CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

BRIEFING MATERIAL

NDA 22350: SAXAGLIPTIN (ONGLYZA)
NDA 200678: SAXAGLIPTIN/METFORMIN (KOMBIGLYZE XR)
APPLICANT: ASTRAZENICA

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING

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Abbreviations

ACCF	American College of Cardiology Foundation
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACEI	Angiotensin-Converting Enzyme Inhibitor
ACR	Albumin to Creatinine Ratio
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease
AE	Adverse Event
AEOS	Adverse Event of Special Interest
Afib	Atrial fibrillation
AHA	American Heart Association
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARB	Angiotensin II Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area-under-the-curve
BMI	Body Mass Index
BMS	Bristol-Meyers Squibb
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin
CAROLINA	Cardiovascular Outcome Study of Linagliptin
CEC	Clinical Event Adjudication Committee
CI	Confidence Interval
CKD	Chronic Kidney Disease
CrCl	Creatinine Clearance
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
CT	Computed Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
CVOT	Cardiovascular Outcomes Trial
CYP	Cytochrome P450
DMC	Data Monitoring Committee
DMEP	Division of Metabolism and Endocrinology Products
DPP4	Dipeptidyl Peptidase-4 Inhibitor
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1	Glucagon-like Peptide-1
HbA1c	Hemoglobin A1c
HCl	Hydrochloride
HDL-C	High Density Lipoprotein-Cholesterol
hHF	Hospitalization for Heart Failure
HLGT	High Level Group Term
HLT	High Level Term
HR	Hazard Ratio
IP	Investigational Product
ITT	Intention-to-Treat
LDL-C	Low Density Lipoprotein Cholesterol
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
mITT	Modified Intention-to-Treat
MRF	Multiple Risk Factors
N	Number
NDA	New Drug Application
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PDUFA	Prescription Drug User Fee Act
PMR	Postmarketing Requirement
PT	Preferred Term
R	Randomization
RF	Renal Failure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAVOR	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus
SD	Standard Deviation
SE	Standard Error
SMQ	Standardized MedDRA Query
sNDA	Supplemental New Drug Application
SOC	System Organ Class
SV	Stroke Volume
T1/2	Elimination Half-life
T2DM	Type 2 Diabetes Mellitus
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
TIMI	Thrombolysis in Myocardial Infarction
TZD	Thiazolidinedione
ULN	Upper Limit of Normal
US	United States
VADT	Veterans Affairs Diabetes Trial
VIVIDD	Vildagliptin in Ventricular Dysfunction Diabetes
WHF	World Heart Federation
XR	Extended-Release
YR	Year

1 SAVOR Draft Discussion Points

Discuss the overall findings in SAVOR and in your discussion specifically address the following:

- Comment on your level of concern with regard to the all-cause mortality findings in SAVOR.
- Comment on your level of concern with regard to the heart failure findings in SAVOR.
- In contrast to glycemic efficacy trials, SAVOR was enriched with a population of patients with type 2 diabetes who also had baseline renal impairment. Please comment on the renal safety findings in SAVOR.
- Comment on any additional safety concerns which were not discussed above (e.g., hypersensitivity, pancreatitis, or other).

Based on information presented today and in the background materials, do the results of SAVOR demonstrate that use of saxagliptin in patients with type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk? Explain your rationale and recommend additional studies if you believe these are needed.

Based on the totality of the safety information presented today and in the background materials, do the results of SAVOR alter the risk-benefit profile of saxagliptin in adults with type-2 diabetes mellitus? Explain your rationale and recommend additional studies if you believe these are needed.

2 INTRODUCTION AND EXECUTIVE SUMMARY

2.1 Introduction

This document provides the briefing material for the April 14, 2015, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) to discuss the results of the cardiovascular outcomes trial (CVOT), Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR), for new drug application (NDA) 22350, Onglyza (saxagliptin) and NDA 200678, Kombiglyze XR (saxagliptin and metformin HCl extended-release) tablets manufactured/marketed by AstraZeneca AB.

2.2 Executive Summary

SAVOR was a large, prospective, multicenter, randomized, double-blind, placebo-controlled trial conducted in 16,492 subjects with type 2 diabetes mellitus with established cardiovascular disease or at high risk of cardiovascular disease. Following a median duration of follow-up of 2.1 years and 1,222 composite primary endpoint events of cardiovascular death, nonfatal myocardial infarction, or non-fatal ischemic stroke, the analysis for the composite MACE endpoint resulted in a point estimate of 1.00, with a 95% upper bound less than 1.3. Therefore, compared to placebo, saxagliptin successfully ruled out a 30% relative increase in CV risk captured using a three component MACE endpoint, however, it failed to demonstrate CV benefit (i.e., statistical superiority). Results for the secondary analysis of MACE plus (i.e., a composite endpoint of MACE plus hospitalization for unstable angina pectoris or hospitalization for coronary revascularization) were consistent with the primary analysis of MACE. However, an increased risk of hospitalization for heart failure was noted in subjects treated with saxagliptin, and FDA sensitivity analyses suggested a potential increased risk of all-cause mortality in saxagliptin-treated subjects.

In SAVOR, a 27% increase in the rate to first event of hospitalization for heart failure was reported in saxagliptin-treated subjects. There is a public health implication of this finding — a substantial number of subjects with hospitalization for heart failure events, regardless of treatment assignment, had recurrent events and/or died during the trial. A safety signal for heart failure was not previously observed in the saxagliptin clinical program. Hospitalization for heart failure was neither a primary nor secondary trial endpoint, and there is the potential for false positive results due to multiple testing. However, the validity of this finding is supported by the large number of events reported in this trial, and the fact that hospitalization for heart failure was based on a pre-specified definition, and clinically adjudicated by an independent, blinded committee of specialists.

All cause-mortality was a pre-specified secondary endpoint and was adjudicated by an independent, blinded adjudication committee of experienced cardiologists. Vital status was obtained for 99% of subjects in SAVOR and a total of 798 deaths occurred on-study. The primary analysis of all-cause mortality (on-study analysis) did not reveal significant differences between groups [Hazard Ratio (95.1% CI); 1.11 (0.96, 1.27)], but sensitivity analyses conducted by FDA, which included only deaths occurring while patients were exposed to treatment (i.e.,

on-treatment analyses), suggested significant or near-significant increases in all-cause mortality. Increases appeared across both CV and non-CV categories of deaths, and exploratory analyses to elucidate the etiology behind the all-cause mortality signal were unrevealing and did not shed light on a mechanism beyond treatment differences. FDA would like the Committee to opine on the all-cause mortality observations in SAVOR given the fact that SAVOR was a large randomized double-blind controlled trial where a large number of deaths were observed.

Secondary objectives in the postmarketing required trial were to include an assessment of the longer-term effects of saxagliptin on several safety parameters that were identified premarketing to be of interest. Generally, these secondary safety outcomes did not reveal new findings. However, SAVOR showed a small imbalance in renal adverse events and in proportions of subjects who had significant shifts in eGFR.

We are convening this meeting of the Endocrinologic and Metabolic Drugs Advisory Committee to discuss the safety findings from SAVOR and seek advice and recommendations on these issues.

3 BACKGROUND

3.1 Product Information

Drug Class

Saxagliptin (Onglyza) belongs to the class of antidiabetic agents known as dipeptidyl peptidase-4 (DPP4) inhibitors. Onglyza was approved by the FDA in 2009 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. In 2010, Kombiglyze XR, a fixed-dose combination product containing saxagliptin and extended-release metformin, was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate. All currently US-approved DPP4 inhibitors are shown in Table 1 along with the corresponding CVOT status.

Table 1: Current U.S. Approved DPP4 Inhibitors* for T2DM

Trade Name (Established Name)	Original Approval Date	CVOT
JANUVIA (sitagliptin)†	October 16, 2006	Ongoing
ONGLYZA (saxagliptin)	July 31, 2009	SAVOR: Completed
TRADJENTA (linagliptin)	May 2, 2011	Ongoing
NESINA (alogliptin)	January 25, 2013	Completed

*Single-entity products; for combination products see Drugs@FDA http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
†approved prior to the issuance of the December 2008 Guidance.

DPP4 inhibitors' mechanism of action for lowering blood glucose is thought to be through inhibition of the DPP4 enzyme, resulting in delayed inactivation of incretin hormones (e.g., glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) and an increase in incretin blood concentrations. This is followed by a decrease in glucagon concentrations and an increase in glucose-dependent insulin secretion from pancreatic beta cells.

Onglyza

Onglyza is formulated as film-coated tablets containing either 2.5 mg or 5 mg of saxagliptin to be administered once daily.[1] For most patients the recommended dosage of Onglyza is 5 mg once daily taken independent of meals. For patients with moderate or severe renal impairment, or end-stage renal disease (creatinine clearance [CrCl] ≤50 mL/min) or for patients receiving strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors the recommended dosage is 2.5 mg once daily.[1,2] Kombiglyze XR is available as tablets containing various combinations of fixed dose saxagliptin and metformin.

Saxagliptin is metabolized hepatically by CYP3A4/5 to an active metabolite (i.e., 5-hydroxy saxagliptin); this metabolite is two-fold less potent than saxagliptin but has greater selectivity than saxagliptin for DPP-4 over DPP-8 (948-fold vs. 391-fold) and DPP-9 (163-fold vs. 75-fold).

Approximately 75% of a dose is cleared renally, primarily as parent drug and metabolite.[1] Saxagliptin and its metabolite have negligible protein binding. The terminal elimination half-lives (t1/2) for saxagliptin and its active metabolite are 2.5 and 3.1 hours, respectively.

The recommendation for a dose of 2.5 mg for patients with moderate, severe and end-stage renal impairment are based on the observation of 40% higher exposure in moderate renal impairment and 110% increased exposure in severe renal impairment (based on AUC_{0-T}). Although exposure is 15% higher in patients with mild renal impairment, this small increase was not deemed important to require a dose adjustment. The active metabolite has 67%, 191%, and 347% higher exposure for mild, moderate, and severe renal impairment, respectively.

3.2 Regulatory History

Developing Drugs to Treat Type 2 Diabetes

Diabetes mellitus affects approximately 29.1 million people (9.3% of the population) in the United States (US), of which 90% to 95% are diagnosed with type 2 diabetes mellitus (T2DM).[3] In the US, diabetes is the leading cause of kidney failure, non-traumatic lower limb amputations, and new cases of blindness. Diabetes has been associated with an increase in the risk of cardiovascular disease, cardiovascular death and all-cause mortality,[4,5] with the majority of people with diabetes dying from cardiovascular causes.

The February 2008 draft Guidance for Industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* states that for efficacy assessment for drugs intended for improvement in glycemic control in patients with diabetes, the preferred primary efficacy endpoint is reduction in HbA1c (generally after six months of treatment).[6] Note that HbA1c is a *surrogate* endpoint supporting a reduced risk of microvascular complications (i.e., nephropathy, neuropathy, and retinopathy) with improved long-term glycemic control. The HbA1c endpoint also reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms). The effect of glucose-lowering therapies on CV risk reduction among patients with type 2 diabetes has been less clear, although recently available data suggests a relatively complex relationship between long-term glycemic control and CV disease. In the United Kingdom Prospective Diabetes Study (UKPDS), subjects originally randomized to intensive glycemic control had significant long-term reductions in MI and in all-cause mortality after 10 years of follow-up.[7] However, three large, randomized controlled trials (i.e., ACCORD,[8,9] ADVANCE,[10] and VADT[11]), which enrolled high-CV risk T2DM patient populations (e.g., long-standing T2DM, established CV disease and/or multiple CV risk factors) failed to demonstrate significant reductions in major adverse CV events with intensive glycemic control.

The February 2008 draft Guidance recommends phase 3 trial data be available for at least 2,500 subjects exposed to the investigational product, with at least 1,300 to 1,500 of these subjects exposed to the investigational product for 1 year or more and at least 300 to 500 subjects exposed for 18 months or more.[6] Therefore, at the time of approval, there may be limited data to address longer latency safety concerns or rarer adverse reactions. Further, since diabetic populations are prone to certain morbidities (such as cardiovascular disease and renal

dysfunction), only longer term safety data would allow for an assessment of these common, but important comorbidities. Studies lasting longer than one year with adjudication of safety endpoints of interest by an endpoint committee blinded to treatment allocation are strongly encouraged.

In December 2008, the Food and Drug Administration issued the Guidance for Industry: *Diabetes Mellitus, Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* which states that applicants of new antidiabetic medications for the treatment of type 2 diabetes should demonstrate that their products are not associated with an unacceptable increase in cardiovascular risk.[12] Recently, the Agency received results of the first two completed CVOTs conducted in accordance with the recommendations in the December 2008 Guidance. The CVOT for Onglyza (saxagliptin) entitled Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus — Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53 or more simply 'SAVOR') is the topic of this Endocrinologic and Metabolic Drugs Advisory Committee meeting.

CV Risk Guidance

On July 1 and 2, 2008, the EMDAC met to discuss the role of CV risk assessment for antidiabetic medications. This meeting led to the December 2008 issuance of the Guidance for Industry: *Diabetes Mellitus, Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*.[12]

The CV Guidance asks sponsors to do the following during the planning stage of their drug development programs for therapies for type 2 diabetes:

- Establish an independent cardiovascular endpoints committee to prospectively and blindly adjudicate major cardiovascular events (MACE) during phase 2 and 3 clinical trials.
- Ensure that the phase 2 and 3 clinical trials are appropriately designed so that a prespecified meta-analysis of MACE can reliably be performed.
- To enroll patients at increased CV risk, such as elderly patients and those with renal impairment.

The Guidance states that to support approvability from a CV safety standpoint, the sponsor should compare the incidence of MACE with the investigational drug to the incidence of MACE with control and show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval, then a postmarketing CVOT generally would be needed to definitively show that the upper bound is less than 1.3.

The saxagliptin NDA was submitted to FDA prior to the July 2008 Advisory Committee meeting and prior to the issuance of the CV Guidance. Still, FDA asked the Applicant to provide adequate evidence of CV safety in accordance with the Guidance to support approvability. Thus, CV safety was a major focus of the pre-approval reviews for saxagliptin.

Summary of Premarketing CV Safety for Saxagliptin

Post-hoc analyses of CV events were used to evaluate CV safety during the NDA review. There were no pre-specified definitions or prospective adjudication of MACE, and because of the retrospective nature of these analyses, some events had insufficient information to definitively determine whether a CV event of interest had actually occurred. Given these inherent difficulties, multiple strategies for identifying MACE events were employed including broad and narrow Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Query (SMQ) searches and an FDA custom MedDRA search. Saxagliptin's CV safety data were discussed at an April 1, 2009, Advisory Committee meeting. All of the various MACE analyses that were conducted satisfied the statistical criteria in the 2008 CV Guidance. The Applicant had proposed including a statement in the full Prescribing Information that saxagliptin is not associated with an increased risk of CV events (and even reported that saxagliptin may be associated with a reduced risk of major CV events based on favorable point estimates[13,14]). However, FDA concluded that such a statement in labeling should not be permitted at that time because of the limitations of the data (e.g., post-hoc, non-adjudicated nature of the analyses, low event rates, low-risk patient population).

One of the voting questions at the EMDAC meeting asked "For the Custom MACE endpoint, the upper bound of the two-sided 95% confidence interval for the risk ratio/odds ratio was less than 1.3. These data involved a total of 11 cardiovascular events in the 24-week double-blind short-term study periods and a total of 40 cardiovascular events in the combined short-term and long-term study periods of median 62-week exposure. Are these data adequate to conclude that postmarketing cardiovascular safety trials are unnecessary?" All 12 voting panel members voted no. Although the Custom MACE endpoint satisfied the 1.3 criterion, there was concern that the low event rates and other limitations described above did not provide sufficient assurance on this more stringent level of confidence on CV safety.

Saxagliptin was approved by the Agency on July 31, 2009, with the postmarketing requirement that the Applicant conduct a CVOT. The primary objective of the postmarketing requirement was to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE observed with saxagliptin to that observed in the control group was less than 1.3, consistent with the CV Guidance.

Secondary objectives in the postmarketing required trial were to include an assessment of the longer-term effects of saxagliptin on the following safety parameters:

- lymphocyte counts
- infections
- hypersensitivity reactions, including angioedema and concomitant use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers [ARBs])
- hepatotoxicity
- bone fracture
- pancreatitis (with clinical narratives to include information on serum amylase and/or lipase concentrations and any imaging study reports)
- skin reactions
- renal impairment

The adverse events listed above were chosen because of either a concern for all drugs in the DPP4 inhibitor class (at the time the PMR was written these included hypersensitivity reactions, hepatotoxicity, pancreatitis, infections, skin reactions, and renal safety) or concerns related to findings in the saxagliptin development program (e.g., bone fractures and lymphocyte counts).

It should be noted that by design, the diabetes CVOTs are enriched for subjects at high risk for cardiovascular disease, in order to increase the event rate in these (generally) event-driven trials. For this reason, these trials are also an opportunity to assess other safety issues in an older population with more advanced stages of diabetes than is typically possible in premarketing development programs.

The initial study protocol for SAVOR was submitted on October 2009, with agreement by the Agency on November 2010. Two protocol amendments were subsequently incorporated. The key regulatory actions for saxagliptin and the postmarketing required study are outlined in Appendix 7.6.

4 SAVOR – OBJECTIVES, DESIGN, AND METHODS

4.1 Objectives

In line with the PMR, the stated primary safety objective was to establish that the upper bound of the two-sided 95.1%[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 ischemic stroke observed with saxagliptin to that observed in the placebo group was less than 1.3.

The Applicant also intended to seek a CV superiority claim to determine if treatment with saxagliptin compared with placebo when added to current background therapy would result in a *reduction* in the composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke in subjects with T2DM (Applicant refers to this as the "superiority" claim).

4.2 Trial Design

SAVOR was an event-driven, multinational, multicenter, randomized, double-blind, placebo-controlled clinical trial.

4.2.1 Population

General Diabetes Characteristics

The population intended to include adult male and female T2DM subjects with a baseline HbA1c of at least 6.5% and ≤12.0%.

Enrichment strategy for CV outcomes

Subjects were to have either a history of established cardiovascular disease (CVD) or multiple risk factors (MRF) for vascular disease, including renal failure. The criterion for 'established CVD' was met if trial participants had a documented history of atherosclerosis (i.e., involving the coronary, cerebrovascular, or peripheral vascular system) and were at least 40 years of age. To qualify for the MRF enrollment criteria, males at least 55 years of age and females at least 60 years of age were required to have at least one of the following risk factors: dyslipidemia, hypertension, or active smoking.

Background antidiabetic therapy and medical treatment for CV risk factors

At baseline, subjects could be either drug naïve or using glucose-lowering medications (with the exception of DPP4 inhibitor or GLP-1 analog use within the previous six months). Open-label background antidiabetic therapy was not supplied as part of the trial, and adjustments, additions, and/or discontinuations of background therapies were permitted at investigators' discretion based on local diabetes treatment guidelines. All subjects were also to be treated to regional standards of care for CV risk factors (e.g., blood pressure, lipids).

1 A single interim analysis, described in Section 3.3.3, was pre-specified in the protocol. The level of significance for the final analysis of this endpoint was corrected for this interim analysis from 5% to 4.9% (two-sided).

Key exclusion criteria

In addition to current/recent use of DPP4 inhibitors or GLP-1 mimetics, key exclusion criteria included non-CV comorbidities that might limit the ability of subjects to complete the trial, chronic dialysis, renal transplantation and/or a serum creatinine ≥6 mg/dL, uncontrolled CV or metabolic risk factors (i.e., BMI >50 kg/m^2, HbA1c ≥12%, BP >180/100 mm Hg, low density lipoprotein-cholesterol [LDL-C] >250 mg/dL, triglycerides >1000 mg/dL, high density lipoprotein cholesterol [HDL-C] <25 mg/dL) or liver function tests >3 times the upper limit of normal [ULN]). Additionally, subjects experiencing an acute vascular (cardiac or stroke) event within two months before randomization were excluded. A complete listing of the inclusion and exclusion criteria for SAVOR is presented in Appendix 7.1.

