upper bound of the 2-sided 95.1% confidence interval (CI) for the estimated risk ratio

comparing the incidence of the composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke observed with saxagliptin to that observed in the placebo group was <1.3. The secondary efficacy variables (secondary composite [CV death, non-fatal MI, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris, or hospitalisation for coronary revascularisation] and all-cause mortality) were analysed similarly to the primary efficacy variable. The primary analysis was performed in a sequential stepwise fashion to control for Type I error and first evaluated the safety of saxagliptin with a non-inferiority analysis, and then tested the superiority of saxagliptin versus placebo. If the null hypothesis of the primary efficacy endpoint was rejected (ie, upper bound of 95.1% CI is <1.0), the closed testing procedure was to apply the same alpha level to the secondary composite endpoint and then all-cause mortality in a fixed stepwise fashion provided the primary endpoint was significant.

Forest plots were used to show HR estimates and 95% CIs for effects within important subgroups for the primary and secondary composite endpoints and their individual components and for all-cause mortality. Prespecified subgroups examined included baseline CV risk category and baseline renal function category (and baseline CV risk category by renal function category), as well as age, gender, race, regions, baseline number of risk factors, baseline duration of T2DM, history of congestive heart failure, baseline diabetes medications, and baseline CV medications including combinations. The CIs for these subgroup analyses were not adjusted for multiple comparisons and were interpreted only descriptively; p-values were provided for interactions only.

To test the robustness of the primary analysis results, sensitivity analyses were conducted for the primary and/or secondary composite efficacy endpoints and/or the secondary efficacy endpoint of all-cause mortality.

For the analyses of diabetic complications and diabetic renal disease progression (other efficacy objectives), the endpoints were tabulated and summarised; the times to these events were analysed using Cox proportional hazards models as done for other time-to-event variables.

For the exploratory efficacy endpoints, changes from baseline in HbA1c, fasting plasma glucose (FPG), and homeostasis model 2 assessment of beta-cell function (HOMA2-β) were summarised for each post-randomisation visit (annually and/or EoT). A repeated measures analysis (mixed models framework) was also used to analyse the response variable change from baseline to each relevant timepoint. The model contained terms for randomised treatment group, baseline measurement, baseline renal function group by CV risk group stratum, time (each relevant visit), and time by randomised treatment group. Additionally, achievement of HbA1c ≤6.5% and <7% was summarised at each post-randomisation visit.

CV endpoints (CV death, non-fatal MI, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris, and hospitalisation for coronary revascularisation) were not to be reported as AEs/serious adverse events (SAEs) by the Sponsors to regulatory agencies; these CV events were presented and analysed as efficacy endpoints. All deaths were adjudicated; those adjudicated to be non-CV deaths were reported

as SAEs. All deaths not attributed to the categories of CV death and not attributed to a non-CV cause, were presumed CV deaths and as such were part of the CV mortality endpoint.

Safety observations were listed regardless of whether the subject was taking blinded IP. For summaries of AEs, the data were summarised for the ITT population in 2 ways: on treatment (subjects treated with at least 1 dose of blinded IP and excluding AEs that occurred after the subject had discontinued randomised study drug [after 1 day for AEs; after 30 days for SAEs]) and overall (included all AEs that occurred on or after randomisation regardless of whether or not the subject had received and/or discontinued randomised study drug).

The subject incidence of AEs, SAEs, and AEs leading to discontinuation of IP was summarised for each treatment group by system organ class (SOC), high level group term (HLGT), and preferred term (PT) coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. Documented CV and non-CV deaths were presented by SOC, HLGT, PT, and treatment.

Analyses were also performed for AEOSI (decrease in lymphocyte counts, decrease in thrombocyte counts, severe infections, opportunistic infections, hypersensitivity reactions, liver abnormalities, bone fractures, skin reactions, pancreatitis, and renal abnormalities) and for other prespecified AEs of hypoglycaemia, cancer, and peripheral oedema. AEOSI were identified by one or more of the following 3 criteria: any subject with an AEOSI category indicated in a specific tickbox by the investigator on the case report form (CRF); any subject with PT matching predefined AEOSI PTs; and/or any subject with laboratory findings meeting AEOSI laboratory criteria. All events of pancreatitis were adjudicated.