4.2.2 Randomized Products, Dosage, and Route of Administration

Investigational products (IP) were provided by Bristol-Myers Squibb (i.e., saxagliptin and placebo tablets). All tablets were yellow, biconvex, round, and film-coated. Randomized IPs were administered orally, once daily, and consisted of:

- Saxagliptin 5 mg tablets (2.5 mg for subjects with an estimated glomerular filtration rate (eGFR) of ≤50 mL/min at baseline or during study).
  OR
- Matching placebo tablets

4.2.3 Trial Plan and Procedures

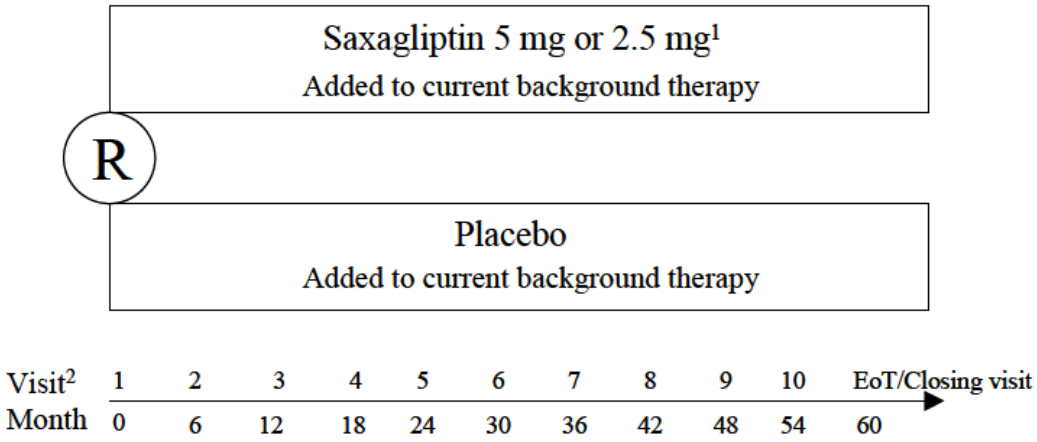
Eligible subjects underwent a combined screening/enrollment/randomization visit following their signed informed consent. Treatment allocation was 1:1, with stratification by CVD status (established CVD or MRF only) and baseline eGFR category estimated according to the Modification of Diet in Renal Disease (MDRD) formula (i.e., >50 mL/min for normal or minor renal impairment; 30 to 50 mL/min for moderate renal impairment; or <30 mL/min for severe renal impairment). Note that the renal impairment categorization for SAVOR was not the same as the National Kidney Foundation categorization[15] used to define stages of chronic kidney disease (CKD)$_2$. This may reflect the recommended saxagliptin dose reduction for chronic renal impairment (i.e., eGFR of <50 mL/min). For subjects receiving the 5 mg/day dose who developed renal impairment (i.e., eGFR ≤50 mL/min) during the trial, a single dose reduction to 2.5 mg daily was allowed. All other therapy for the management of subjects' diabetes and CVD were prescribed at the discretion of the investigators.

Study visits were to occur every six months for assessment of clinical events related to the objectives of the study, tolerability and safety, treatment compliance, and provision of study medication. Between visits (i.e., at three month intervals), trial participants were contacted by

2 Stage 1 with normal or high GFR (GFR > 90 mL/min)
Stage 2 Mild CKD (GFR = 60-89 mL/min)
Stage 3A Moderate CKD (GFR = 45-59 mL/min)
Stage 3B Moderate CKD (GFR = 30-44 mL/min)
Stage 4 Severe CKD (GFR = 15-29 mL/min)
Stage 5 End Stage CKD (GFR <15 mL/min)

phone. The trial remained double-blinded until the end of subject follow-up. The schematic of the study design is displayed in Figure 1.

Figure 1: Trial Schematic



Source: Reproduced from the Applicants' Clinical Study Report (page 24 of 15,624; labeled as Figure 1).
Abbreviations: EoT, End of treatment; R, Randomization.
[1] For subjects with moderate to severe renal insufficiency, i.e., eGFR ≤50 mL/min
[2] The duration of the study was dependent on the accrual of a predetermined number of CV events. Visits were withdrawn or added as required every 6 months until the study was closed.

Subjects could be discontinued from study medication voluntarily or for safety reasons as judged by the Investigator, Applicant and/or a representative.

Study-specific discontinuation criteria included: increase of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3 times the ULN and increase of total bilirubin >1.5 times ULN confirmed at a repeated measurement within 4 days; increase of ALT or AST >10 times ULN confirmed at a repeated measurement within 4 days; or pregnancy

4.3 Statistical Methods

4.3.1 Analysis Populations and Censoring Windows

The statistical analysis plan defined the intention-to-treat (ITT) analysis population as all randomized subjects. FDA defined an additional analysis population for sensitivity analyses that included all randomized subjects who received at least one dose of study medication. This will be referred to as the mITT-FDA analysis population.

To account for the relation of the occurrence of an event and treatment exposure, the following analyses were conducted for the primary and secondary endpoints:

- The *on-study* analysis included all events that occurred while the subject was in the study, irrespective of treatment exposure (i.e., this included all events that occurred while a subject was on treatment or off treatment).

- The *on-treatment* analysis included only events that happened while the subject was exposed to study treatment, i.e., events that happened after the subject's last treatment dose were censored. Two ascertainment windows were used in the on-treatment analyses, 7 and 30 days. The on-treatment +7 days and on-treatment + 30 days analyses censored events that occurred more than 7 and 30 days, respectively, after the last treatment dose.

4.3.2 Endpoints

The following endpoints were pre-specified in the study protocol.

- **Primary Endpoint (MACE)**: The primary endpoint was the time to first major adverse cardiovascular event (MACE), where MACE is defined as a composite of cardiovascular death (CV death), non-fatal myocardial infarction (MI) or non-fatal ischemic stroke.

- **Secondary Endpoint (MACE+)**: MACE+ was the time to first MACE+ event, where MACE+ is defined as a composite of CV death, non-fatal MI, non-fatal ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris or hospitalization for coronary revascularization.

- **Secondary Endpoint (All-cause Mortality)**: All-cause mortality was assessed as the time to any documented death.

These endpoints were prospectively adjudicated using pre-specified definitions by an independent clinical events committee (CEC), blinded to treatment allocation. The CEC was composed of specialists in CV and pancreatic medicine. A description of the adjudication process is presented in Appendix 7.4

The definitions of primary and secondary endpoints are provided in Appendix 7.2, and were established to conform to the 2010 draft version of Standardized Definitions for End Point Events in Cardiovascular Trials[16] (updated 2014)[17] and criteria developed by the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction.[18]

4.3.3 Methods of Statistical Analysis

A single pre-specified interim analysis was performed for the primary MACE endpoint when 50% of the total number of events had been accrued. This analysis was planned to test for superiority at the 1-sided 0.15% level using the Lan-deMets spending function approach with O'Brien-Fleming boundaries as implemented in East 5.2. The study was not intended to be stopped for ruling out the 1.3 risk margin at the interim. Tests conducted at trial completion were to be based on the one-sided alpha-adjusted 0.0245 level.

The pre-specified primary analysis for all primary and secondary endpoints was an on-study analysis based on the ITT population. This primary analysis was, for all endpoints, based on a Cox proportional hazards models stratified by baseline renal function category and baseline CV risk group with a fixed effect for treatment. This analysis, unadjusted for covariates, was used to obtain hazard ratios and two-sided 95.1% confidence intervals for the final study analyses.

Additional sensitivity analyses were conducted based on the mITT-FDA analysis population, that incorporate the various censoring schemes as defined in the previous section. These analyses also

used time-to-event methods, namely, Cox proportional hazards models as was done in the primary analysis.

4.3.4 Sample Size Considerations

A single interim analysis was planned for the primary endpoint when 50% of the total number of events had been accrued. This analysis was planned to test for "superiority" at the 1-sided 0.15% level using the Lan-deMets spending function approach with O'Brien-Fleming boundaries as implemented in East 5.2. Although the study was not intended to be stopped for non-inferiority at the interim unless superiority was also met, the one-sided alpha level used for the final analysis was 0.0245.

The 16,500 patient sample size was expected to yield 1,040 primary endpoint events (MACE) under the assumption of a 2.1% annual event rate on placebo, a 17% reduction of risk in the saxagliptin group, an approximately 15-month accrual period with an approximate 3-year additional follow-up period, and a 2.8% rate of annual study discontinuation. The number of events was expected to provide 85% power to test for superiority of saxagliptin versus placebo at the 2.45% one-sided level of significance and at least 98% power for the test of the alternative hypothesis that the hazard ratio of saxagliptin to placebo for the primary MACE endpoint was less than 1.3 at the 2.45% one-sided significance level assuming that the underlying hazard ratio is 1.0.

5 SAVOR - RESULTS

5.1 Demographics and Clinical Characteristics at Baseline

SAVOR randomized 16,492 subjects to saxagliptin or placebo. The baseline demographics (Table 2) and clinical characteristics (Table 3) of the randomized groups are summarized below. Treatment groups at baseline appear to be well-balanced for demographics and clinical characteristics.

Overall, the trial population was predominantly White (75%) and male (67%), with a mean age of 65 years. The trial was conducted worldwide with the majority of sites in North America and Europe, and with each region contributing approximately 32% and 39% of the subjects randomized into this trial, respectively.

Clinically, the enrichment strategy appears to have been successful in enrolling subjects at relatively higher risk for CV events. More than 50% of the population had a body mass index (BMI)>30 kg/m^2. The mean duration of diabetes was approximately 12 years, and approximately 18% of subjects had a duration of diabetes of >20 years. The majority had a history of established CVD (78%). Approximately 15% of subjects had an estimated glomerular filtration rate (eGFR) <50 mL/min. Most subjects (95%) were using antidiabetic therapy prior to randomization, with 40% using insulin, indicating a more advanced stage of type 2 diabetes. Further, almost all subjects were using at least one other medication for CV disease.

Of note, the Applicant reported that approximately 8% of subjects had a baseline HbA1c <6.5%, which is below the protocol specified range for this trial, a finding which may reflect trial entry

criteria that allowed inclusion of subjects with HbA1c≥6.5% from the last documented laboratory measurement within the previous six months.

Table 2: Baseline Demographics (ITT population)

Demographic Variable	Saxagliptin (n=8280)	Placebo (n=8212)
Age, mean ± SD — yr	65.1 ± 8.5	65.0 ± 8.6
<65 yr — no. (%)	3990 (48.2)	3941 (48.0)
≥65 yr — no. (%)	4290 (51.8)	4271 (52.0)
≥75 yr — no. (%)	1169 (14.1)	1161 (14.1)
Female sex — no. (%)	2768 (33.4)	2687 (32.7)
Race — no. (%)		
White	6241 (75.4)	6166 (75.1)
Asian	896 (10.8)	884 (10.8)
Black/African American	278 (3.4)	290 (3.5)
American Indian/Alaskan Native	18 (0.2)	33 (0.4)
Native Hawaiian or Other	11 (0.1)	11 (0.1)
Multiracial	768 (9.3)	758 (9.2)
Other	68 (0.8)	70 (0.9)
Ethnic Group (Hispanic/Latino) — no. (%)	1778 (21.5)	1763 (21.5)
Region — no. (%)		
North America	2635 (31.8)	2631 (32.0)
US only	2141 (25.9)	2145 (26.1)
Latin America	1348 (16.3)	1363 (16.6)
Europe/Africa	3512 (42.4)	3450 (42.0)
Asia/Pacific	785 (9.5)	768 (9.3)

Source: Modified from Scirica BM, et al. N Engl J Med 2013;369:1317-26,[19] the Applicants' Clinical Study Report (pages 74-84 of 15624, labeled as Tables 10-13), and derived from the adsl xpt dataset.

Abbreviations: no., number; SD, standard deviation; and yr, years.

Table 3: Baseline Clinical Characteristics (ITT population)

Clinical Characteristic	Saxagliptin (n=8280)	Placebo (n=8212)
BMI, mg/m^2 — mean± SD	31.1 ± 5.5	31.2 ± 5.7
<30 mg/m^2 — no. (%)	3827 (46.2)	3820 (46.5)
≥30 mg/m^2 — no. (%)	4446 (53.7)	4370 (53.2)
Duration of T2DM, mean ± SD — yr	12.0 ± 9.0	11.9 ± 8.7
<5 yr — no. (%)	1975 (23.9)	1941 (23.6)

Clinical Characteristic	Saxagliptin (n=8280)	Placebo (n=8212)
≥5 to <10 yr — no. (%)	1957 (23.6)	1968 (24.0)
≥10 yr — no. (%)	4338 (52.4)	4298 (52.3)
Cardiovascular Diseases and Risk Factors		
Established CVD — no. (%)	6494 (78.4)	6465 (78.7)
Prior myocardial infarction — no. (%)	3147 (38.0)	3090 (37.6)
Prior heart failure — no. (%)	1056 (12.8)	1049 (12.8)
Prior coronary revascularization — no. (%)	3566 (43.1)	3557 (43.3)
Multiple Risk factors — no. (%)	1786 (21.6)	1747 (21.3)
Hypertension — no. (%)	6725 (81.2)	6767 (82.4)
Dyslipidemia — no. (%)	5895 (71.2)	5844 (71.2)
Current Smoker* — no. (%)	1072 (13.0%)	1147 (14.0%)
Glycemic Status		
HbA1c% — mean ± SD	8.0±1.4	8.0±1.4
<6.5% — no. (%)	590 (7.1)	673 (8.2)
6.5 to <7.0% — no. (%)	1442 (17.4)	1414 (17.2)
7.0 to <8.0% — no. (%)	2759 (33.3)	2657 (32.4)
8.0 to <9.0% — no. (%)	1577 (19.0)	1562 (19.0)
≥9% — no. (%)	1761 (21.3)	1764 (21.5)
Not reported — no. (%)	151 (1.8)	142 (1.7)
Fasting plasma glucose, mg/dL — mean ± SD	156±56	157±57
eGFR, mL/min — mean ± SD	72.5±22.6	72.7±22.6
<30 mL/min — no. (%)	172 (2.1)	164 (2.0)
30 to ≤50 mL/min — no. (%)	1122 (13.6)	1118 (13.6)
>50 mL/min — no. (%)	6986 (84.4)	6930 (84.4)
Urinary albumin-to-creatine ratio, mg/g		
Median (interquartile range)†	16.0 (6.0-66.0)	17.0 (6.0-70.0)
<30 mg/g — no. (%)	4867 (58.8)	4829 (58.8)
≥30 to ≤300 mg/g — no. (%)	2217 (26.8)	2209 (26.9)
>300 mg/g — no. (%)	832 (10.0)	806 (9.8)
Baseline diabetes medication — no. (%)		
Any use	7910 (95.5)	7793 (94.9)
Any insulin	3423 (41.3)	3364 (41.0)
Any non-insulin diabetes medication use	6673 (80.6)	6543 (79.7)
≥2 Non-insulin diabetes medication use	2969 (35.9)	2951 (35.9)
Sulfonylurea	3327 (40.2)	3259 (39.7)

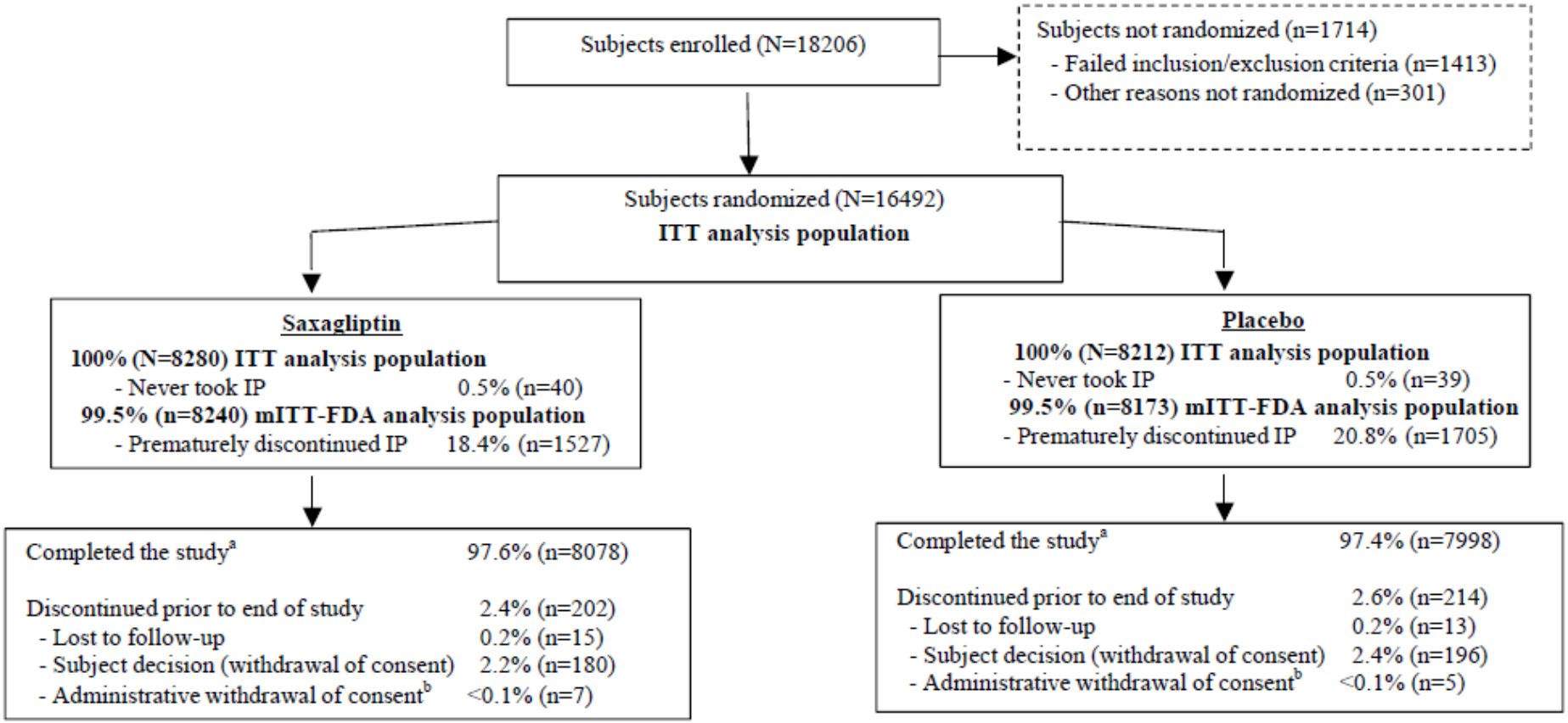
Clinical Characteristic	Saxagliptin (n=8280)	Placebo (n=8212)
Thiazolidinediones	510 (6.2)	460 (5.6)
Baseline CVD medication — no. (%)		
Any use	8142 (98.3)	8072 (98.3)
Aspirin	6249 (75.5)	6155 (75.0)
Statin	6482 (78.3)	6435 (78.4)
ACEI	4435 (53.6)	4505 (54.9)
ARB	2332 (28.2)	2263 (27.6)
Beta-blocker	5101 (61.6)	5061 (61.6)
Non-aspirin anti-platelet medication	1986 (24.0)	1960 (23.9)
Other cardiovascular medication‡	6108 (73.8)	6051 (73.7)
Diuretics	3525 (42.6)	3540 (43.1)

Source: Modified from Scirica BM, et al. N Engl J Med 2013;369:1317-26,[19] the Applicants' Clinical Study Report (pages 74-84 of 15624, labeled as Tables 10-13; and pages 1535, labeled as Table 11.1.4.3), and derived from the adsl xpt dataset.
Note — Data presented in the table ignored missing values.
* Smoking history was not available for one subject each in the Saxagliptin and Placebo arms.
† Analysis included 7916 patients in the saxagliptin arm and 7844 in the placebo arm.
‡ Included aldosterone inhibitors, alpha blockers, anti-arrhythmic agents, calcium antagonists, direct renin inhibitors, diuretics, ezetimibe, fibric acid, niacin, nitrates, oral anti-coagulants, other anti-anginal agents, and other antihypertensive agents.
Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; no., number; and T2DM, type 2 diabetes mellitus.

5.2 Subject Disposition

Overall, 97.5% of subjects completed the study – 97.6% in the saxagliptin group and 97.4% in the placebo group. The 416 (2.5%) subjects who discontinued prior to the end of the study were similarly distributed between arms in terms of percentages and reasons for loss-to-follow-up. The flowchart in Figure 2 shows overall subject disposition.

Figure 2: Subject Disposition



Source: Adapted from the Applicant's Clinical Study Report (page 65 of 15624, labeled as Figure 3).
Subjects could be counted in more than one category
Abbreviations: AE, Adverse event; IP investigational product; ITT intention-to-treat; mITT-FDA modified intention-to-treat
[a] Subjects who completed the study included subjects ongoing in the study at the time of study closure or who had died
[b] Due to site closure

Public records were searched and vital status (alive/dead) was obtained for 127 (1.5%) subjects in the saxagliptin arm and 142 (1.7%) subjects in the placebo arm. Only 75 (0.9%) subjects on the saxagliptin arm and 72 (0.9%) subjects on the placebo arm had no vital status reports. These data are summarized in Table 4. Thus, 99.1% subjects in the saxagliptin arm, and 99.1% subjects in the placebo arm either completed the study or discontinued but had vital status available.

Table 4: Vital Status Information for Discontinued Subjects (ITT)

	Saxagliptin (N=8280)	**Placebo (N=8212)**
	% of Subjects (Number of Subjects)	
Total Discontinued	2.4 (120)	2.6 (214)
Alive	1.4 (120)	1.5 (126)
Dead	< 0.1 (7)	0.2 (16)
Searched, no data found	0.7 (61)	0.7 (58)
Search not performed	0.2 (14)	0.2 (14)

Source: Clinical study report (page 65/15624); obtained by public records searches as permitted by countries.

Table 5 shows the percentage of subjects that reached more than 1 year, 2 years, and 3 years of follow-up until discontinuation or primary MACE event by treatment arm, regardless of whether the subject was still taking the investigational product, i.e., regardless of treatment exposure. Approximately half of the subjects were followed for up to two years, and no subjects were followed for more than 3 years. Overall, time of follow-up was similar between the two treatment groups.

Table 5: Percentage of Subjects who Reached Follow-up Periods (ITT)

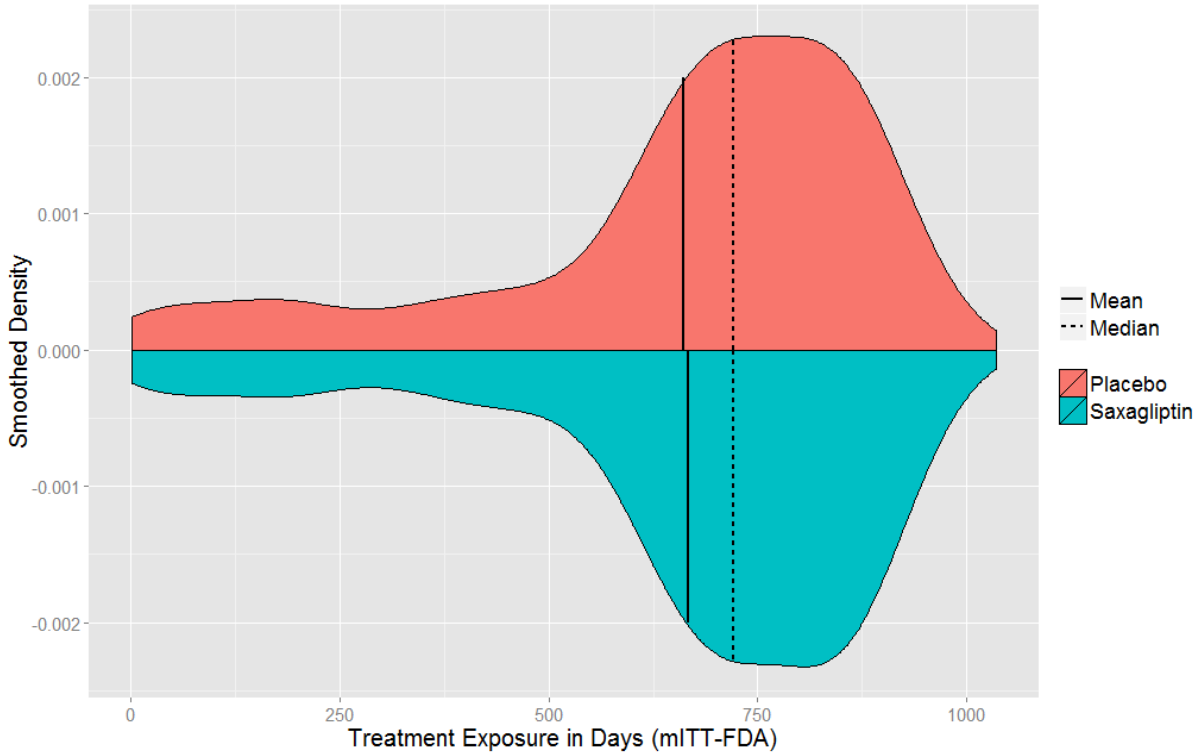
Follow-up period	**Saxagliptin (N=8280)**	**Placebo (N=8212)**
≥ 1 year	94.5%	94.4%
≥ 2 years	52.3%	52.3%
≥ 3 years	0	0

Source: FDA analysis from adtte.xpt.

5.3 Treatment Exposure

Treatment exposure was similar between arms for subjects who had both start and end dates of treatment recorded, as illustrated by the violin plot in Figure 3 below. Median treatment exposure was 721 days (approximately 2 years) for both treatment groups.

Figure 3: Split Violin Plot of Treatment Exposure (mITT-FDA)



Source: FDA analysis using adth.xpt.

5.4 Cardiovascular Safety

5.4.1 Primary MACE

Table 6 presents the pre-specified time-to-first-event analysis on the ITT population (i.e., includes all MACE regardless of treatment exposure) of the primary MACE endpoint using all events observed during the study (i.e., an on-study analysis). A total of 1,222 subjects experienced a MACE; 613 subjects out of 8280 subjects randomized to saxagliptin experienced a MACE and 609 subjects out of 8212 randomized placebo subjects. Event rates were approximately 3.8 per 100 person-years (PY) in both treatment groups.

The Kaplan-Meier survival plot in Figure 4 shows that the primary-MACE-free survival curves for the saxagliptin arm and the placebo arm for the ITT population are very similar. Based on the pre-specified primary analysis, that is the ITT population that includes all MACE regardless of treatment exposure, the estimated hazard ratio for MACE was 1.00 with a 95.1% confidence interval of (0.89, 1.12). Thus, SAVOR met the safety objective by ruling out the 1.3 risk margin; however, it failed to establish the superiority of saxagliptin to placebo.

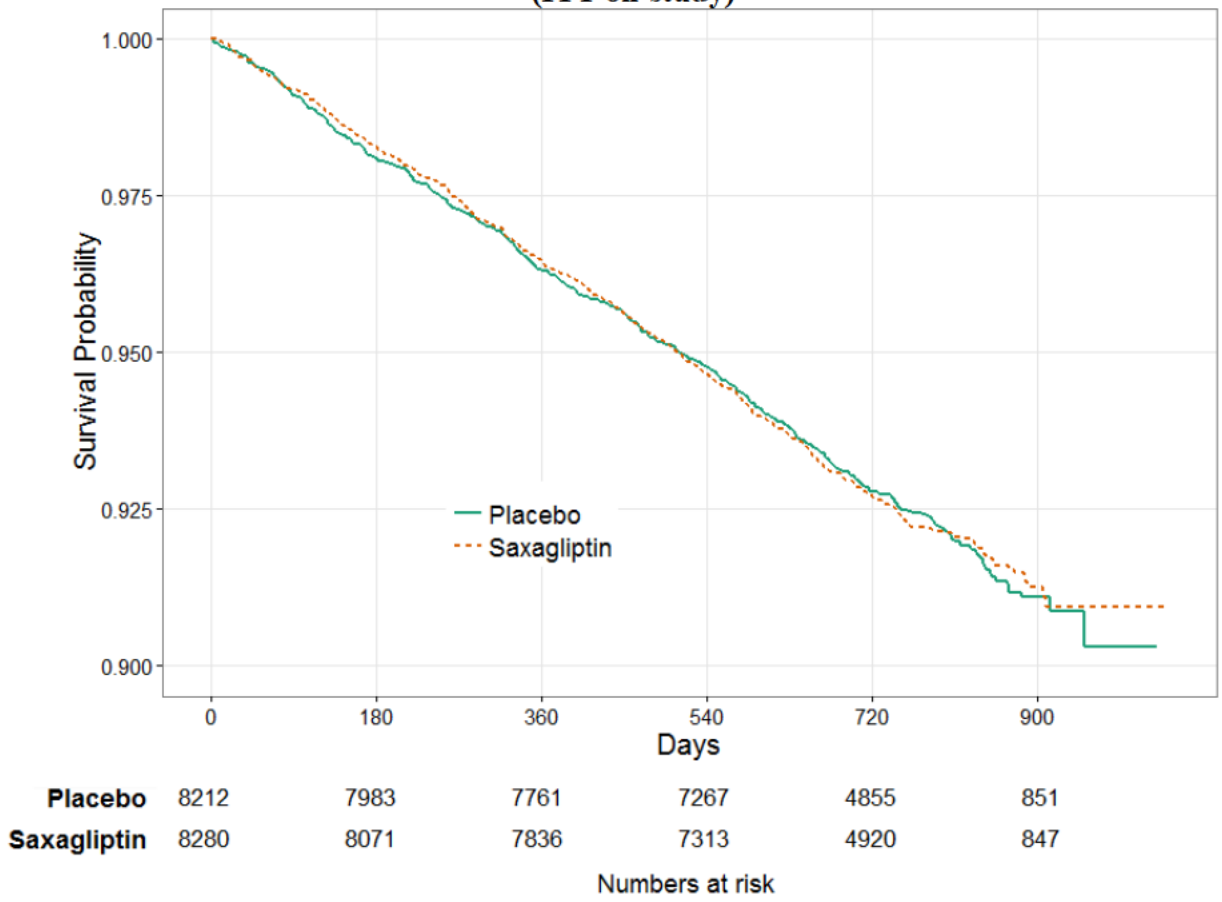
Table 6: Pre-specified Analysis of Primary MACE Endpoint (ITT)

	Saxagliptin N= 8280	**Placebo** N= 8212	**Hazard Ratio*** (95.1% CI)
MACE patient years of follow-up	16308.77	16156.01	
Number of MACE events (rate per 100 PY)	613 (3.76)	609 (3.77)	1.00 (0.89, 1.12)

* Hazard ratios are based upon a Cox proportional hazards model stratified by baseline renal function category and baseline CV risk group with a fixed effect for treatment using an on-study analysis.

Source: FDA analysis using adtte.xpt, also available in sponsor's Table 19 of Clinical Study Report (page 100/15624).

Figure 4: Plot of Kaplan-Meier Primary MACE Survival Curves by Treatment Arm (ITT on-study)



Source: FDA analysis using adtte.xpt, also available in sponsor's Figure 4 of Clinical Study Report (page 103/15624).

Exploratory analyses of the individual components of the primary MACE endpoint (i.e., CV death, non-fatal MI and non-fatal ischemic stroke) are presented in Table 7 for the on-study analysis in the ITT population. The majority of MACE events were CV death and non-fatal MI. The estimated hazard ratio for CV death is 1.03; those for non-fatal MI and non-fatal ischemic stroke are 0.91 and 1.16, respectively. Confidence intervals for each component include the null value of 1 and no individual component demonstrates a statistically significant effect.

Table 7: Description of Components of Primary MACE Endpoint (ITT)

	Saxagliptin N= 8280	Placebo N= 8212	Hazard Ratio‡ (95.1% CI)
	n (%)		
Primary MACE events	613 (7.4%)	609 (7.4%)	1.00 (0.89, 1.12)
Components†:			
CV death	269 (3.2%)	260 (3.2%)	1.03 (0.87, 1.22)
Non-fatal MI	240 (2.9%)	260 (3.2%)	0.91 (0.77, 1.09)
Non-fatal ischemic stroke	143 (1.7%)	123 (1.5%)	1.16 (0.91, 1.47)

†Analyses for components capture all CV deaths, non-fatal MIs and non-fatal ischemic strokes. Some subjects experienced multiple events, hence totals of component events exceed number of primary MACE events which only considers the first event for each subject.
‡ Hazard ratios are based upon a Cox proportional hazards model stratified by baseline renal function category and baseline CV risk group with a fixed effect for treatment using an on-study analysis.

Source: FDA analysis using adtte.xpt, also available in sponsor's Table 19 of Clinical Study Report (page 100/15624).

The FDA performed sensitivity analyses for the primary MACE endpoint using the mITT-FDA population which includes only randomized subjects who had at least one dose of study treatment. Proximity of events to treatment exposure was evaluated by the use of multiple censoring schemes: an on-study analysis includes all events observed either on-treatment or off-treatment; on-treatment analyses include events observed while on treatment and within a censoring window of 7 or 30 days.

Table 8 presents results for these sensitivity analyses of the MACE endpoint. The estimated hazard ratio for the on-study analysis is 1.00 with a 95.1% confidence interval of (0.89, 1.12). On-treatment analyses that include censoring windows of 7 and 30 days are also consistent with the results of the pre-specified primary analysis for the primary MACE endpoint, i.e., these results support the conclusion that the risk margin of 1.3 can be ruled out for primary MACE.

Table 8: Sensitivity Analyses of MACE Endpoint (mITT-FDA†)

	Saxagliptin N=8240	Placebo N=8173	Hazard Ratio‡ (95.1% CI)
	n (%)		
On-study Analysis	610 (7.4%)	607 (7.4%)	1.00 (0.89, 1.12)
On-treatment Analysis +30 days	526 (6.4%)	498 (6.1%)	1.04 (0.92, 1.18)
On-treatment Analysis + 7 days	511 (6.2%)	482 (5.9%)	1.04 (0.92, 1.18)

† mITT-FDA is defined as randomized subjects who had at least 1 recorded dose; in contrast to the Applicant's definition no additional censoring mechanisms are incorporated
‡ All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories

Source: FDA analysis using adtte.xpt. Partial results also presented in sponsor's Figure 5 (page 104/15624) of Clinical Study Report.

5.4.2 Secondary Endpoint: MACE+

As a reminder, MACE+ was the time to first MACE+ event, where MACE+ is defined as a composite of CV death, non-fatal MI, non-fatal ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris or hospitalization for coronary revascularization. Table 9 presents the pre-specified time-to-first-event analysis on the ITT population for MACE+ using all events observed during the study (i.e., an on-study analysis). The hazard ratio for MACE+ is 1.02 and the associated confidence interval is (0.94, 1.11). The upper bound of 1.11 for the confidence interval rules out a risk margin of 1.3. The results of these pre-specified analyses are supportive of the results for primary MACE.

Table 9: Pre-specified Analysis for Composite Secondary MACE+ Endpoint (ITT)

	Saxagliptin N=8280	**Placebo** N=8212	**Hazard Ratio‡** (95.1% CI)
	n (%)		
MACE+	1059 (12.8%)	1034 (12.6%)	1.02 (0.94, 1.11)

‡Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories using an on-study analysis.

Source: FDA analysis using adtte xpt, information also available in sponsor's Table 20 of Clinical Study Report (page (page 113/15624).

Exploratory analyses of the individual components of the secondary MACE+ endpoint are presented in Table 10. Except for the hospitalization for heart failure component, hazard ratio confidence intervals for components of secondary MACE+ all include the null value of 1. For the hospitalization for heart failure (hHF) component, the estimated hazard ratio for hHF was 1.27 with 95.1% confidence interval (1.07, 1.51) which excludes 1 (i.e., is statistically significant at the 4.9% level).

Table 10: Description of Components of Secondary MACE+ Endpoint (ITT)

	Saxagliptin N= 8280	**Placebo** N= 8212	**Hazard Ratio‡** (95.1% CI)
	n (%)		
Secondary MACE+ events	1059 (12.8%)	1034 (12.6%)	1.02 (0.94, 1.11)
Components†:			
CV death	269 (3.2%)	260 (3.2%)	1.03 (0.87, 1.22)
Non-fatal MI	240 (2.9%)	260 (3.2%)	0.91 (0.77, 1.09)
Non-fatal ischemic stroke	143 (1.7%)	123 (1.5%)	1.16 (0.91, 1.47)
Hospitalization for Heart Failure	**289 (3.5%)**	**228 (2.8%)**	**1.27 (1.07, 1.51)**
Hospitalization for Unstable Angina	97 (1.2%)	81 (1.0%)	1.19 (0.89, 1.61)
Coronary revascularization	423 (5.1%)	459 (5.6%)	0.91 (0.80, 1.05)

†Analyses capture all components of MACE+. Some subjects experienced multiple events, hence totals of component events exceeds number of secondary MACE+ events which only considers first event for each subject.
‡All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories using an on-study analysis.

Source: FDA analysis using adtte.xpt, also available in Applicant's Table 20 of Clinical Study Report (page 113/15624).

5.4.3 Hospitalization for Heart Failure

The CEC defined a hospitalization for heart failure (hHF) event as an inpatient admission or emergency department visit resulting in at least a 12-hour stay for patients with a clinical presentation of heart failure requiring additional or increased therapy for symptom management (please refer to the Appendix 7.2).

Hospitalization for heart failure was a component of the secondary MACE+ endpoint, but was not a pre-specified stand-alone endpoint. Given that hospitalization for heart failure was neither a primary nor secondary trial endpoint, there is the potential for false positive results due to multiple testing. However, the validity of the finding of an increased risk of hHF is supported by the large number of events reported in this trial, and the fact that hospitalization for heart failure was based on a pre-specified definition, clinically adjudicated by an independent, blinded committee of specialists. Because the analyses of the components of the secondary MACE+ endpoint indicated that hHF could potentially be the cause for significant differences in hazard ratios between treatment arms, further exploratory analyses of the hHF endpoint were performed by FDA and are shown in Tables 11 and 12. Other exploratory analyses presented in this section were performed by the Applicant unless otherwise noted.

It could be argued that CV adverse events constitute competing risks. For example, a subject who experiences death cannot experience any events afterwards, and a subject who experiences non-fatal MI would not be followed for other non-fatal MACE or hHF after the first event in a time-to-first-event analysis. For this reason, one can look at alternative composite endpoints that incorporate hHF to further explore the hHF safety signal. FDA examined composite endpoints that included subjects with either hHF or primary MACE, either hHF or CV death, and either hHF or all cause death. These exploratory analyses were conducted on the ITT population using an on-study analysis. Confidence intervals are presented at the nominal two-sided alpha=0.05 level.

Table 11 presents a summary of component events for those subjects who had either a primary MACE or a hHF event, and Table 12 combines hHF with either primary MACE, CV death or all-cause mortality. While the excess of 35 hHF events among subjects without primary MACE in the saxagliptin treatment arm does not result in significance at the unadjusted 5% level for the composite "hHF or primary MACE" endpoint, the composite of hHF with either CV death or all-cause death results in confidence lower bounds that equal or exceed 1. These exploratory analyses do not allay concerns regarding the excess hHF events in the saxagliptin arm.