The incidence of AEs, deaths, SAEs, AEs leading to discontinuation of IP, and AEOSI were also presented by select subgroups (as defined for efficacy analyses).

Haematology and serum chemistry parameters were summarised by treatment over all scheduled visits. Laboratory marked abnormalities (MAs), identified using predefined criteria, occurring at any time during the treatment period were summarised by treatment group.

Vital sign (systolic and diastolic blood pressures and heart rate) and biometric parameters (weight and waist circumference) were summarised by treatment group at each scheduled time of assessment. Physical examination findings at each scheduled follow-up visit were summarised (Normal, Abnormal-same as baseline, and Abnormal-new or worsened).

Subject population

Randomisation targets with respect to region, CV risk categories, and renal function were met and evenly distributed between the 2 treatment groups. The ITT population consisted of a total of 16492 randomised subjects (8280 in the saxagliptin group and 8212 in the placebo group) of which 99.5% of subjects in each treatment group received at least one dose of IP. Overall, 97.5% of subjects completed the study. A total of 2.5% of subjects discontinued prior to the end of the study; 0.2% of subjects were lost to follow-up. The overall mean duration in the

study (time from randomisation to last study contact) for the ITT population was 2.0 years in both treatment groups. The demographics and baseline characteristics were balanced between the saxagliptin and placebo groups. The study population was 66.9% male and 33.1% female with a mean age at randomisation of 65.0 years. Fourteen percent of subjects were ≥75 years of age. The majority of the population was White (75.2%) with Asian and Multiracial race groups making up 10.8% and 9.3%, respectively, of the overall study population. A total of 21.5% of subjects were of Hispanic or Latino ethnicity. Overall, 25.0% of subjects had baseline HbA1c levels <7%. A higher proportion of placebo-treated subjects started insulin and oral diabetes medication during the study compared to saxagliptin-treated subjects. The concomitant use of CVD medications during the study was similar for the 2 treatment groups.

Summary of efficacy results

Saxagliptin achieved the primary safety endpoint of non-inferiority versus placebo demonstrating no increased risk of the primary composite endpoint of CV death, non-fatal MI, or non-fatal ischaemic stroke (HR 1.00; 95.1% CI 0.89, 1.12; p-value for non-inferiority <0.001), with similar results during and after the first year of follow-up. The study did not achieve the primary efficacy endpoint of superiority of saxagliptin versus placebo for the primary composite endpoint (p-value for superiority 0.986). As a result, the formal statistical testing was stopped but the nominal p-values are provided for the purpose of descriptive evaluation.

Regarding the individual components of the primary composite endpoint (CV death, non-fatal MI, or non-fatal ischaemic stroke), as well as all MI (fatal and non-fatal) and all ischaemic stroke (fatal and non-fatal), the HRs were consistent with the overall primary composite endpoint with CIs that included 1.0: CV death HR1.03 (95% CI 0.87, 1.22); non-fatal MI HR 0.92 (95% CI 0.77, 1.09); non-fatal ischaemic stroke HR1.15 (95% CI 0.91, 1.47); all MI (fatal and non-fatal) HR 0.95 (95% CI 0.80, 1.12); and all ischaemic stroke (fatal and non-fatal) HR 1.11 (95% CI 0.88, 1.39). Estimated HRs favouring saxagliptin in one component were balanced by HRs favouring placebo in another component (eg, non-fatal MIs vs non-fatal ischaemic stroke).

No increased risk was observed for saxagliptin versus placebo for the secondary composite endpoint (CV death, non-fatal MI, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris, or hospitalisation for coronary revascularisation) (HR 1.02; 95% CI 0.94, 1.11), thus supporting the primary non-inferiority safety analysis.

Regarding the additional individual components of the secondary composite endpoint not included in the primary composite endpoint, the HRs for hospitalisation for coronary revascularisation and hospitalisation for unstable angina pectoris were consistent with the overall secondary composite endpoint with CIs that included 1.0: hospitalisation for unstable angina pectoris HR 1.19 (95% CI 0.89, 1.61), hospitalisation for coronary revascularisation HR 0.92 (95% CI 0.80, 1.04). However, for the third additional individual component of the secondary composite endpoint, more subjects for saxagliptin compared with placebo were hospitalised for heart failure (HR 1.27; 95% CI 1.07, 1.51). Additional analyses of this observation revealed that these events were true hospitalisations for heart failure and that the

clinical characteristics of subjects with an event in the 2 treatment groups were similar. The risk of subsequent hospitalisation for heart failure and the case mortality rate for subjects with an adjudicated diagnosis of hospitalisation for heart failure were also similar between saxagliptin and placebo groups. Despite the imbalance in hospitalisation for heart failure, results for the primary and secondary composite endpoints are balanced.

For the secondary endpoint of all cause mortality, the primary (ITT) analysis did not demonstrate a treatment difference for saxagliptin vs placebo (HR 1.11; 95% CI 0.96, 1.27), which was consistent with the primary non-inferiority safety analysis. In the ITT analysis, the proportions of subjects who died in the saxagliptin and placebo groups were 5.1% (420/8280) and 4.6% (378/8212), respectively, while the corresponding proportions for the modified intention-to-treat (mITT) analysis were 3.6% (297/8240) and 3.0% (248/8173), respectively, and for the Per Protocol analysis were 4.9% (366/7526) and 4.5% (329/7373). Results for all-cause mortality and CV death were generally consistent between the mITT and on-treatment safety analyses (see summary of safety results below).[0]

The findings of the prespecified sensitivity analyses were consistent with the primary ITT analysis results for the primary and secondary composite endpoints and the secondary endpoint of all-cause mortality.

The results of the prespecified subgroup analyses based on baseline CV risk and baseline renal function, demographics, and baseline use of diabetes and CVD medications for the primary and secondary composite endpoints and all-cause mortality were generally similar across subgroups and were consistent with the results for the overall population. However, using a p-value criterion of <0.1 as a conservative approach, some possible treatment interactions for one or more of the primary and secondary endpoints were identified (p-value for interaction >0.04 to <0. 1) for randomisation strata, age, number of CV risk factors, some diabetes and CVD medication categories, and region. . However, in light of multiplicity issues and the unclear clinical plausibility of these interaction effects in some of the subgroups, these observations should be interpreted with caution.

Compared to placebo, saxagliptin resulted in less need for treatment intensification for diabetic control (initiation of new, or increases in current, oral diabetes medications or insulin (HR 0.79; 95% CI 0.75, 0.83); lower HbA1c (means of 7.6% vs 7.9%) and higher achievement of HbA1c goals of ≤6.5% and <7.0% (proportions of subjects with HbA1c <7%: 38.4% vs 27.4% to 28.9%); lower FPG (means of 152.8 to 154.4 mg/dL vs 158.7 to 159.8 mg/dL); and more favourable changes in homeostasis model assessment beta cell function (HOMA2-β) at 2 years (61.7% vs 56.4%).

Event rates for all time-to-event renal disease progression endpoints were similar for both treatment groups, with HR 95% CIs that included 1.0. This included: doubling of serum creatinine (HR 1.04; 95% CI 0.83, 1.30); the composite of initiation of chronic dialysis and/or renal transplant and/or a serum creatinine >6.0 mg/dL (530 µmol/L) (HR 0.90; 95% CI 0.61, 1.32); and the composite of death, doubling of serum creatinine levels, initiation of chronic dialysis and/or renal transplant and/or a serum creatinine >6.0 mg/dL (530 µmol/L) (HR 1.08;

95% CI 0.96, 1.22). However, saxagliptin subjects had less progression of albuminuria compared with placebo (difference vs placebo of -4.9% [95% CI -7.4%, -2.5%]).

Summary of safety results

The extent of exposure to IP in the safety (ITT) population was similar between the saxagliptin and placebo groups for the total population (mean 1.82 and 1.81 years/subject for the saxagliptin and placebo groups, respectively) and when stratified by baseline CV risk and by baseline renal function.

The proportion of subjects with at least 1 on-treatment AE (including hypoglycaemia) was similar between the saxagliptin and placebo groups (72.5% and 72.2%, respectively). More saxagliptin-treated subjects than placebo-treated subjects had at least 1 on-treatment AE reported by the investigator to be treatment-related (890 [10.8%] vs 783 [9.6%] subjects). The proportion of subjects with SAEs reported by the investigator to be treatment-related was low in both treatment groups (58 [0.7%] subjects in the saxagliptin group and 39 [0.5%] subjects in the placebo group).