Table 11: Component Events for Subjects with Primary MACE or Hospitalization for Heart Failure (hHF) (ITT on-study)

	Saxagliptin N=8280	**Placebo** N=8212
	n (%)	
hHF or primary MACE	784 (9.5%)[£]	745 (9.1%)[£]
Component events:		
CV Death	269 (3.2%)[£]	260 (3.2%)[£]
Non-fatal MI or Non-fatal ischemic stroke (no CV death)	344 (4.2%)[£]	349 (4.2%)[£]
hHF without primary MACE	171 (2.1%)[£]	136 (1.7%)[£]

[£] Numbers in parenthesis are percentages of all ITT subjects for associated study arm.

Source: FDA analysis using adtte.xpt.

Table 12: Hospitalization for Heart Failure (hHF) in Exploratory Composite Endpoints (Primary MACE, CV-death, or All-Cause Death) (ITT)

	Total N=16492	**Saxagliptin** N= 8280	**Placebo** N= 8212	**Hazard Ratio*** (95% CI)
	n (%)			
hHF or primary MACE	1529 (9.3%)	784 (9.5%)	745 (9.1%)	1.05 (0.95, 1.16)
hHF or CV Death	925 (5.6%)	493 (6.0%)	432 (5.3%)	1.14 (1.00, 1.30)
hHF or all-cause Death	1180 (7.2%)	633 (7.6%)	547 (6.7%)	1.16 (1.03, 1.30)

*All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories using an on-study analysis.

Source: FDA analysis using adtte.xpt.

Baseline characteristics of subjects who experienced hHF

The baseline demographics and clinical characteristics of the subjects who did and did not experience hHF events are presented by treatment group in Table 13. Subjects with hHF events during the trial were older and more often male. They had a longer duration of T2DM on average (median duration of 12.7 years). Additionally, higher proportions of subjects with events had other comorbidities, such as renal impairment and established CVD (e.g., previous MI, heart failure, coronary artery disease, and/or atrial fibrillation/flutter). Overall, 12.8% of participants

(2,105 subjects) had a baseline history of heart failure. However, more than 40% of subjects with hHF events in both treatment arms had a baseline reported medical history of heart failure. Using a multivariable analysis, the Applicant found that a baseline history of heart failure (adjusted HR 4.18, 95% CI 3.48 – 5.02) was the baseline characteristic that was the most strongly associated with the risk of hHF regardless of treatment assignment followed by markers of renal disease (an eGFR ≤60 mL/min and the albumin/creatinine ratio). Including randomization assignment in this model, the Applicant's analysis showed an adjusted HR for saxagliptin that was similar to the overall trial results (adjusted HR 1.29, 95% CI 1.08-1.54).

Both insulin product and thiazolidinedione product labeling contain a warning that fluid retention and heart failure can occur with concomitant use of these products. While, baseline insulin use in SAVOR was more frequent in subjects with hHF events compared to those without events, the proportions of subjects in each treatment arm were similar. The use of thiazolidinediones in the trial was limited but also balanced between treatment arms, for both hHF subsets.

Higher proportions of subjects with hHF events were receiving CV medications (e.g., ACEIs, aspirin, statins, beta blockers or diuretics). There is some concern that use of DPP4 inhibitors may increase substance P concentrations (a DPP4 substrate) with concomitant ACEI therapy, potentially resulting in substance P-mediated activation of the sympathetic nervous system and decreased degradation of neuropeptide Y1-36 (NPY1-36), a vasoconstrictor, which may have potentially deleterious effects in subjects with left ventricular dysfunction.[20] Although the percentages of subjects who used ACEIs at baseline were higher in subjects with hHF events, there was no important difference between treatment arms. In exploratory subgroup analysis of baseline ACEI use, the Applicant reported that the hazard ratio of the time to first hHF event for saxagliptin vs. placebo for subjects not receiving ACEIs at baseline had a point estimate of 1.42 and a 95% confidence interval of (1.09, 1.88), while a similar analysis for subjects who were receiving ACEIs at baseline resulted in an estimated HR of 1.18 with 95% CI of (0.94, 1.48).

Table 13: Subject Demographics and Clinical Characteristics for Subjects with and without Adjudicated hHF Events (ITT)

Patient Characteristics	Subjects with hHF Events		Subjects without hHF Events	
	Saxagliptin (N=289)	Placebo (N=228)	Saxagliptin (N=7991)	Placebo (N=7984)
Demographics				
Mean age (yr ± SD)	68.0 ± 9.3	68.2 ± 9.1	64.9 ± 8.5	65.0 ±8.6
Age ≥65	183	149	4107	4122
Age ≥75	81	56	1088	1105
Male	216	161	5296	5364
White race	244	180	5997	5986
North American region	114	90	2521	2541
European region	127	100	3385	3350
Mean duration of T2DM (yr ± SD)	14.4 ± 9.7	14.7 ± 9.8	11.9 ± 8.93	11.8 ± 8.7
Established CVD	259	208	6163	6195
CVD Medical History and Risk Factors				
Established CVD	259	208	6163	6195
MI	163	119	2984	2971
Heart failure	124	102	932	947
NYHA I	26	22	294	281
NYHA II	72	63	551	562
NYHA III	22	16	77	85
NYHA IV	4	1	10	19
Afib/flutter	71	49	525	557
CV Risk Factors				
Hypertension	229	192	6496	6575
Dyslipidemia	233	178	5662	5666
Current smoking	36	31	1036	1116
Renal Status				
Mean ± SD eGFR (mL/min/1.73 m^2)	59.4 ± 23.0	59.3 ± 24.7	72.9 ± 22.48	73.0 ± 22.42
Baseline eGFR				
>50	172	139	6814	6791
≥30 to ≤50	96	66	1026	1052
<30	21	23	151	141
Antidiabetic Medication Use				
Any use	278	223	7504	7441
Insulin	165	137	3258	3227
Sulfonylurea	88	68	3239	3191
Thiazolidinedione	11	7	499	453

Patient Characteristics	Subjects with hHF Events		Subjects without hHF Events	
	Saxagliptin (N=289)	Placebo (N=228)	Saxagliptin (N=7991)	Placebo (N=7984)
CV Medication Use				
Any use	**288**	**228**	7854	7844
ACEI	**163**	**140**	4272	4365
ARB	**79**	**63**	2253	2200
ACEI/ARB	**228**	**188**	6250	6329
Aspirin	**236**	**180**	6013	5975
Beta blocker	**224**	**193**	4877	4868
Statin	**241**	**188**	6241	6247
Diuretic	**209**	**169**	3316	3370
Aldosterone antagonist	**88**	**86**	254	267

Source: Derived from the Applicants' Clinical Study Report Addendum (pages 31-44 of 676 and labeled as Tables 6-8, and pages 241-246, labeled as Tables 1.4.1 and 1.4.2).
Abbreviations: ACEI, angiotensin converting enzyme inhibitor; Afib/flutter, atrial fibrillation/atrial flutter; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RF, renal failure; SD, standard deviation; and T2DM, type 2 diabetes mellitus; yr, year.

Clinical Manifestations of hHF

During the trial, there was no evidence of chronic volume overload in the saxagliptin arm (e.g., body weight gain or edema compared with placebo).

Overall, the clinical manifestations of subjects with hHF events were consistent with those attributed to heart failure, and similar between treatment arms (Table 14). Dyspnea was the most common symptom present regardless of treatment (86% vs. 92% of saxagliptin- and placebo-treated subjects, respectively). The Applicant's pre-specified criteria for a hHF event included admission to an inpatient unit or an emergency room visit that resulted in at least a 12 hour stay, AND the presence of at least one pre-specified manifestation, which included dyspnea, AND additional and/or increased therapy to manage the condition. Since dyspnea is considered a nonspecific indicator for hHF events, the Agency requested that the Applicant also perform a time to hHF event analysis which excluded subjects who presented with dyspnea as the only clinical manifestation (i.e., 40 subjects randomized to saxagliptin and 31 to the control arm). The results of this analysis were similar to those originally conducted by the Applicant (i.e., HR 1.264; 95% CI, 1.049 to 1.524), again favoring the placebo arm.

Table 14: Clinical Manifestations of Subjects with Adjudicated hHF Events (ITT)

Clinical Presentation	Saxagliptin (N=289) n (%)*	Placebo (N=228) n (%)*
All with CRF page	284 (98.3)	226 (99.1)
Dyspnea	248 (85.8)	209 (91.7)
Dyspnea with no other clinical manifestation	40	31
Dyspnea with at least 1 other clinical manifestation	208	178
Peripheral edema	146 (50.5)	118 (51.8)
Pulmonary edema	97 (33.6)	89 (39.0)
Radiographic evidence of worsening heart failure	93 (32.2)	69 (30.3)
Orthopnea/paroxysmal nocturnal dyspnea	81 (28.0)	67 (29.4)
Pulmonary vascular crackles	60 (20.8)	42 (18.4)
Elevated jugular venous pressure	35 (12.1)	19 (8.3)
Unspecified	19 (6.6)	7 (3.1)
Worsening 3rd heart sound	7 (2.4)	4 (1.8)
Without CRF information	5 (1.7)	2 (0.9)

Source: Adapted from the Applicant's Summary of Clinical Efficacy (page 84 of 150, and labeled as Tables 18).
Abbreviations: CRF, case report form; N, total number of events; n, number with the respective clinical manifestation.
* The percentages are derived using the total number of subjects with hHF as the denominator.

The adjudicated causes of death for subjects who were hospitalized for heart failure are presented in Table 15. Overall, the case fatality rate for subjects with hHF events, regardless of treatment assignment, was approximately 26%, attributed mostly to CV causes. Sudden cardiac death is not an uncommon cause of death for patients with heart failure. For the subjects who died of CV causes, a numeric imbalance was observed for sudden cardiac death that favored the placebo arm (i.e., 17 vs. 9 saxagliptin- and placebo-treated subjects, respectively). A numeric imbalance in sudden cardiac death was also reported for the mortality analysis that included all randomized subjects. Non-CV deaths occurred more frequently in the saxagliptin treatment arm (however 3 of these deaths were due to malignancy which is not likely to be related to hHF). Otherwise, there are no remarkable imbalances, and numbers are generally too small to draw meaningful conclusions. The overall case-fatality rate following hHF for saxagliptin vs. placebo was analyzed by the Applicant (HR 1.12; 95% CI, 0.79 to 1.60) with a point estimate favoring placebo, but a wide confidence interval.

Table 15: Adjudicated Causes of Death in the Subset of Subjects with hHF Events (ITT)

Most Likely Cause	Subjects with hHF Events	
	Saxagliptin (N=289) n (%)*	Placebo (N=228) n (%)*
All Deaths	**77 (26.6)**	**60 (26.3)**
Cardiovascular Death†	**66 (22.8)**	**56 (24.6)**
Heart failure or cardiogenic shock	39 (13.5)	36 (15.8)
Sudden cardiac death	17 (5.9)	9 (3.9)
Missing	5 (1.7)	3 (1.3)
Cerebrovascular event	2 (0.7)	5 (2.2)
Other cause	2 (0.7)	1 (0.4)
Acute MI	1 (0.4)	2 (0.9)
Non-Cardiovascular Deaths†	**11 (3.8)**	**4 (1.8)**
Pulmonary failure	1 (0.4)	0 (0.0)
Hemorrhage (not intracranial)	2 (0.7)	2 (0.9)
Malignancy	3 (1.0)	0 (0.0)
Renal failure	3 (1.0)	1 (0.4)
Infection	2 (0.7)	1 (0.4)

Source: Adapted from the Applicant's Summary of Clinical Efficacy (page 89 of 150, labeled as Table 20).
Abbreviations: MI, myocardial infarction; and N, number of subjects with an hHF event.
* The percentages are derived using the total number of subjects with hHF as the denominator.

In addition to over a quarter of patients dying following hHF events, a substantial number of subjects with hHF events in both treatment arms were subsequently readmitted for recurrent episodes of heart failure (i.e., 26.5% and 26.1% for saxagliptin and placebo arms, respectively) during the trial.

Biomarkers

In subjects with heart failure, serum and plasma concentrations of brain natriuretic peptide (BNP) increase, as do the concentrations of the biologically inactive prohormone, proBNP. ProBNP, comprising 108 amino acids, is secreted mainly by the left ventricle of the heart and, in this process, is cleaved into physiologically active BNP (77-108) and the N-terminal fragment NT-proBNP (1-76). Data exist to suggest that NT-proBNP determination helps to identify patients with heart failure, and changes in NT-proBNP concentration can be used to evaluate the success of treatment in patients with heart failure. However, it may be most useful clinically as an exclusion test due to consistent and very high negative predictive values.

NT-Pro BNP levels are loosely correlated with New York Heart Association (NYHA) functional class (Table 16).[21]

Table 16: Interpretive Levels of NT-ProBNP with Heart Failure (NYHA Function Class)

Interpretive Levels for HF		
Functional Class	**5th to 95th Percentile**	**Median**
I	31-1,110 pg/mL	377 pg/mL
II	55-4,975 pg/mL	1,223 pg/mL
III	77-26,916 pg/mL	3,130 pg/mL
IV	*	*

Source: Adapted from: http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/84291.
*In a Mayo Clinic study of 75 patients with CHF, only 4 were characterized as Class IV. Accordingly, range and median are not provided.[21]

In SAVOR the biomarker NT-proBNP was measured in 12,301 patients (74.6% of the overall trial) at randomization and in a randomly selected subset of patients at 2 years or the end of treatment, whichever was earlier. Blood samples were collected in serum separator plastic tubes and then centrifuged and stored frozen in aliquots at −20° to −80°C at the enrolling site until shipped to the Biomarker Research/TIMI Clinical Trials Laboratory (Boston, MA), where they were maintained at −80°C. Serum NT-proBNP concentrations were measured at the first thaw using a sandwich immunoassay[3].

The changes from baseline to year 2 or end-of-trial for NT-proBNP are presented in Table 17. There were no important treatment differences for changes from baseline for this variable.

Table 17: Mean and Median Changes from Baseline in NT-proBNP (pg/mL) (ITT)

	Treatment	**Baseline Value**				**Follow-up Value**			**Change from Baseline**		
		N	**Mean**	**Median (IQR)**	**SE**	**Mean**	**Median**	**SE**	**Mean (95% CI)**	**SE**	**Median**
NT-proBNP											
Baseline	Saxagliptin	6115	376	142 (65-336)	12						
	Placebo	6116	381	139 (63-330)	16						
Year 2/EoT	Saxagliptin	1012	250	107	17	331	122	29	81 (40, 122)	21	4
	Placebo	1008	275	107	48	348	126	41	73 (27, 118)	23	10

Source: Adapted from the Applicant's Clinical Study Report, Addendum 1 (pages 591-593 of 676, labeled as Tables 4.10.1, 4.10.2, and 4.10.3).
Abbreviations: CI, confidence interval; EoT, end of trial; NT-proBNP, N terminal pro-brain natriuretic hormone; SE, standard error.
Baseline defined as the last sample taken prior to first dose of Study drug usually (visit 1).
Laboratory assessments were taken during and up to 14 days after the last dose of double-blind treatment.

3 (proBNP II; Roche Diagnostics, Indianapolis, IN). Immunoassay for the in vitro quantitative determination of N-terminal pro-Brain natriuretic peptide in human serum and plasma, used as an aid in the diagnosis of individuals suspected of having congestive heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and congestive heart failure. The test may also serve as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease. Analytic range 5 to 35,000 pg/mL. Functional Sensitivity: 50 pg/mL. Within-run coefficient of variation 4.2% at a level of 44 pg/mL and 2.7% at a level of 33,606 pg/mL.
Source: http://www.accessdata fda.gov/cdrh_docs/reviews/K072437.pdf
NT-proBNP conversion: 300 pg/mL=35 pmol/L

The Applicant's time to first hHF event analysis based on the baseline NT-proBNP quartile is presented in Table 18. Subjects with a baseline NT-proBNP in the highest quartile were at greatest risk for hHF events in both treatment arms, although there was no significant treatment-by subgroup interaction.

In quartile 4 (NT-proBNP concentrations greater than 332 pg/mL) an excess risk for heart failure with saxagliptin vs. placebo was observed (HR 1.326, 95% CI, 1.05 to1.67).[22] Note that this risk is similar to the risk observed in the overall trial (reproduced here for convenience [HR 1.27, 95% CI, 1.07, 1.51]). The Applicant reported that the absolute risk excess for heart failure with saxagliptin was greatest in the highest NT-proBNP quartile (2.1%) compared with quartiles 1 (0.0%), 2 (0.7%), and 3 (0.2%). This finding was not sensitive to method as similar results were seen when evaluating NT-proBNP according to deciles or an established dichotomous cut point.

Table 18: Time to hHF by Baseline NT-proBNP (pg/mL) Quartile (ITT)

Quartile* Range (pg/mL)	Saxagliptin (N=8280)			Placebo (N=8212)			HR (95% CI)
	n	Events (%)	Events/ 100 PY	n	Events (%)	Events/ 100 PY	
1 (5 – 64)	1508	1 (0.07)	0.03	1550	1 (0.06)	0.03	1.040 (0.07 - 16.62)
2 (65 – 141)	1524	19 (1.25)	0.61	1534	10 (0.65)	0.32	1.830 (0.85 - 3.94)
3 (142-333)	1544	30 (1.94)	0.97	1515	32 (2.11)	1.05	0.909 (0.55 - 1.50)
4 (333 – 46,627)	1539	165 (10.72)	5.96	1517	126 (8.31)	4.50	1.326 (1.05 - 1.67)
							Interaction p-value 0.3973

Source: Adapted from the Applicant's Clinical Study Report, Addendum 1 (page 579 of 676, and labeled as Table 4.8.1).
Abbreviations: CI, confidence interval; HR, hazard ratio; N, sample size; and NT-proBNP, N-terminal pro-B type natriuretic peptide; PY, patient-years.
*The cutoff points for quartiles were: 25th - 64.12 pg/mL, 50th - 140.6 pg/mL, and 75th - 332.1 pg/mL.

In the Scirica et al paper, it was reported that in a subgroup analysis of patients with normal renal function and no reported history of heart failure, a level of NT-proBNP in quartile 4 (>332 pg/mL) was still associated with a higher risk of hospitalization for heart failure (4.3% versus 0.6%) compared with lower levels of NT-proBNP.[22]

Abnormal concentrations of circulating cardiac troponin are found in patients with HF, often without obvious myocardial ischemia and frequently in those without underlying CAD. This suggests ongoing myocyte injury or necrosis in these patients. In SAVOR, in the subset of patients with baseline and follow-up biomarkers, there were no meaningful differences between placebo and saxagliptin in the median change in concentrations from baseline to 2 years or end of treatment of high-sensitivity troponin T.

Premarketing Data

The Applicant stated that a safety signal for heart failure was unexpected and not previously observed in their preclinical and clinical development programs, or during postmarketing surveillance.

In the preclinical program, saxagliptin did not appear to have significant effects (i.e., <25% inhibition at 10 μM) on the 42 receptors and ion-channels and 11 enzymes tested in *in vitro* studies. In their *in vivo* studies, no relevant histopathologic or hemodynamic changes, or effects on conduction, contractility, and/or heart weight (a possible indicator of cardiac insufficiency) were reported across several species at exposure levels more than 50- to 600-fold the human equivalent dose of 5 mg for up to six to 12 months.

In the saxagliptin Phase 1 clinical program, there were no consistent effects on biomarkers of muscle injury (e.g., creatine kinase, AST, and/or lactate dehydrogenase) at doses up to 400 mg/day for 14 days. Saxagliptin had no significant prolongation effect on the QT interval in a Thorough QT Study.

No increase in the risk for heart failure was observed across a pool of 20 placebo-controlled Phase 2b/3 clinical trials involving 5701 saxagliptin-treated patients and 3455 controls.[14] However, in these trials hHF events were too few in number to be able to draw conclusions (i.e., 21 for saxagliptin-treated subjects vs. 18 for controls). The Phase 2b/3 clinical trial pool was comparatively younger, had a shorter duration of T2DM and had fewer co-morbid conditions (e.g., renal dysfunction) than the SAVOR population which was enriched for CV risk (Table 19). Therefore, the lack of an hHF safety signal in the premarketing development program is not reassuring for safety with regard to hHF in a sicker population.