Within both the CVD and the MRF baseline CV risk strata, the proportions of subjects with at least 1 on-treatment AE, SAE, or AE leading to discontinuation of IP were similar in the saxagliptin and placebo groups. A trend towards an increased incidence of AEs with decreased baseline renal function was observed in all AE categories for both treatment groups. Among subjects with severe renal impairment, the proportion of subjects with at least 1 on-treatment AE was higher in the saxagliptin group compared with the placebo group (147/170 [86.5%] vs 123/164 [75.0%] subjects).

The overall AE profile associated with each treatment group was generally similar by SOC and HLGT. In the saxagliptin group, the 3 most frequently reported SOCs were infections and infestations (28.1% vs 27.9% for placebo), musculoskeletal and connective tissue disorders (19.5% vs 18.9% for placebo), and gastrointestinal disorders (17.3% vs 16.8% for placebo). In the SOC metabolism and nutrition disorders, a lower proportion of saxagliptin-treated subjects than placebo-treated subjects had AEs (1253 [15.2%] vs 1436 [17.6%] subjects). In the SOC skin and subcutaneous tissue disorders, a higher proportion of saxagliptin-treated subjects had on-treatment AEs than did placebo-treated subjects (822 [10.0%] vs 722 [8.8%] subjects). One subject in the placebo group had SAEs of toxic epidermal necrolysis and Stevens-Johnson syndrome. The investigator considered the events to be causally unrelated to IP but related to allopurinol.

In the saxagliptin group, the most commonly occurring on-treatment AEs by PT (excluding hypoglycaemia) were diabetes mellitus (512 [6.2%] vs 633 [7.7%] subjects for placebo), dizziness (371 [4.5%] vs 338 [4.1%] subjects for placebo), and hypertension (357 [4.3%] vs 323 [4.0%] subjects for placebo). The proportion of subjects with AEs of diabetes mellitus was lower in the saxagliptin group compared with the placebo group (6.2% vs 7.7%).

The proportions of subjects in the saxagliptin and placebo groups who had any on-treatment clinical event with a fatal outcome and an onset date within 30 days of last dose of IP were

4.0% (332/8240) and 3.4% (281/8173), respectively. The corresponding proportions overall (on and off treatment combined) were 5.1% (424/8280) and 4.7% (383/8212), respectively. The proportions of subjects in the saxagliptin and placebo groups who had an on-treatment event with an outcome of CV death (confirmed by adjudication) were 2.7% (222/8240) and 2.3% (188/8173), respectively. The corresponding proportions overall (on and off treatment combined) were 3.2% (269/8280) and 3.2% (260/8212) for the saxagliptin and placebo groups, respectively. The proportions of subjects in the saxagliptin and placebo groups who had an on-treatment AE with an outcome of non-CV death (confirmed by adjudication) were 1.3% (107/8240) and 1.1% (90/8173), respectively. The corresponding proportions overall (on and off treatment combined) were 1.8% (149/8280) and 1.4% (119/8212), respectively. The number of subjects with AEs that started in the off-treatment period (>30 days after last dose of IP) and had a fatal outcome was 42 in the saxagliptin group and 29 in the placebo group.

The SOCs with the highest frequency of fatal on-treatment AEs (adjudicated as non-CV death) in both treatment groups were neoplasms benign, malignant and unspecified (including cysts and polyps) (39 [0.5%] and 44 [0.5%] subjects in the saxagliptin and placebo groups, respectively) and infections and infestations (24 [0.3%] and 15 [0.2%] subjects, respectively). There were 4 fatal on-treatment AEs reported by the investigator to be treatment-related (1 in the saxagliptin group [rhabdomyosarcoma] and 3 in the placebo group [diarrhoea, pancreatitis, and chronic renal failure]). Within the CV risk and baseline renal function strata, the proportions of subjects with on-treatment AEs leading to death were generally similar across SOCs between the saxagliptin and placebo groups.

The proportion of subjects with on-treatment SAEs was similar between the 2 treatment groups (1960 [23.8%] subjects in the saxagliptin group and 1914 [23.4%] in the placebo group). The proportions of subjects with on-treatment SAEs by individual SOC and HLGT were similar between the 2 treatment groups. The most frequently reported on-treatment SAEs by PT (≥1% in either treatment group) were pneumonia (133 [1.6%] and 103 [1.3%] subjects in the saxagliptin and placebo groups, respectively); non-cardiac chest pain (98 [1.2%] and 97 [1.2%] subjects, respectively), and angina pectoris (78 [0.9%] and 97 [1.2%] subjects, respectively). Within the CV risk and baseline renal function strata, the proportions of subjects with on-treatment SAEs were generally similar across SOCs between the saxagliptin and placebo groups.

The proportions of subjects with AEs leading to discontinuation of IP were similar between the 2 treatment groups (391 [4.7%] in the saxagliptin group and 401 [4.9%] in the placebo group). There was only 1 SOC (gastrointestinal disorders) with HLGT frequency of ≥0.5% in either treatment group. The proportions of subjects with AEs leading to discontinuation of IP were similar between the 2 treatment groups across SOCs and HLGTs. The most frequently reported AEs leading to discontinuation of IP (PT frequency ≥0.2% in either treatment group) were nausea (33 [0.4%] and 18 [0.2%] subjects in the saxagliptin and placebo groups, respectively); diarrhoea (24 [0.3%] and 21 [0.3%], respectively), dizziness (19 [0.2%] and 16 [0.2%], respectively), headache (18 [0.2%] and 12 [0.1%], respectively), and abdominal pain (13 [0.2%] and 7 [<0.1%], respectively).

For AEOSI and other prespecified AEs:

- The proportions of subjects with on-treatment AEs were similar between the saxagliptin and placebo groups for decreased lymphocyte count (33 [0.4%] and 29 [0.4%]), decreased thrombocyte count (43 [0.5%] and 43 [0.5%]), severe infection (469 [5.7%] and 452 [5.5%]), liver abnormalities (48 [0/6%] and 58 [0.7%]), bone fracture (216 [2.6%] and 216 [2.6%]), skin reaction (92 [1.1%] and 112 [1.4%]), cancer (296 [3.6%] and 322 [3.9%]), and peripheral oedema (320 [3.9%] and 327 [4.0%]).

- One saxagliptin-treated subject had an AE of lymphocytopenia (PT lymphopenia) on Day 357 that the investigator considered to be a non-clinically significant laboratory finding. This subject experienced liver cancer (PT hepatic neoplasm) on Day 405, and died of this malignancy on Day 453.

- One saxagliptin-treated subject had an SAE of bleeding due to thrombocytopenia reported on Day 320 that led to his death. The bleeding was due to bladder cancer that was diagnosed and reported as an SAE the same day. On Day 335, the subject had an SAE of myocardial infarction, and he died on Day 339. The investigator reported that the death was related to the bleeding due to thrombocytopenia. The death was adjudicated as a non-CV death due to malignancy.

- AEs of opportunistic infections were generally infrequent in both treatment groups (7 [<0.1%] subjects in the saxagliptin group and 10 [0.1%] subjects in the placebo group). There were no fatal AEs of opportunistic infections.

- The proportion of subjects with on-treatment AEs of hypersensitivity reaction was similar between the saxagliptin and placebo groups (71 [0.9%] and 69 [0/8%]). The proportion of subjects with SAEs of hypersensitivity reaction was higher in the saxagliptin group than in the placebo group (14 [0.2%] and 4 [<0.1%]). Reports of saxagliptin-treated subjects with an on-treatment PT of angioedema were numerically more frequent than for placebo-treated subjects (7 [<0.1%] vs 1 [<0.1%]) and most of these subjects were receiving ACE inhibitor therapy. Of the 7 on-treatment AEs of angioedema in the saxagliptin group, 5 were SAEs, and 2 were nonserious AEs. None of the events was fatal. All events resolved, and no recurrent events were reported.

- The proportions of subjects with AEs of pancreatitis confirmed by adjudication for the saxagliptin and placebo groups, respectively, were as follows: definite acute pancreatitis 17 (0.2%) and 9 (0.1%) subjects; possible acute pancreatitis 6 (<0.1%) and 7 (<0.1%) subjects; chronic pancreatitis, 2 (<0.1%) and 6 (<0.1%) subjects; unlikely to be pancreatitis 9 (0.1%) subjects in each treatment group. The proportion of subjects with on-treatment AEs of pancreatitis was similar between the saxagliptin and placebo groups (30 [0.4%] and 28 [0/3%]). There were no fatal AEs of pancreatitis in the saxagliptin group and 1 in the placebo group.