Table 19: Comparison of Demographics and Baseline Characteristics between SAVOR and the Saxagliptin Phase 2b/3 Clinical Program

Patient Characteristics	SAVOR		Pool of 20 RCTs	
	Saxagliptin (n=8280)	**Placebo (n=8212)**	Saxagliptin (n=5701)	Comparator (n=3455)
Age, yr — number (%)				
<65	**3990 (48.2)**	**3941 (48.0)**	4681 (82.1)	2766 (80.1)
≥65	**4290 (51.8)**	**4271 (52.0)**	1020 (17.9)	689 (19.9)
≥75	**1169 (14.1)**	**1161 (14.1)**	132 (2.3)	91 (2.6)
Female sex — number (%)	**2768 (33.4)**	**2687 (32.7)**	2899 (50.9)	1696 (49.1)
Race — number (%)				
White	**6241 (75.4)**	**6166 (75.1)**	3707 (65.0)	2034 (58.9)
Asian	**896 (10.8)**	**884 (10.8)**	1319 (23.1)	1001 (29.0)
Black/African American	**278 (3.4)**	**290 (3.5)**	217 (3.8)	102 (3.0)
Other	**865 (10.4)**	**872 (10.6)**	458 (8.0)	318 (9.2)
BMI, kg/m^2 — number (%)				
<30	**3827 (46.2)**	**3820 (46.5)**	2914 (51.1)	1888 (54.6)
≥30	**4446 (53.7)**	**4370 (53.2)**	2780 (48.8)	1564 (45.3)
Duration of diabetes, yr — number (%)				
<5	**1975 (23.9)**	**1941 (23.6)**	3593 (63.0)	2081 (60.2)
≥5 to <10	**1957 (23.6)**	**1968 (24.0)**	1273 (22.3)	791 (22.9)
≥10	**4338 (52.4)**	**4298 (52.3)**	834 (14.6)	582 (16.8)
eGFR, mL/min — number (%)				
<30	**172 (2.1)**	**164 (2.0)**	37 (0.6)	41 (1.2)
30 to ≤50	**1122 (13.6)**	**1118 (13.6)**	90 (1.6)	68 (2.0)
>50	**6986 (84.4)**	**6930 (84.4)**	5571 (97.7)	3343 (96.8)

Source: Modified from Applicants' Clinical Study Report (pages 74-84 of 15624, labeled as Tables 10-13) and Iqbal et al., Cardiovasc Diabetol. 2014,13:33.[14]

Data from other DPP4 Inhibitors

DPP4 is an enzyme involved in the inactivation of regulatory peptides, neuropeptides, circulating hormones and chemokines.[23] This enzyme is expressed on the surface of T-lymphocytes, epithelial cells and endothelial cells, and is involved in the degradation of numerous biologically active peptides that may affect the heart.[24] Experimental (*in vitro* and *in vivo*) and clinical studies, suggest that inhibition of DPP4 may be associated with anti-inflammatory properties, improved metabolic effects, and ultimately, the potential for cardiovascular protection.[20,24] However, there is some concern that DPP4 inhibitors (e.g., sitagliptin) may augment sympathetic nervous system-mediated vasoconstriction[25] and renovascular response to angiotensin II,[26] possibly due to increased DPP4 substrates (i.e., neuropeptide Y, and/or substance P in the

presence of ACEIs[26,27]). The administration of alogliptin and sitagliptin for six weeks resulted in endothelial dysfunction (i.e., a reduction in flow-mediated dilatation),[28] considered an independent risk factor for CV events in diabetic patients.[29] Whether any of these effects may be implicated in the pathogenesis of heart failure with the use of saxagliptin is unknown.

In addition to SAVOR, four other large, randomized, double-blind, placebo-controlled CVOTs of DPP4 inhibitors have either been submitted for review or are ongoing.

The trial "Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE)" enrolled 5380 T2DM subjects post-acute coronary syndrome.[30] In EXAMINE, there were 195 hHF events, with numerically more events reported in the alogliptin (i.e., 106/2701 [2.6%]) vs. placebo (i.e., 89/2679 [2.2%] treatment arms (HR 1.19; 95% CI, 0.9, 1.6). While not statistically significant the point estimate favors placebo.

Other ongoing trials:

- Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS): N = ~14,000 subjects with preexisting CVD (ongoing, final data collection date for primary outcome measure is March 2015)[31]

- Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA): N = ~6000 subjects with pre-existing cardiovascular disease OR specified diabetes end-organ damage OR age ≥70 years OR two or more specified CV risk factors (ongoing; anticipated completion is September 2018)[32]

- Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA): N= ~8300 at high risk of CV events defined as albuminuria (micro or macro) AND previous macrovascular disease, AND/OR impaired renal function (ongoing; anticipated completion is January 2018)[33]

Additionally, the Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) Trial is a 52-week multicenter, randomized, double-blind, placebo-controlled clinical trial that evaluated the effects of vildagliptin 50 mg twice daily on left ventricular function in 254 subjects with T2DM (ages 18-85) and congestive heart failure (NYHA class I-III; baseline ejection fractions approximately 30%).[34] Although the findings of this trial have yet to be published, top-line results were presented at the Heart Failure Congress 2013 of the European Society of Cardiology Heart Failure Association.[35-37] This study met its primary end point of noninferiority compared with placebo for change in left ventricular ejection fraction (LVEF) from baseline to 52 weeks (i.e., 0.54; 95% CI, -1.97 to 3.06; p=0.670). Plasma BNP concentrations in both the vildagliptin and placebo arms decreased by 28% and 14%, respectively. However, increases in left ventricular end diastolic volume (LVEDV; 17.06 mL; 95% CI, 4.62 to 29.51, p=0.007), left ventricular end systolic volume (LVESV; 9.44 mL; 95% CI, -0.49 to 19.38 vs. placebo) and stroke volume (SV; p=0.002) in the vildagliptin arm were reported. There were also numerically more deaths in the vildagliptin arm (11 vs. 4 deaths, respectively). The placebo-subtracted difference in HbA1c change from baseline to week 16 was -0.62% (95% CI, -0.93 to -0.3). Since these data have not

been submitted to the Agency or undergone formal peer review, they should be interpreted with caution.

The results from published literature (e.g., meta-analyses, cohort studies) that assessed the risk of heart failure with DPP4 inhibitor use have been discordant, reporting either no risk,[38,39] an increased risk (~16 to 84%),[40,41] or a reduction in risk (~ -19 to -45%).[14,42] Limitations to these studies often included retrospective and/or observational study designs, limited generalizability of findings due to inclusion of healthier diabetic patients, inadequate power, failure to prespecify/validate endpoints, limited patient-level data, the potential for coding errors or outcome misclassifications, insufficient follow-up, and/or lack of formalized adjudication by independent, blinded specialists. These limitations and discrepant results highlight the utility of large, prospective, CVOTs with sufficient follow-up, and prespecified, independent, blinded adjudication of events by a CEC.

The possibility of a DPP4 inhibitor drug (or incretin) class effect must be considered. The discordance in smaller clinical trials and meta-analyses among drugs in the DPP4 inhibitor class and even between studies for the same DPP4 inhibitor could stem from the differing patient populations studied, with differing prevalence of heart failure, renal failure, or other variables at baseline. While FDA believes that results from other CVOTs are and will be extremely important in understanding heart failure risk, the possibility that the DPP4 inhibitors have varying degrees of impact on this safety outcome based on their particular characteristics (e.g., potency, selectivity for DPP enzymes), cannot be ruled out based on the currently available data.

Additional Considerations regarding hHF

In the published report of the SAVOR heart failure findings, the Applicant questions whether glycemic changes in the myocardium accustomed to years of hyperglycemia could potentially exacerbate cardiac dysfunction by altering the balance of free fatty acid oxidation and glycolysis (a compensatory mechanism to protect the heart against ischemia and infarction).[22] We were not able to assess the effect of glycemic control on the outcomes in SAVOR because HbA1c (or any measure of glycemia for that matter) was not routinely assessed during the trial, and there was too much missing data for a reliable analysis. Therefore, it is not possible to conclude that glycemic changes did not contribute to the hHF risk finding. However, if this were the case, a hospitalization for heart failure risk might be expected for antihyperglycemic agents in general.

As noted above, potential interactions of DPP-4 inhibitors with other drugs, e.g., ACEIs have been posited to have adverse hemodynamic consequences. Note, however, that it is not possible to definitively assess the effect of co-administration of saxagliptin and ACEI on heart failure risk because longitudinal changes cannot be evaluated (i.e., no details about the specific medication, dose, route of administration, or start and stop dates were collected).

The Applicant also performed additional analyses to evaluate whether other concomitant medications may be predictive of an increased risk for hHF events. With the exception of beta-blockers, which appeared to be associated with a lower risk for subjects with vs. without baseline use (HR 1.18; 95% CI, 0.97 to 1.43 vs. 1.82; 95% CI, 1.21 to 2.77, favoring placebo for both), there were no apparent treatment interactions for most baseline medication use. However,

compared to placebo, the rate to first hHF event was higher in the saxagliptin arm for subjects receiving insulin at baseline (HR 1.39; 95% CI, 1.09 to 1.77). Baseline sulfonylurea use did not appear to alter the risk for hHF events, and thiazolidinedione use was not explored further, since the numbers of subjects with hHF events receiving these medications were limited (i.e., 11 in the saxagliptin arm and 7 in the placebo arm). It should be noted that subjects were not randomized by baseline concomitant medication use, and therefore the results of these exploratory analyses may reflect other factors.

5.5 All-cause Mortality

As a reminder, vital status was available for 99.1% of the randomized subjects; only 147 subjects lacked vital status follow-up – 75 in the saxagliptin arm and 72 in the placebo arm.

Baseline Characteristics of Subjects Who Died During the Study

The baseline demographics and clinical characteristics of the subjects who remained alive or died during the study for the ITT population are presented by treatment group in Table 20. Subjects who died tended to be older, and were more likely to have renal impairment and long-standing diabetes. A smaller fraction of US subjects died in the saxagliptin arm than in the placebo arm, and this trend was reversed outside of the US.

Table 20: Select Subject Demographics and Clinical Characteristics for Subjects Who Died or Lived (ITT)

Patient Characteristics	Dead		Alive	
	Saxagliptin (N=420)	**Placebo (N=378)**	Saxagliptin (N=7860)	Placebo (N=7834)
Demographics				
Age ≤65 years	**165**	**126**	4206	4173
Age >65 years	**255**	**252**	**3654**	**3661**
Male	**293**	**266**	5219	5259
US region	**91**	**101**	2050	2044
Outside US region	**329**	**277**	5810	5790
Duration of T2DM <10 years	**166**	**142**	3766	3767
Duration of T2DM ≥10 years	**253**	**236**	4085	4062
Risk Factors				
Current smoking	**63**	**50**	1009	1097
Not current smoker	**357**	**328**	6850	6736
eGFR, mL/min				
>50	**288**	**250**	6698	6680
≥30 to ≤50	**105**	**103**	1017	1015
<30	**27**	**25**	145	139

Source: Derived from the adsl xpt, adth xpt, rsmh xpt, and rscm(1-5) xpt.
Abbreviations: eGFR, estimated glomerular filtration rate.

For the ITT population, a total of 420 on-study deaths (5.1%) were observed in the saxagliptin arm and 378 on-study deaths (4.6%) were observed in the placebo arm Table 21. All of these deaths were included in the pre-specified on-study analysis for all-cause mortality in the ITT population.

There were 9 off-study deaths, 4 in the saxagliptin arm and 5 in the placebo arm. These were not included in the all-cause mortality analyses and would not alter the findings from all-cause mortality analyses.

As shown in Table 21, the pre-specified Cox proportional hazards model based upon an on-study analysis for time-to-all-cause mortality estimated the hazard ratio to be 1.11 with an associated 95.1% confidence interval of (0.96, 1.27). The estimate of the hazard ratio indicates the potential for an excess risk of mortality in the saxagliptin arm, not a reduction. However, the confidence interval covers a hazard ratio of 1 and thus does not provide sufficient evidence to conclude that the hazard rates for all-cause mortality differ between treatment arms.

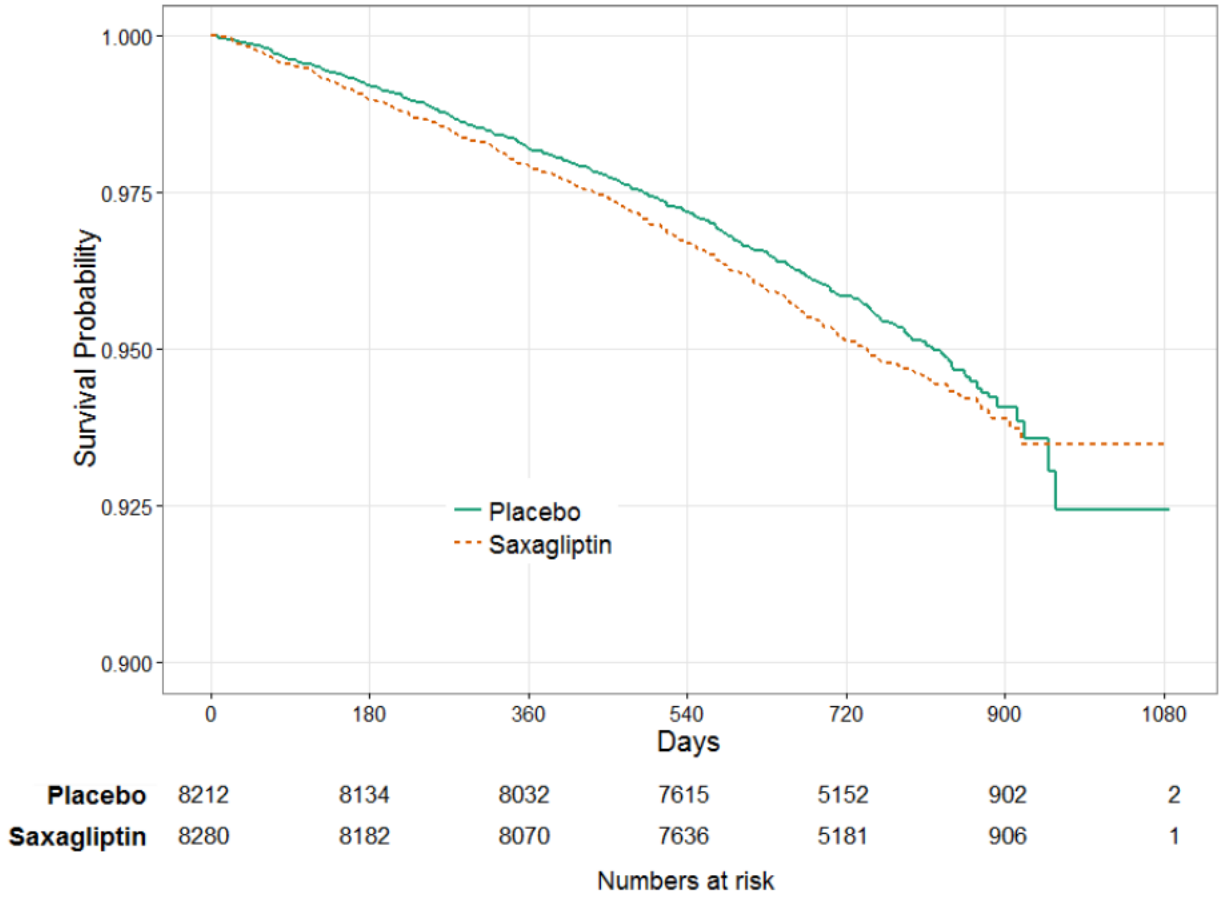
Table 21: Pre-specified Analysis for All-cause Mortality Endpoint (ITT)

	Saxagliptin N=8280	**Placebo N=8212**	**Hazard Ratio** (95.1% CI)
On Study Deaths (%)	420 (5.1%)	378 (4.6%)	1.11 (0.96, 1.27)

Source: FDA analysis using adth xpt. Information also available in Table 21 of Clinical Study Report (page 125/15624).

The Kaplan-Meier plot in Figure 5 indicates that the survival curve for the saxagliptin arm is consistently below (i.e. greater all-cause mortality) that for the placebo arm except after 900 days from randomization. However, the number of study subjects with follow-up greater than 900 days is relatively small and therefore the survival estimates computed for these large follow-up times are less precise.

Figure 5: Kaplan-Meier Survival Plot of All-cause Mortality (ITT on-study)



Source: FDA analysis using adth xpt. Figure 15 on page 126 of the Clinical Study report has an equivalent plot.

Sensitivity analyses on the mITT-FDA population are provided in Table 22 using on-study and on-treatment censoring schemes. The on-study mITT-FDA analysis results are similar to those obtained for the on-study ITT population. Although the point estimate of the hazard ratio indicates the potential for increased risk of all-cause mortality in the saxagliptin arm, the confidence interval does not indicate a statistically significant difference. The on-treatment

analysis with a censoring window of 30 days after last treatment dose indicates the potential of an increased risk with a lower bound for the confidence interval just below the null value of 1 [HR: 1.18, CI: (0.99, 1.39)]. The on-treatment analysis with a censoring window of 7 days after last treatment dose estimates a hazard ratio of 1.23 with 95.1% confidence interval of (1.02, 1.48) which suggests a significantly increased risk of all-cause mortality associated with saxagliptin at the unadjusted 4.9% level. Overall, there is a general trend of increasing hazard ratio estimates as follow-up for all-cause mortality is censored closer to treatment exposure.

Table 22: Sensitivity Analyses for All-cause Mortality Endpoint (mITT-FDA)

	Saxagliptin N=8240	**Placebo** N=8173	**Hazard Ratio*** (95.1% CI)
On-study Deaths	416 (5.1%)	376 (4.6%)	1.10 (0.96, 1.27)
On-treatment† + 30 days Deaths	297 (3.1%)	248 (2.5%)	1.18‡ (0.99, 1.39)
On-treatment† + 7 days Deaths	256 (3.1%)	204 (2.5%)	1.23 (1.02, 1.48)

† Events were censored at last dose + 30/7 days as appropriate.
* All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories.

Source: FDA analysis using adth xpt. Also available partly in Figure 16 of Clinical Study Report (page 127/15624).

Subgroup Analyses of All-cause Mortality

In an attempt to identify potential effect modifiers, the Agency performed exploratory subgroup analyses of the all-cause mortality endpoint (Table 23) for the ITT population that includes all deaths (i.e. on-study analysis). Results of these additional explorations did not clearly identify differences in all-cause mortality within subgroups except in the subgroup of subjects less than 65 years of age which resulted in a confidence interval that excludes 1, not favoring saxagliptin. It is not known if this finding is real or due to chance.

Table 23: All-Cause Mortality Subgroup Analysis (ITT – on study)

Subject Characteristic at Baseline	Saxagliptin N=8280	Placebo N=8212	Hazard Ratio (95% CI)
Age, years			
≤65 (N=8670; 52.6%)	165/4371 (3.8)	126/4299 (2.9)	1.28 (1.02, 1.63)
>65 (N=7822; 47.4%)	255/3909 (6.5)	252/3913 (6.4)	1.02 (0.86, 1.21)
Sex			
Female (N=5455; 33.1%)	127/2768 (4.6)	112/2687 (4.2)	1.10 (0.85, 1.42)
Males (N=11037; 66.9%)	293/5512 (5.3)	266/5525 (4.8)	1.11 (0.94, 1.31)
Race			
White (N=12407; 75.0%)	317/6241 (5.1)	300/6166 (4.9)	1.05 (0.89, 1.23)
Black or African American (N=586; 3.6%)	14/278 (5.0)	12/290 (4.1)	1.20 (0.56, 2.60)
Asian (N=1780; 10.8%)	36/896 (4.0)	25/884 (2.8)	1.42 (0.85, 2.37)
Native Hawaiian/other Pacific Islander (N=22; 0.1%)	1/11 (9.1)	0/11 (0)	-
American Indian or Alaska Native (N=51; 0.3%)	0/18 (0)	2/33 (6.1)	-
Multi-racial (N=1526; 9.3%)	48/768 (6.3)	34/758 (4.5)	1.43 (0.92, 2.23)
Other (N=138; 0.8%)	4/70 (5.7)	5/68 (7.4)	0.85 (0.23, 3.18)
Body Mass Index, kg/m^2			
<30 (N=7647; 46.4%)	207/3827 (5.4)	183/3820 (4.8)	1.13 (0.92, 1.37)
≥30 (N=8845; 53.6%)	213/4453 (4.8)	195/4392 (4.4)	1.09 (0.90, 1.32)
eGFR, mL/min			
>50 (N= 13916; 84.4%)	459/6986 (6.6)	452/6930 (6.5)	1.01 (0.88, 1.15)
≥30 to ≤50 (N= 2240; 13.6%)	128/1122 (11.4)	125/1118 (11.2)	1.01 (0.79, 1.30)
<30 (N= 336; 2.0%)	26/172 (15.1)	32/164 (19.5)	0.79 (0.47, 1.33)
HbA1c[1]			
≥8% (N=9453, 57.32%)	216/4751 (4.55)	182/4702 (3.87)	1.18 (0.97, 1.44)
<8% (N=6608, 40.07%)	188/3305 (5.69)	183/3303 (5.54)	1.03 (0.84, 1.26)
Duration of Diabetes[2]			
≥ 10 years (N=7841, 47.5%)	167/3932 (4.2)	142/3909 (3.6)	1.17 (0.93, 1.46)
< 10 years (N=8636, 52.4%)	254/4338 (5.9)	236/4298 (5.5)	1.06 (0.89, 1.27)
CVD Status			
Established CVD (N=12959, 78.6%)	357/6494 (5.5)	331/6465 (5.1)	1.08 (0.93, 1.25)
Multiple Risk Factors (N=3533; 21.4%)	63/1786 (3.5)	47/1747 (2.7)	1.32 (0.90, 1.93)

[1] There were 224 saxagliptin subjects and 207 placebo subjects missing HBA1c at baseline. Of these 16 saxagliptin and 13 placebo subjects were on-study deaths.

[2] 15 subjects had missing values for duration of diabetes (10 on saxagliptin arm and 5 on placebo) and were deleted from this analysis.

Source: FDA analysis using adtte.xpt, adsl.xpt, and adth.xpt.

Exploration of Causes of Death

To explore causes of death in more detail, we looked at all-cause mortality by adjudicated cause of death (Table 24).

Table 24: All-Cause Mortality by Adjudicated Cause of Death (ITT)

Cause of Death	Saxagliptin (N=8280)	Placebo (N=8212)
	n (%)	
All deaths	**420 (5.1%)**	**378 (4.6%)**
Overall CV death	269 (3.3%)	260 (3.2%)
Sudden cardiac death	131 (1.6%)	109 (1.3%)
Due to heart failure or cardiogenic shock	44 (0.5%)	40 (0.5%)
Missing	35 (0.4%)	42 (0.5%)
Due to an acute MI	23 (0.3%)	19 (0.2%)
Due to cerebrovascular event	22 (0.3%)	35 (0.4%)
Other cause	14 (0.2%)	15 (0.2%)
Overall non-CV death	151 (1.8%)	121 (1.5%)
Malignancy	53 (0.6)	58 (0.7)
Infection	46 (0.6)	28 (0.3)
Pulmonary failure	13 (0.2)	8 (<0.1)
Accident/trauma	11 (0.1)	5 (<0.1)
Renal failure	10 (0.1)	5 (<0.1)
Hemorrhage (not intracranial)	8 (<0.1)	3 (<0.1)
Other	5 (<0.1)	1 (<0.1)
Hepatic failure	3 (<0.1)	4 (<0.1)
Gastrointestinal causes	1 (<0.1)	4 (<0.1)
Suicide	1 (<0.1)	2 (<0.1)

Source: Derived from the adsl.xpt, adth.xpt, and adtte.xpt.
Abbreviations: eGFR, estimated glomerular filtration rate.

FDA reviewed clinical narratives for the non-CV death events. After reviewing a substantial number of narratives it became apparent that causes of death were often multifactorial and categorization based on adjudication could be misleading. We noted that a subject could have had multiple serious morbid medical conditions days to weeks prior to a death. While no egregious miscoding has been identified, the analysis of causes of death by examining adjudicated causes appears to be limited with regard to shedding light on the all-cause mortality signal. Some of the deaths that we reviewed could have been attributed to multiple categories. For this reason FDA is not reassured that the observation that causes of death span multiple disparate etiologies, and we do not necessarily view this pattern of variable cause as evidence the mortality signal is due to chance.

As a case-in-point, the following two clinical narrative summaries are provided (a full narrative for the first case is provided in Appendix 7.7):

> **E1931023:** 64 y/o White male with a history of dyslipidemia, hypertension and T2DM was randomized to saxagliptin 5 mg/day. The subject experienced treatment-emergent SAEs of pulmonary sarcoidosis (Day 425; a CT scan showed advanced pulmonary fibrosis); cholelithiasis (Day 461); hyperglycemia (Day 521); supraventricular tachycardia (Day 532); pancreatitis (Day 549; prolonged existing hospitalization and adjudicated as chronic pancreatitis); pneumonia (Day 576; hospitalized); congestive heart failure (Day 580); sub-diaphragmatic abscess (Day 601; hospitalized), and respiratory failure (Day 603; placed on a mechanical ventilation) that preceded a death adjudicated as 'respiratory failure' (Day 603). The subject was receiving saxagliptin at the time of death.

> **E8204052:** 74 y/o White female with a history of angina pectoris, dyslipidemia, hypertension, coronary artery disease, renal impairment, and T2DM was randomized to saxagliptin 2.5 mg/day. The subject experienced treatment-emergent SAEs of non-ST elevation MI (Day 164), congestive heart failure (Days 164 and 358), septic shock (Day 164), acute renal failure (Day 164; requiring dialysis), asthenia (Day 234), and renal failure (Day 358). She also developed the following AEOSI: urosepsis (Day 164), cellulitis of the left foot (Day 234), urinary tract infection (Days 234 and 356), acute cystitis (Day 234) left leg cellulitis (Day 358) and left heel wound (Day 326). The patient died on Day 371, adjudicated as renal failure. The subject was receiving saxagliptin at the time of death.

Additional difficulties encountered when reviewing narratives included questionable CV vs. non-CV adjudication. Standardized definitions and blinded adjudication processes are helpful for reducing bias in studies primarily designed for comparisons of MACE. However, in terms of elucidating an explanation for the all-cause mortality signal, these classifications have not been particularly useful.

As another case-in-point, the following narrative summary is shown:

> **E1078001:** 74 year old White male from Canada: On Day 651, the patient developed an event of Subarachnoid bleeding (PT: Subarachnoid haemorrhage). The event met SAE criteria on Day 651 and also was identified as a potential clinical endpoint by the investigator. This was a serious event because the patient was hospitalized on Day 651. The investigator became aware of the event on Day 657. The investigator reported the following: symptoms and course, "Patient was at the gym on treadmill, fell down unconscious and presented a cranial trauma. He received atropine to treat bradycardia and transferred to ER. The cause of the fall is not known."; diagnostic investigations and results, "ct scan shown subarachnoid bleeding and subdural hematoma, cranial and ethmoidal fracture suspected, not confirmed"; treatment of AE, "respiratory assistance, blood transfusion, IV fluid. Bad prognostic, surgery was not an option."; and other comments, "cerebral death declared on (b) (6) and died on (b) (6) They don't know what happen first, bradycardia 2nd to fall, bradycardia cause of fall." "Cervical brain CT scan on (b) (6) [showed] massive subarachnoid hemorrhage with some areas at the vertex as well, bilaterally, where concomitant subdural hematomas are suspected. There was slight pneumocephalus, especially at the base of the skull. Obliteration of the right sphenoidal sinus as well as several ethmoidal sinuses."; "[Per] medical death certificate, cause of death [was] cerebral death due to…traumatic brain injury, organ donation, [and] traumatic epistaxis, atherosclerotic heart disease, diabetes".
>
> The event was referred to the Clinical Event adjudication Committee and adjudicated: Death classification is cardiovascular death (death due to cerebrovascular event [primary hemorrhagic stroke]). Cerebrovascular event classification is stroke (CVA) with stroke type primary hemorrhagic. The patient died as a consequence of the stroke <=30 days from the date of onset.

Role of Intensive Glycemic Control

As noted previously, three large, randomized controlled trials (i.e., ACCORD,[8,9] ADVANCE,[10] and VADT[11]), which enrolled high-CV risk T2DM patient populations (e.g., long-standing T2DM, established CV disease and/or multiple CV risk factors) failed to demonstrate significant reductions in major adverse CV events with intensive glycemic control. In ACCORD, an increased mortality rate in the intensive (goal of <6%) compared with the standard care treatment arm was observed, but with a similar increase in cardiovascular deaths; no clear explanation was discovered. Intensive control was associated with higher rates of severe hypoglycemia in all three trials. The ADA states that 'Lowering A1C to approximately 7% or less has been shown to reduce microvascular complications of diabetes, and, if implemented soon after the diagnosis of diabetes, it is associated with long-term reduction in macrovascular disease. Those with long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets.'[43] The literature related to all-cause mortality reported in diabetes CVOTs is summarized in Appendix 7.8.

We considered HbA1c reduction in the saxagliptin arm as a possible contributing factor to the observation of increased all-cause mortality. Design features of SAVOR do not permit definitive evaluation of this hypothesis, but exploratory analyses are shown below. HbA1c was an exploratory endpoint and not included in the pre-specified testing hierarchy. HbA1c was measured at baseline, the annual follow-up visits, and at the end of treatment (EoT)/Closing visit. In essence, SAVOR and other CVOTs for type 2 diabetes are safety trials that enroll a vulnerable population to facilitate accruing a large number of events of the safety endpoint of interest, so that off-target effects of glucose-lowering therapies on MACE can be assessed. These trials are not designed to assess the effect of intensive glycemic control on MACE.

At one year, 87% of randomized subjects had an HbA1c value. Among the 13% of subjects for whom an HbA1c value was not reported, 376 (saxagliptin: 200; placebo: 176) died prior to their annual laboratory evaluation. At year two, 79% and 77% of subjects randomized to saxagliptin and placebo, respectively had an HbA1c value. Of those without a value, it could not be assessed for 743 subjects that died prior to the end of the analysis window (saxagliptin: 391; placebo: 352).

FDA analyzed change in HbA1c separately for years 1 and 2 using an ANCOVA model. For year 1, the analysis was performed on the subset of randomized patients that had a baseline and follow-up HbA1c value, or were alive at the end of the applicant's analysis window (1 year + 180 days). The analysis population for year 2 was defined in a similar manner. Missing HbA1c values were imputed using multiple imputation, where imputed values were centered about a subject's baseline value. FDA considered baseline centering reasonable as it approximates the average HbA1c change at year 1 for those no longer receiving study treatment.

Results from the FDA analysis are as follows. At year 1, the saxagliptin group had an estimated average excess HbA1c reduction of 0.30% compared to placebo with nominal 95% CI (0.27, 0.34). At year 2, the saxagliptin group had an estimated average excess HbA1c reduction of 0.24% compared to placebo with nominal 95% CI (0.19, 0.28).

It is noted that 24.5% (2028/8280) of subjects in the saxagliptin arm started non-IP antidiabetic medications during the study compared with 31.3% (2572/8212) of subjects in the placebo arm.

The following analyses were conducted by the Applicant and not confirmed by FDA. At baseline, approximately 25% (i.e., 4119/16492) of subjects randomized had baseline HbA1c concentrations <7%. In this patient subset, the rates per 100 patient-years for any hypoglycemia event were 8.32 and 5.59 for the saxagliptin and placebo control arms, respectively (HR 1.47; 95% CI, 1.24 to 1.75). Although events were infrequent (i.e., 45 vs. 24, respectively) the rate of major hypoglycemic events was also increased in the patient subset of baseline HbA1c <7% (HR 1.96; 95% CI, 1.20 to 3.26).

Further explorations of death by cause, e.g., CV and non-CV death conducted by the FDA are presented in the subsections below.

5.5.1 Cardiovascular Death

Exploratory analyses of adjudicated events of CV death Table 25 show that hazard ratio point estimates for CV death in all four analyses (ITT and mITT-FDA populations on-study analyses, and on-treatment+30 and -+7 day analyses) exceed 1; the on-study estimates for the ITT and the mITT-FDA populations are very similar – 1.04 and 1.03, respectively with the same 95.1% CI of (0.87, 1.23). The on-treatment+30 day and on-treatment+7 day estimates of hazard ratios are higher at 1.16 and 1.17 respectively, with 95.1% CI lower bounds of 0.96 and 0.95 respectively. This pattern is similar to the all-cause mortality analyses showing a general trend of increasing hazard ratio estimates as follow-up for CV-mortality is censored closer to treatment exposure.

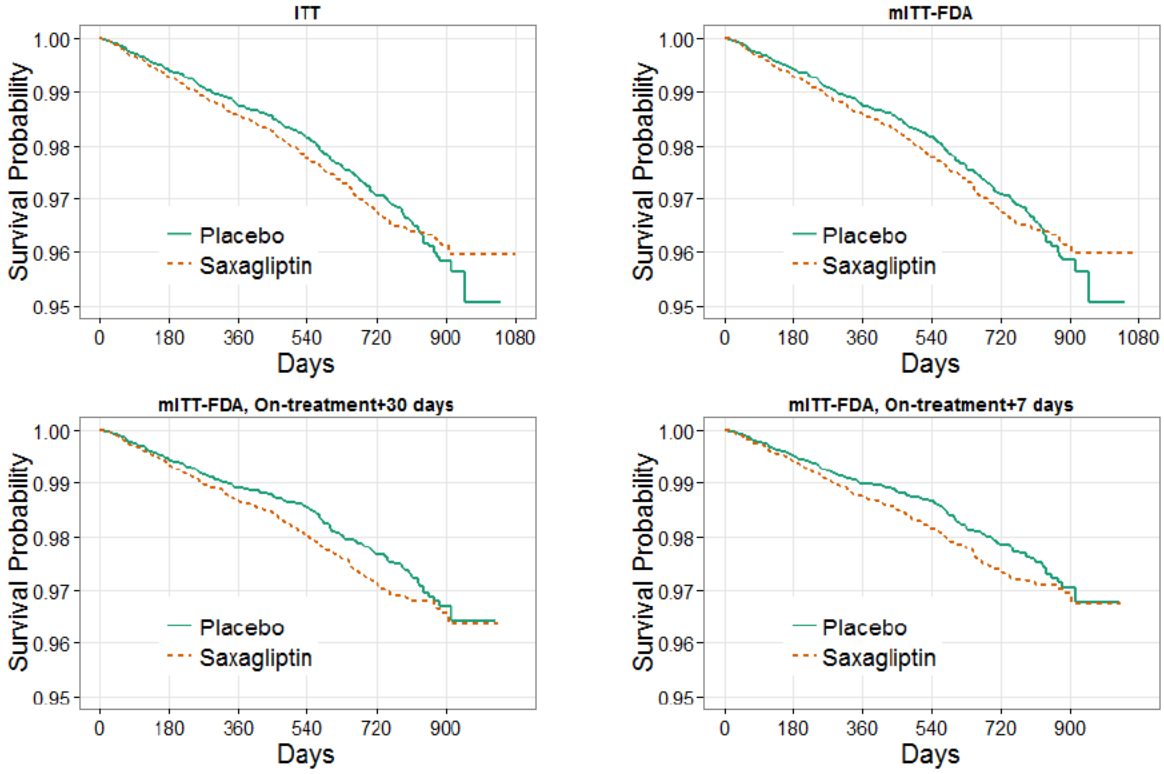
Table 25: Exploratory Analyses of CV Death (ITT and mITT-FDA)

	Saxagliptin	**Placebo**	**Hazard Ratio*** (95.1% CI)
ITT, On-study	269/8280 (3.2%)	260/8212 (3.2%)	1.03 (0.87, 1.23)
mITT-FDA, On-study	266/8240 (3.2%)	258/8173 (3.1%)	1.03 (0.86, 1.22)
mITT-FDA, On-treatment +30 days	216/8240 (2.6%)	182/8173 (2.2%)	1.17 (0.96, 1.42)
mITT-FDA, On-treatment+7 days	196/8240 (2.4%)	164/8173 (2.0%)	1.18 (0.95, 1.45)
* All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories.			

Source: FDA analysis using adth xpt.

Kaplan-Meier survival plots depicted in Figure 6 for all four analyses indicate that the CV-death-free survival curve for the saxagliptin arm is below that for the placebo arm and remains below it until about 800 days from randomization. The difference between the curves is larger for the on-treatment+30 day and on-treatment+7 day analyses. The curves appear to diverge early in the trial.

Figure 6: Kaplan-Meier Survival Plots for CV death (ITT and mITT-FDA)



Source: FDA analysis using adth xpt.

A summary of specific causes of adjudicated CV death is listed in Table 26 below. Among the CV deaths, the specific cause with the greatest numerical imbalance was 'Sudden cardiac death'.

Table 26: Adjudicated Causes of CV Deaths (ITT population)

Cause of CV Death	Saxagliptin (N=8280)	Placebo (N=8212)
	n (%)	
Overall CV death	269 (3.3%)	260 (3.2%)
Sudden cardiac death	131 (1.6%)	109 (1.3%)
Due to heart failure or cardiogenic shock	44 (0.5%)	40 (0.5%)
Missing	35 (0.4%)	42 (0.5%)
Due to an acute MI	23 (0.3%)	19 (0.2%)
Due to cerebrovascular event	22 (0.3%)	35 (0.4%)
Other cause	14 (0.2%)	15 (0.2%)

Source: FDA analysis using adth xpt.0

Because cardiac arrhythmias can be a cause of sudden cardiac death, we examined the incidence MedDRA PTs of cardiac arrhythmias among subjects who died with the adjudicated cause of 'sudden cardiac death'. The overall incidences were similar between groups.

Table 27: Adverse Events of Arrhythmia in the Subset of Subjects with Sudden Cardiac Death (ITT)

MedDRA High Level Group Term	Saxagliptin (N=131) n	Placebo (N=109) n
CARDIAC ARRHYTHMIAS	**32**	**30**
Preferred Terms		
Cardiac arrest	14	17
Cardio-respiratory arrest	8	5
Atrial fibrillation	7	3
Arrhythmia	2	2
Atrioventricular block complete	1	0
Extrasystoles	1	0
Ventricular fibrillation	1	2
Bradyarrhythmia	0	1
Tachyarrhythmia	0	1
Ventricular arrhythmia	0	1

Source: Derived from the rsdl xpt, rsae xpt, and adth xpt datasets.
Abbreviations: N, total number of events; n, number with the respective preferred term.

We also looked for evidence of an imbalance in arrhythmias among all subjects with adjudicated CV death. There were fewer reported cardiac arrhythmias in the saxagliptin arm.

Table 28: Adverse Events of Arrhythmia in the Subset of Subjects with CV Death (ITT)

MedDRA High Level Group Term	Saxagliptin (N=269) n	Placebo (N=260) n
CARDIAC ARRHYTHMIAS	**48**	**59**
Preferred Terms		
Cardiac arrest	16	22
Atrial fibrillation	14	16
Cardio-respiratory arrest	12	8
Arrhythmia	2	4
Extrasystoles	2	0
Ventricular arrhythmia	2	2
Atrioventricular block complete	1	1
Bradycardia	1	0
Ventricular fibrillation	1	2
Bradyarrhythmia	0	3
Nodal arrhythmia	0	1
Paroxysmal arrhythmia	0	1
Sick sinus syndrome	0	2
Tachyarrhythmia	0	1
Tachycardia	0	2
Ventricular tachycardia	0	2

Source: Derived from the rsdl.xpt, rsae.xpt, and adth.xpt datasets.
Abbreviations: N, total number of events; n, number with the respective preferred term.