- The proportions of subjects with on-treatment AEs of renal abnormalities, including SAEs and AEs leading to discontinuation of IP, were similar between the saxagliptin and placebo groups (307 [3.7%] subjects in the saxagliptin group and and 269 [3.3%]) subjects in the placebo group. The number of subjects with a PT of acute renal failure was higher in the saxagliptin group than in the placebo group (99 [1.2%] and 73 [0.9%]).

- The proportion of subjects with an AE or SAE of pancreatic cancer was lower in the saxagliptin group than in the placebo group (4 [<0.1%] vs 9 [0.1%] subjects, respectively). There were 2 subjects in the saxagliptin group and 6 subjects in the placebo group (<0.1% in each group) with fatal AEs of pancreatic cancer.

- Any on-treatment hypoglycaemia (as reported on the CRF or derived from AE PTs) was reported more frequently in the saxagliptin group (5620 events, 1410 [17.1%] subjects) than in the placebo group (4844 events, 1207 [14.8%] subjects). SAEs of hypoglycaemia were higher in the saxagliptin group compared to the placebo group (67 [0.8%] vs 43 [0.5%]) subjects, although the numbers of events were low.

  - The event rate of any hypoglycaemia per 100 subject-years in subjects treated with SU at baseline was 9.74 in the saxagliptin group and 6.80 in the placebo group; for subjects with baseline HbA1c <7%, the rates were 12.40 and 6.49; for subjects with baseline HbA1c ≥7%, the rates were 8.96 and 6.92. In subjects not treated with SU at baseline, the event rates were 10.26 and 9.85 in the saxagliptin and placebo groups; for subjects with baseline HbA1c <7%, the rates were 6.27 and 5.11; for subjects with baseline HbA1c ≥7%, the rates were 12.00 and 12.11).

  - The event rate of any hypoglycaemia per 100 subject-years in subjects treated with insulin at baseline was 17.14 for the saxagliptin group and 16.51 for the placebo group. For subjects not treated with insulin at baseline, the event rates were 5.83 for the saxagliptin group and 3.99 for the placebo group.

  - The event rate of any hypoglycaemia per 100 subject-years in subjects treated with metformin alone at baseline was 2.42 in the saxagliptin group and 2.63 in the placebo group.

Changes in haematology and clinical chemistry parameters were generally similar between the saxagliptin and placebo groups:

- There were small decreases over time in mean and median absolute lymphocyte counts in the saxagliptin group compared with the placebo group (-0.064×10^9 cells/L [median -0.080×10^9 cells/L] in the saxagliptin group and 0.020×10^9 cells/L [median (0.010×10^9 cells/L] in the placebo group). There were no appreciable mean changes from baseline for any other haematology parameter in either treatment group. The number of subjects with MAs in lymphocytes was similar between the saxagliptin and placebo groups (22 [0.3%] and 14 (0.2%)

subjects in the saxagliptin and placebo groups, respectively); the number of subjects with MAs in thrombocytes was lower in the saxagliptin group than the placebo group (2 [<0.1%] saxagliptin-treated vs 5 [<0.1%] placebo-treated subjects).

- The mean and median changes over time in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were similar between the 2 treatment groups. Mean and median values were within normal range. The proportions of subjects with MAs in AST, ALT, or total bilirubin were low and similar between the 2 treatment groups. Liver abnormalities meeting the biochemical criteria for potential Hy's Law cases (ALT and/or AST >3 times the upper limit of normal (ULN) and total bilirubin >2 times ULN) were infrequent and numerically lower in the saxagliptin group (11 [0.1%] and 18 [0.2%]).

- Changes in renal function parameters (serum creatinine, eGFR) were similar between the 2 treatment groups. Mean values in urine albumin/creatinine ratio decreased over time for the saxagliptin group at 1 year and appeared to return towards baseline values at 2 years, and increased over time for the placebo group. The proportions of subjects with MAs in serum creatinine were similar between the 2 treatment groups.

Small reductions from baseline in mean BP measurements and a small increase in heart rate were observed in both treatment groups. No clinically meaningful changes from baseline were observed for biometrics and physical findings for either treatment group.