Heart Failure as an Etiology

As is clear from data presented in previous sections, the data do not point to the all-cause mortality signal being simply due to an increased risk of hHF with immediate fatal complications. A possible more complex relationship between hHF and mortality was explored, but no important insight was gained. Overall, the case fatality rate for patients with hHF events, regardless of treatment was approximately 26% (Data shown previously). Within 14 days following an hHF event, there was a numeric imbalance in all-cause mortality not favoring saxagliptin (i.e., 17 v. 11 deaths in the saxagliptin and placebo treatment arms, respectively). These data are presented in Table 29. Heart failure is associated with sudden cardiac death. A numeric imbalance was observed for sudden cardiac death that favored the placebo arm (i.e., 17 v. 9 saxagliptin- and placebo-treated patients, respectively).

FDA looked at the Cardiac Failure Broad and Narrow MedDRA SMQs to examine incidence rates and look for patterns by vital status. However, FDA did not perform statistical analyses of the incidence rates. For the broad SMQ for Cardiac Failure for subjects alive at the end of the trial there were 635 reports in the saxagliptin group and 626 in the placebo group (8.12% vs. 8.03%), and for subjects who died there were 106 reports in the saxagliptin group and 103 in the placebo group (25.48% vs. 27.39%). For the narrow SMQ for Cardiac Failure for subjects alive at the end of the trial there were 293 reports in the saxagliptin group and 258 in the placebo group (3.74% vs. 3.31%). For subjects who died there were 90 reports in each group (21.63% vs. 23.94%). Additionally, searches of the datasets using Broad and Narrow Standardized MedDRA Queries (SMQ) for Cardiomyopathy, did not suggest a treatment difference in the all-cause death patient subset.

The effects of baseline NT-proBNP on the occurrence of all-cause mortality were assessed by the Applicant and by FDA (FDA results similar to Applicant's results, data not shown). The number of deaths included in the all-cause mortality and CV death categories increased with increasing baseline quartile of NT-proBNP, regardless of treatment assignment. The all-cause mortality and CV death analyses performed by the Applicant by NT-proBNP quartile is presented in Table 35. Patients with baseline NT-proBNP in the highest quartile (i.e., saxagliptin 196/1539 [12.74%] v. placebo 178/1517 [11.73%]) were at greatest risk for death from all causes. This was also observed for the CV death endpoint. The event rate per 100 patient-years for all-cause mortality and CV death increased with increasing baseline quartile of NT-proBNP, for both treatment arms. No differential treatment effect was observed in patients based on quartile of NT-proBNP compared to the overall SAVOR trial population for either death endpoint. These exploratory analyses do not help elucidate the reason for the all-cause mortality signal.

Table 29: Time to All-Cause Mortality or CV Death by Baseline NT-proBNP Quartile (ITT Population)

NT-proBNP Quartile at Baseline	Saxagliptin (N=8280			Placebo (N=8212)				Interaction p-value
Range (pg/mL)	N	Events (%)	Events/100 py	N	Events (%)	Events/100 py	HR (95% CI)	
All-Cause Mortality								
1 (5 – 64)	1508	14 (0.93)	0.44	1550	18 (1.16)	0.55	0.800 (0.40, 1.61)	0.4283
2 (65 – 141)	1524	37 (2.43)	1.17	1534	38 (2.48)	1.19	0.976 (0.62, 1.54)	
3 (142-333)	1544	72 (4.66)	2.29	1515	51 (3.37)	1.65	1.386 (0.97, 1.98)	
4 (333 – 46,627)	1539	196 (12.74)	6.67	1517	178 (11.73)	6.05	1.113 (0.91, 1.36)	
CV Death								
1 (5 – 64)	1508	5 (0.33)	0.16	1550	9 (0.58)	0.27	0.577 (0.19, 1.72)	0.5201
2 (65 – 141)	1524	18 (1.18)	0.57	1534	20 (1.3)	0.63	0.906 (0.48, 1.71)	
3 (142-333)	1544	43 (2.78)	1.37	1515	33 (2.18)	1.07	1.275 (0.81, 2.01)	
4 (333 – 46,627*)	1539	143 (9.29)	4.87	1517	136 (8.97)	4.62	1.053 (0.83, 1.33)	

Source: Modified from the Applicants Summary of Clinical Efficacy (page 103-104 of 150, labeled as Tables 27 and 28).
Abbreviations: CV, cardiovascular; CI, confidence interval; HR, hazard ratio; N, sample size; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; py, patient-year.
*Outliers: there were 5 subjects with values larger than 20000 -- all on the placebo arm, 3 of whom died and 2 lived.

5.5.2 Non-Cardiovascular Death

Exploratory analyses of non-CV deaths are presented in Table 30. Hazard ratio estimates for the ITT and mITT-FDA on-study analyses are similar with hazard ratio estimates of 1.24 and 1.23, respectively and 95.1% confidence intervals of (0.98, 1.58) and (0.97, 1.57), respectively. The hazard ratio estimate for the on-treatment+30 day analysis is 1.19 with an associated 95.1% confidence interval of (0.86, 1.64). A much larger hazard ratio estimate of 1.47 is estimated for the on-treatment+7 day analysis with associated 95.1% confidence interval of (0.98, 2.2).

Table 30: Exploratory Analyses of Non-CV Death (ITT and mITT-FDA)

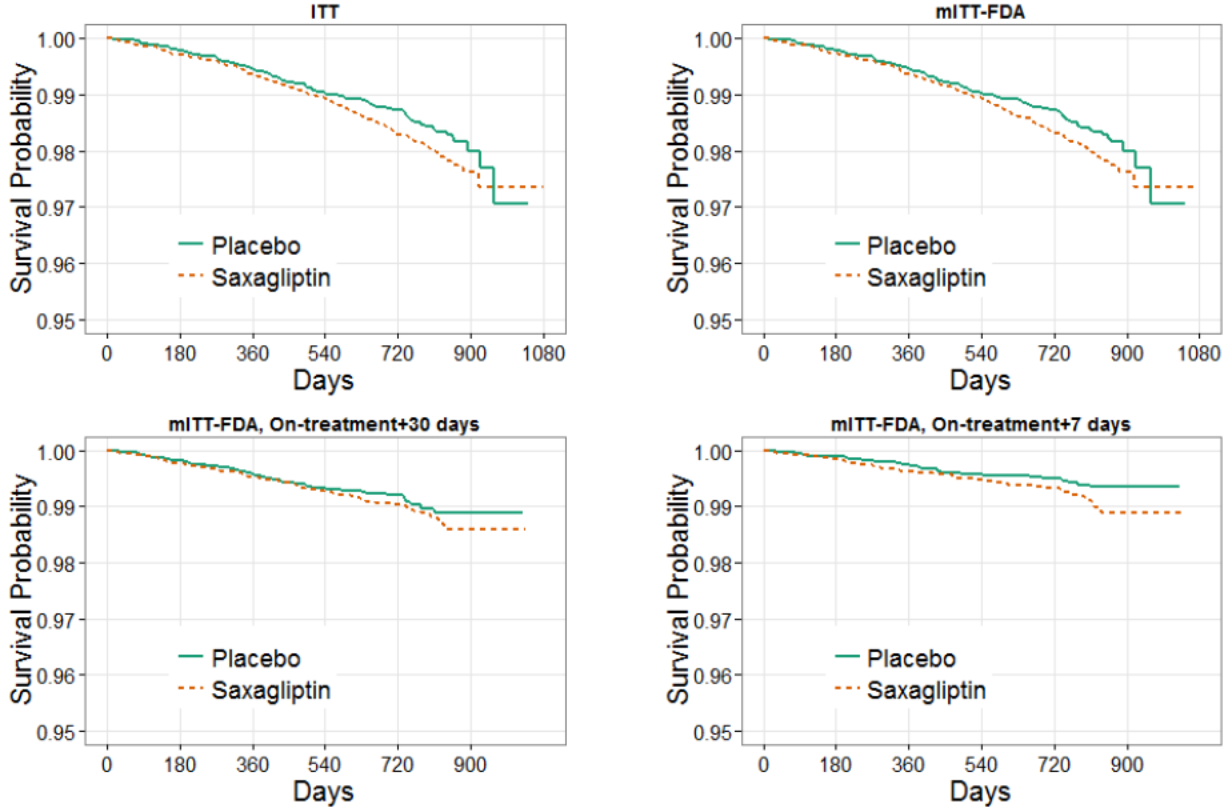
	Saxagliptin	Placebo	Hazard Ratio* (95.1% CI)
ITT, On-study	151/8280 (1.8%)	118/8212 (1.4%)	1.27 (1.00, 1.62)
mITT-FDA, On-study	150/8240 (1.8%)	118/8173 (1.4%)	1.26 (0.99, 1.61)
mITT-FDA, On-treatment +30 days	81/8240 (1.0%)	66/8173 (0.8%)	1.21 (0.87, 1.67)
mITT-FDA, On-treatment+7 days	60/8240 (0.7%)	40/8173 (0.5%)	1.47 (0.98, 2.2)

*All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories.

Source: FDA analysis using adth xpt.

Non-CV-death-free Kaplan-Meier survival curves are shown in Figure 7. While curves for the ITT and mITT-FDA on-study analyses begin to separate midway through the follow-up period, with decreased survival in the saxagliptin arm, the survival curves for the on-treatment+30 and on-treatment+7 day analyses are closer together until the end of the follow-up period.

Figure 7: Kaplan-Meier Survival Plots for non-CV Death (ITT and mITT-FDA)



Source: FDA analysis using adth xpt.

A summary of adjudicated causes of death for non-CV deaths are presented in Table 31 for the ITT population.

Table 31: Adjudicated Causes of Non-CV Deaths (ITT population)

Cause of Death	Saxagliptin (N=8280)	Placebo (N=8212)
	n (%)	
Overall non-CV death	**151 (1.8%)**	**121 (1.5%)**
Malignancy	53 (0.6)	58 (0.7)
Infection	46 (0.6)	28 (0.3)
Pulmonary failure	13 (0.2)	8 (<0.1)
Accident/trauma	11 (0.1)	5 (<0.1)
Renal failure	10 (0.1)	5 (<0.1)
Hemorrhage (not intracranial)	8 (<0.1)	3 (<0.1)
Other	5 (<0.1)	1 (<0.1)
Hepatic failure	3 (<0.1)	4 (<0.1)
Gastrointestinal causes	1 (<0.1)	4 (<0.1)
Suicide	1 (<0.1)	2 (<0.1)

Source: FDA analysis using adth xpt.

A summary of adjudicated causes of non-CV death are shown in Table 32 for the mITT-FDA population with both 7- and 30-day censoring windows.

Table 32: Adjudicated Causes of non-CV Deaths (mITT-FDA populations)

Cause of Death	Saxagliptin (N=8240)	Placebo (N=8173)	Saxagliptin (N=8240)	Placebo (N=8173)
Analysis Population	**mITT-FDA, On-treatment +7 days n (%)**		mITT-FDA, On-treatment +30 days n (%)	
Overall non-CV death	60 (0.7)	40 (0.5)	81 (1.0)	66 (0.8)
Infection	**16 (0.2)**	**12 (0.1)**	**25 (0.3)**	**15 (0.2)**
Malignancy	15 (0.2)	15 (0.2)	21 (0.3)	29 (0.4)
Accident/trauma	7 (0.1)	4 (<0.1)	10 (0.1)	4 (<0.1)
Renal failure	7 (0.1)	2 (<0.1)	8 (0.1)	3 (<0.1)
Pulmonary failure	6 (0.1)	1 (<0.1)	8 (0.1)	5 (0.1)
Hemorrhage (not intracranial)	5 (0.1)	0 (0)	5 (0.1)	2 (<0.1)
Other	3 (<0.1)	1 (<0.1)	3 (<0.1)	1 (<0.1)
Suicide	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (< 0.1)
Hepatic failure	0 (0)	2 (<0.1)	0 (0)	2 (<0.1)
Gastrointestinal causes	0 (0)	2 (<0.1)	0 (0)	4 (<0.1)

Source: FDA analysis using adth xpt.

Infection

The largest imbalance in adjudicated causes of non-CV death in the ITT population was seen for deaths related to infections (i.e., 46 in saxagliptin-treated subjects and 28 in the placebo control arm). Therefore, FDA explored serious events of infection in more details. These data (shown below) did not provide further insight into the mortality signal in terms of specific infection

types. Other adjudicated causes of death with numeric imbalances were explored and did not provide meaningful information (not shown in the background materials).

SAEs of infection that occurred within 30 days of death for all subjects who died are presented as MedDRA high level terms (HLTs) in Table 33. Overall, there were more subjects in the saxagliptin arm who experienced infections within 30 days of death in this subset of subjects. Higher proportions of saxagliptin-treated subjects had infection SAEs coded as lower respiratory tract/lung infections and sepsis HLTs compared to placebo.

Table 33: MedDRA High Level Term for All SAEs of Infections within 30 Days of Death for the Subset of Subjects Who Died (ITT)

MedDRA High Level Term	Saxagliptin (N=420)	Placebo (N=378)
	n	n
INFECTIONS AND INFESTATIONS	**64**	**44**
Lower respiratory tract and lung infections	32	19
Sepsis, bacteremia, viremia and fungemia NEC	22	13
Abdominal and gastrointestinal infections	6	3
Urinary tract infections	3	3
Clostridia infections	1	2
Streptococcal infections	1	0
Pseudomonal infections	1	1
Infections NEC	1	2
Adenoviral infections	1	0
Legionella infections	1	0
Pneumocystis infections	1	0
Retroviral infections	1	0
Staphylococcal infections	0	1

Source: Derived from the rsdl.xpt, rsae.xpt, and adth.xpt datasets.
Abbreviations: N, total number of events; n, number with the respective preferred term.

Premarketing data showed that saxagliptin is associated with small dose-related mean decreases in absolute lymphocyte count, although the decreases in lymphocyte count were not associated with clinically relevant adverse reactions. This information is in saxagliptin product labeling[1], and SAVOR, for which lymphocyte counts were an outcome of interest, appears to have confirmed the decreases in lymphocyte counts with saxagliptin (see section 4.6.3.1). The reason for this finding may possibly be related to the role of DPP4 in immune regulation.[44-47]

5.6 Additional Safety Findings

In this section, safety findings are presented for the ITT population, defined as all randomized subjects including all events that occurred during the study (also referred to as the "Overall"

population). In addition, safety findings are also presented for the mITT population (referred to as the "On-treatment" population), which included AEs occurring while the subject was on treatment. AEs were deemed on treatment if, for non-serious AEs, the event occurred on or before the first day after the last blinded drug dosing date, or for SAEs, the event occurred on or before the 30th day after the last blinded drug dosing date, or the individual/subject end-of-study date (whichever was earlier). All AEs were treatment-emergent.

The overall summary of adverse events reported in SAVOR is presented in Table 34 below. More than 70% of subjects, regardless of treatment assignment or analysis population, experienced an AE during the study, with approximately 24% experiencing at least one SAE following exposure. The proportions of subjects discontinuing study medication due to AEs or SAEs were similar between treatment arms.

Table 34: Summary of Adverse Events for the mITT and ITT Analysis Populations

Adverse Events	On-Treatment (mITT)*		Overall (ITT)	
	Saxagliptin (N=8240)	Placebo (N=8173)	Saxagliptin (N=8280)	Placebo (N=8212)
Number (%) of Subjects with:				
At least 1 AE	5976 (72.5)	5904 (72.2)	6100 (73.7)	6046 (73.6)
AE leading to death	107 (1.3)	90 (1.1)	149 (1.8)	119 (1.4)
At least 1 SAE	1996 (24.2)	1933 (23.7)	2148 (25.9)	2095 (25.5)
Permanently discontinued study medication due to SAE	129 (1.6)	159 (1.9)	129 (1.6)	159 (1.9)
Permanently discontinued study medication due to AE	405 (4.9)	410 (5.0)	406 (4.9)	410 (5.0)

Source: Adapted from the Applicant's Clinical Overview (page 33 of 68, labeled as Table 2), and confirmed with the rsae xpt and adsl xpt datasets.
Note: This table includes hypoglycemic events, but excludes adjudicated CV events as presented in the Applicant's Clinical Overview (page 33 of 68 and labeled as Table 2). There were an additional 2093 subjects (1059 saxagliptin subjects and 1034 placebo-treated subjects not included in these numbers.
Abbreviations: AE, adverse event; N, number; and SAE, serious adverse event.
*mITT (On-treatment) population included AEs on treatment if, for non-serious AEs, the event occurred on or before the first day after the last blinded drug dosing date, or for SAEs, the event occurred on or before the 30th day after the last blinded drug dosing date, or the individual/subject end-of-study date (whichever was earlier).

5.6.1 Nonfatal Serious Adverse Events

A total of 3874 subjects exposed (i.e., mITT analysis population) to study medication experienced SAEs (excluding the adjudicated CV events) during the double-blind treatment period, of which 1960 (23.8%) occurred in saxagliptin-treated subjects and 1914 (23.4%) subjects receiving placebo (please refer to Table 35). Although there were numerically higher numbers of SAEs in the saxagliptin treatment arm for many of the SOCs, events were similar for both the mITT and ITT analysis populations, without obvious imbalances between treatment arms.

Table 35: Nonfatal Serious Adverse Events by System Organ Class (mITT and ITT populations)

Body System or Organ Class	On-Treatment (mITT)		Overall (ITT)	
	Saxagliptin (N=8240)	Placebo (N=8173)	Saxagliptin (N=8280)	Placebo (N=8212)
ALL SAEs — number (%)	**1960 (23.8)**	**1914 (23.4)**	**2114 (25.5)**	**2075 (25.3)**
INFECTIONS AND INFESTATIONS	469 (5.7)	452 (5.5)	530 (6.4)	509 (6.2)
CARDIAC DISORDERS	361 (4.4)	408 (4.9)	394 (4.8)	439 (5.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	282 (3.4)	295 (3.6)	311 (3.8)	335 (4.1)
NERVOUS SYSTEM DISORDERS	203 (2.5)	190 (2.3)	232 (2.8)	208 (2.5)
GASTROINTESTINAL DISORDERS	189 (2.3)	220 (2.7)	182 (2.2)	209 (2.5)
VASCULAR DISORDERS	191 (2.3)	210 (2.6)	216 (2.6)	233 (2.8)
RENAL AND URINARY DISORDERS	163 (2.0)	136 (1.7)	192 (2.3)	166 (2.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	170 (2.1)	158 (1.9)	191 (2.3)	171 (2.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	167 (2.0)	142 (1.7)	189 (2.3)	157 (1.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	159 (1.9)	134 (1.6)	184 (2.2)	154 (1.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	155 (1.9)	151 (1.8)	166 (2.0)	166 (2.0)
METABOLISM AND NUTRITION DISORDERS	117 (1.4)	120 (1.5)	134 (1.6)	144 (1.8)
HEPATOBILIARY DISORDERS	62 (0.8)	73 (0.9)	75 (0.9)	78 (0.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	62 (0.8)	56 (0.7)	67 (0.8)	62 (0.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	35 (0.4)	42 (0.5)	44 (0.5)	47 (0.6)
PSYCHIATRIC DISORDERS	26 (0.3)	25 (0.3)	31 (0.4)	30 (0.4)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	27 (0.3)	25 (0.3)	31 (0.4)	31 (0.4)
EYE DISORDERS	23 (0.3)	25 (0.3)	27 (0.3)	26 (0.3)
INVESTIGATIONS	23 (0.3)	22 (0.3)	27 (0.3)	28 (0.3)
EAR AND LABYRINTH DISORDERS	20 (0.2)	14 (0.2)	21 (0.3)	15 (0.2)
IMMUNE SYSTEM DISORDERS	12 (0.1)	2 (<0.1)	13 (0.2)	6 (<0.1)
ENDOCRINE DISORDERS	9 (0.1)	5 (<0.1)	11 (0.1)	5 (<0.1)

Body System or Organ Class	On-Treatment (mITT)		Overall (ITT)	
	Saxagliptin (N=8240)	Placebo (N=8173)	Saxagliptin (N=8280)	Placebo (N=8212)
SURGICAL AND MEDICAL PROCEDURES	2 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)

Source: Applicant's Clinical Study Report (pages 9669-9679 of 15624, and labeled as Table 11.3.4.1.3, and confirmed using the rsae.xpt dataset available at: \\cdsesub1\evsprod\NDA022350\0166\m5\datasets.
Subjects with events in more than one category are counted in each of those categories.
This table does not include adjudication-confirmed CV events or hypoglycemic events.

5.6.2 Dropouts/Discontinuations

The proportions of subjects in the mITT population who discontinued study medications for AEs were similar between treatment arms (i.e., 4.7% and 4.9% in saxagliptin-treated subjects and placebo-treated subjects, respectively). The most frequently reported AEs leading to discontinuation of study medication (i.e., ≥0.2% in either treatment arm) included nausea, diarrhea, dizziness, headache, and abdominal pain (please refer to Table 36 below). The Applicant reports that discontinuations of study medication were similar when stratified by the CV risk categories (i.e., CVD vs. MRF).

Table 36: Adverse Events Leading to Discontinuation of Study Medications in ≥0.2% of Subjects (mITT)

Adverse Event MedDRA Preferred Term	Saxagliptin (N=8240)	Placebo (N=8173)
ALL Subjects with at Least 1 Event	**391 (4.7)**	**401 (4.9)**
Nausea	33 (0.4)	18 (0.2)
Diarrhea	24 (0.3)	21 (0.3)
Dizziness	19 (0.2)	16 (0.2)
Headache	18 (0.2)	12 (0.1)
Abdominal Pain	13 (0.2)	7 (<0.1)

Source: Derived from the Applicant's Clinical Study Report (pages 14594-14608 of 15624, and labeled as Table 11.3.5.1.1).

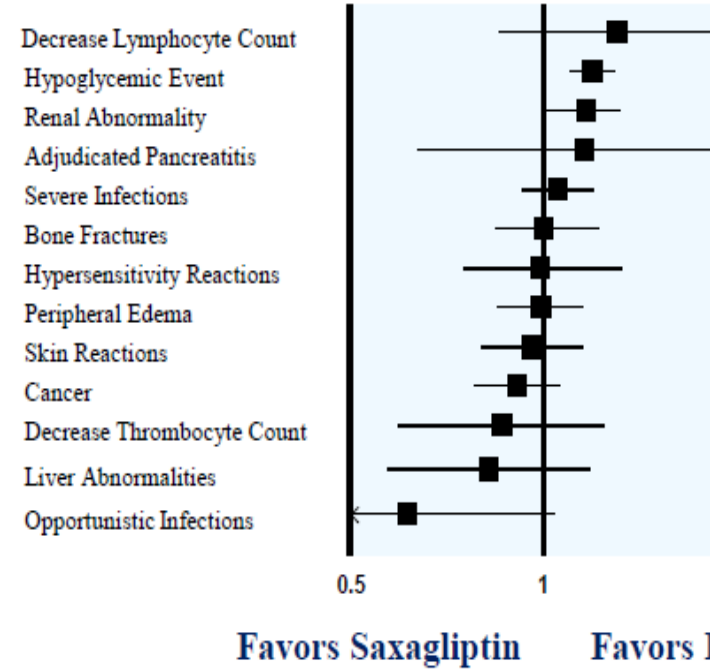
5.6.3 Adverse Events of Interest

In SAVOR, adverse events of special interest (AEOSI) were prespecified and in accordance with the PMR. They included: a decrease in lymphocyte or thrombocyte counts, severe infections, opportunistic infections, hypersensitivity reactions, liver abnormalities, bone fractures, skin reactions, pancreatitis, and renal abnormalities. A list of the prespecified MedDRA PTs for each AEOSI is included as an Appendix 7.5. These events were identified by the following three criteria:

1. Reported in the CRFs as an AEOSI by the clinical investigator
2. Searching the full database for MedDRA preferred terms (PTs) that match the prespecified list of terms for the respective AEOSI
3. Meeting prespecified clinical laboratory datasets for laboratory test results that meet prespecified laboratory criteria

The HR estimates provided by the Applicant for AEOSI are presented in Figure 8. Compared to the placebo control arm, the event rates of first AEOSI were higher for subjects in the saxagliptin arm for decreases in lymphocyte counts, renal abnormalities, adjudicated pancreatitis, and severe infections. Further discussion of these AEOSI is presented below. For the other AEOSI, an imbalance that favored the placebo control arm was not observed. Note that the Sponsor also included hypoglycemia in this analysis. However, hypoglycemia is not discussed in this section because comparisons would be confounded by differences in glycemic control. Severe hypoglycemia was discussed previously.

Figure 8: Forest Plot of Adverse Events of Special Interest (ITT)



Adverse Event of Special Interest	Total Patients	Saxagliptin Events	Saxagliptin Rate/100py	Placebo Events	Placebo Rate/100py	HR (95% CI)
Decrease Lymphocyte Count	16492	50	0.3	39	0.24	1.27 (0.84, 1.94)
Hypoglycemic Event	16492	1462	10.05	1276	8.61	1.16 (1.08, 1.25)
Renal Abnormality	16492	401	2.45	370	2.28	1.14 (1.00, 1.30)
Adjudicated Pancreatitis	16492	24	0.14	21	0.13	1.13 (0.63, 2.06)
Severe Infections	16492	585	3.63	567	3.54	1.03 (0.91, 1.15)
Bone Fractures	16492	241	1.47	240	1.47	1.00 (0.83, 1.19)
Hypersensitivity Reactions	16492	98	0.59	99	0.60	0.98 (0.74, 1.30)
Peripheral Edema	16492	347	2.13	353	2.18	0.98 (0.84, 1.13)
Skin Reactions	16492	236	1.44	247	1.52	0.95 (0.79, 1.13)
Cancer	16492	326	1.99	359	2.21	0.90 (0.77, 1.05)
Decrease Thrombocyte Count	16492	54	0.32	63	0.38	0.85 (0.59, 1.22)
Liver Abnormalities	16492	55	0.33	67	0.41	0.81 (0.57, 1.16)
Opportunistic Infections	16492	22	0.13	36	0.22	0.61 (0.35, 1.02)

Source: Adapted from the Applicant's Clinical Overview (pages 38-40 of 68, labeled as Figures 7, 8, 9).
Abbreviations: AEOSI, adverse event of special interest; CI, confidence interval; CRF, case report form; HR, hazard ratio; Lab, clinical laboratory parameter; PT, MedDRA preferred term; and py, patient-year.
Note: The CRFs, PTs and Labs were used to identify events of "decrease lymphocyte count," "renal abnormality," "decrease thrombocyte count," and "liver abnormalities," while CRFs, and PTs were used for most of the remaining AEOSI.

5.6.3.1 Decrease in Lymphocyte Count

In SAVOR, subjects experienced a reduction in the mean lymphocyte count from baseline to end of exposure in the saxagliptin treatment arm (i.e., -0.064×10^9 cells/L vs. 0.020×10^9 cells/L in the placebo arm), and with 22/7186 (0.3%) of saxagliptin-treated subjects and 14/7047 (0.2%) of subjects receiving placebo experiencing a marked laboratory abnormality in the lymphocyte count (i.e., $\leq 0.5 \times 109$ cells/L) for subjects who had any on-treatment measurements. No association between lymphocyte count change and infection was detected by the Applicant.

5.6.3.2 Renal Abnormalities

Renal abnormalities were prespecified as AEOSI in SAVOR, and included events recorded in the case report forms (CRF), investigator-reported AEs derived from a prespecified list of MedDRA PTs (Appendix 7.5), and laboratory abnormalities (assessed annually and at the EoT, and performed centrally). Laboratory renal abnormalities included at least one of the following: a doubling of serum creatinine from baseline, a serum creatinine concentration >6 mg/dL, or a categorical change from baseline in albuminuria (i.e., normoalbuminuria to microalbuminuria, and microalbuminuria and macroalbuminuria). Note that these endpoints included single occurrences, i.e., they did not have to be persistent.

Additionally, prespecified 'efficacy' endpoints for renal disease progression were included in the protocol: a doubling of serum creatinine; the composite of initiation of chronic dialysis and/or renal transplant and/or a serum creatinine of >6.0 mg/dL.

AE reporting:
There were more renal abnormality events reported in saxagliptin-treated subjects (5.8%) compared to subjects randomized to placebo (5.1%). Recall that the rate for the time-to-first renal abnormality adverse event (Figure 8) favored the placebo arm (HR 1.14; 95% CI, 1.00 to 1.30) in an analysis conducted by the Applicant. A more detailed breakdown of events is shown in (Table 37). The most frequently reported AE PTs included renal impairment (i.e., 2.1% [170/8280] vs. 1.9% [155/8212]), acute renal failure (1.4% [119/8280] vs. 1.2% [102/8212]), and renal failure (0.8% [70/8280] vs. 0.9% [72/8212]), for saxagliptin vs. placebo arms, respectively. The proportions of patients with renal events increased with worsening baseline renal function and increased age, regardless of treatment assignment, but differences between treatment arms for these subsets were not apparent.

Table 37: Number of Subjects with Renal Abnormalities (ITT)

Events	Saxagliptin (N=8280)	Placebo (N=8212)
ALL Renal Events	**483 (5.8)**	**422 (5.1)**
Events derived from the CRF	474 (5.7)	414 (5.0)
Events derived from AE PTs	358 (4.3)	325 (4.0)
Events derived from laboratory data	161 (1.9)	153 (1.9)

Source: Derived from the Applicant's Clinical Study Report (page 2028 of 12468, and labeled as Table 11.3.6.10.1.1).
Identification of AEs based on a prespecified list of MedDRA PTs (refer to Appendix 5, page 93).
Abbreviations: AE, adverse event; CRF, case report form; and PT, preferred term.

Laboratory results:
Changes from baseline to EoT in serum creatinine (i.e., 0.058 mg/dL in 6127 saxagliptin-treated subjects vs. 0.054 mg/dL in 5034 subjects randomized to placebo) and eGFR (i.e., -2.49 mL/min/1.73 m^2 in saxagliptin-treated subjects vs. -2.365 mL/min/1.73 m^2 in 5932 placebo-treated subjects, respectively) did not appear to favor either treatment arm. However, the saxagliptin treatment arm had numerically more subjects (i.e., 231/7238; 3.2%) with marked elevations in serum creatinine (i.e., >2.5 mg/dL) than the placebo control arm (i.e., 212/7104; 3.0%). Since not all patients had laboratory samples collected at each study visit, the number of subjects in theses analyses is lower than the number of subjects included in the ITT analysis population.

At baseline, the mean urine ACRs were 181 ± 675.8 mg/g in 7916 saxagliptin-treated patients vs. 179.2 ± 652.0 mg/g in 7844 placebo-treated patients). Mean changes from baseline to EoT were increased in 5838 saxagliptin-treated subjects (i.e., 22.2 ± 483.2 mg/g) and 5638 placebo-treated subjects (i.e., 56.9 ± 604.0 mg/g) for whom an ACR measurement was available. Shifts from normoalbuminuria (albumin to creatinine ratios [ACR] <30 mg/g) to microalbuminuria (ACR ≥30 to ≤300 mg/g) occurred in 14.8% (555/3743) of saxagliptin-treated patients vs. 16.9% (617/3641) of those randomized to placebo, and from microalbuminuria to macroalbuminuria (>300 mg/g) in 11.6% (181/1561) vs. 16.5% (249/1505) of subjects, respectively. These shifts favored the saxagliptin arm.

Differences in the time to first event of renal progression, in analyses performed by the Applicant, were not significantly different between treatment arms for other renal progression endpoints besides albuminuria (Table 38).

Table 38: Time to First Event of Renal Progression (ITT)

Renal Progression Endpoint	Saxagliptin (N=8280)			Placebo (N=8212)			HR (95% CI)
	N	Events (%)	Events/100 py	N	Events (%)	Events/100 py	
Variable							
Doubling of serum creatinine	8280	153 (1.8)	0.92	8212	147 (1.8)	0.89	1.04 (0.83, 1.30)
Dialysis and/or renal transplantation and/or serum creatinine >6.0 mg/dL	8280	51 (0.6)	0.31	8212	55 (0.7)	0.33	0.90 (0.61, 1.32)

Source: Adapted from the Applicant's Clinical Study Report (page 138 of 15624, labeled as Figure 22; and page 2090 of 15624, labeled as Table 11.2.3.1.1.1).

5.6.3.3 Pancreatitis and Pancreatic Cancer

Pancreatitis

In SAVOR, all potential cases of pancreatitis and related information (diagnosis, severity and concomitant risk factors), were reviewed and adjudicated by the CEC. In accordance with published guidelines,[49-51] the Applicant classified potential cases of pancreatitis as: 1) definite acute; 2) possible acute; 3) chronic; or 4) unlikely (definitions are provided in Appendix 7.3).

In total, 70 investigator-reported events of pancreatitis were observed in 63 subjects (i.e., 35 events in 33 saxagliptin-treated subjects and 35 events in 30 subjects receiving placebo). The exposure-adjusted rate of subjects with events per 1000 treatment-years (based on the first event) was two for each treatment arm. Discontinuation of study medication due to events were similar between saxagliptin (6/35 events) and placebo (7/35 events) arms. The median duration of pancreatitis events was seven days in the saxagliptin arm and 12 days in the placebo arm, with resolution observed for 80% (28/35) and 85.7% (30/35) of events, respectively. A single fatal event of pancreatitis was reported in the placebo arm.

The adjudication of pancreatitis cases was performed by two gastroenterologists blinded to treatment assignment. The adjudicated AEs of pancreatitis are presented in Table 39 below. The Applicant reported that adjudication-confirmed cases were similar between treatment arms, with 24 (0.3%) saxagliptin-treated subjects and 21 (0.3%) subjects in the placebo control arm having adjudicated events (HR 1.13; 95% CI, 0.63 to 2.06; Figure 8). However, more events of definite or possible acute pancreatitis were reported in the saxagliptin treatment arm (i.e., 22 subjects [0.3%] vs. 16 subjects [0.2%], respectively), with a numeric imbalance in definite acute pancreatitis events favoring the placebo control arm (i.e., 17 subjects vs. 9 subjects, respectively). In the published report of pancreatitis findings from SAVOR,[52] the authors reported that treatment arms were not statistically different for pancreatitis subgroups (i.e., definite acute, possible acute, and chronic), however occurrences of events were limited.

Table 39: Adjudicated Adverse Events of Pancreatitis (ITT)

Adverse Events	Saxagliptin (N=8280)	Placebo (N=8212)
PANCREATITIS	24 (0.3)	21 (0.3)
Definite acute pancreatitis	17 (0.2)	9 (0.1)
Typical abdominal pain	17	9
Acute pancreatitis enzymes	17	8
Pancreatitis abnormal imaging	6	3
Possible acute pancreatitis	6 (<0.1)	7 (<0.1)
Enzymes	4	4
Abnormal imaging	1	1
Past history	1	4
Chronic pancreatitis	2 (<0.1)	6 (<0.1)

Source: Modified from the Applicant's Clinical Study Report (page 1581 of 12468, labeled as Table 11.3.6.8.1.1).
Note: Since pancreatitis AEs were prespecified and adjudicated, the results from the ITT population are presented in this table.

Pancreatic Cancer

In 2013, the FDA issued a Drug Safety Communication to inform health care professionals on possible increased risk of pancreatitis and pancreatic duct metaplasia in subjects with T2DM treated with incretin mimetics, including the DPP4 inhibitor pharmacologic class.[53] Further, chronic pancreatitis may be associated with an increased risk for pancreatic cancer.[54-57] In response to a request from the Agency, all malignancies in SAVOR, including pancreatic cancers, were considered AEOSI. Pancreatic cancers were defined using the MedDRA HLGT pancreatic neoplasms malignant (excluding islet cell and carcinoid) and PTs pancreatic neuroendocrine tumor metastatic and pancreatic neoplasm.

The proportion of subjects with AEs of pancreatic cancer was relatively low for both treatment arms (i.e., 5 [<0.1%] vs. 12 [0.1%] for saxaglipin- and placebo-treated subjects, respectively), with fatal events occurring in two subjects in the saxagliptin arm and six subjects in the placebo arm (Table 40).

Table 40: Pancreatic Cancer Adverse Events (ITT)

Adverse Events	Saxagliptin (N=8280)	Placebo (N=8212)
Subjects with ≥1 pancreatic cancer adverse event	5 (<0.1)	12 (0.1)
Pancreatic carcinoma	2 (<0.1)	8 (<0.1)
Adenocarcinoma pancreas	1 (<0.1)	1 (<0.1)
Pancreatic carcinoma metastatic	1 (<0.1)	2 (<0.1)
Pancreatic neoplasm	1 (<0.1)	0
Pancreatic neuroendocrine tumor metastatic	0	1 (<0.1)

Source: Adapted from the Applicant's Clinical Study Report (page 6094 of 12468, labeled as Table 11.3.6.13.2.1).

5.6.3.4 Infections

In the ITT population, infection-related SAEs, identified using both the CRF and investigator-reported PTs, were reported in 7.1% (586/8280) of saxagliptin-treated subjects and 6.9% (567/8212) of subjects receiving placebo. In an analysis conducted by the Applicant, the HR for time to first infection-related SAE was reported as 1.03 (95% CI, 0.91 to 1.15) for saxagliptin compared to placebo (Figure 8). Discontinuations of study medication due to SAEs of infection occurred in 26 saxagliptin-treated subjects and 22 subjects in the placebo arm, while 37 (0.4%) and 25 (0.3%) subjects in the saxagliptin and placebo arms, respectively, had SAEs coded as 'leading to death.' Pneumonia was the most frequently reported MedDRA PT for SAEs of infection, and was reported for 1.8% (151/8280) vs. 1.4% (118/8212) of subjects, respectively. The Applicant notes that most events of pneumonia were identified by chest X-ray and treated with antibiotics, with subsequent resolution of the infection. The number of fatal pneumonia events (i.e., 11 vs. 7 events, respectively), favored the placebo arm.

Hepatotoxicity

Mean serum ALT, AST, and total bilirubin were within the normal laboratory reference limits, and changes from baseline were not clinically meaningful. The occurrence of marked elevations of both serum transaminase concentrations (associated with hepatocellular injury) and total bilirubin (associated with liver dysfunction) that met the biochemical criteria for potential Hy's Law cases did not favor either treatment group (Table 41). For these cases, the Applicant identified alternative etiologies, risk factors and concomitant medications known to be associated with hepatic impairment.

Table 41: Marked Abnormalities in Liver Enzyme and Function Tests (ITT)

Hepatic Parameter	Saxagliptin (N=7565)*	Placebo (N=7468)*
Marked Elevation of ALT and/or AST — number (%)		
Results reported concurrently and within 14 days of last dose		
ALT and/or AST >10 × ULN and total bilirubin >2 × ULN	2 (<0.1)	5 (<0.1)
ALT and/or AST >3 × ULN and total bilirubin >2 × ULN	11 (0.1)	18 (0.2)
ALT and/or AST >3 × ULN and total bilirubin >1.5 × ULN	17 (0.2)	20 (0.2)
Results reported any time during the study		
ALT and/or AST >3 ×ULN and total bilirubin >2 × ULN	14 (0.2)	23 (0.3)

Source: Modified from the Applicant's Clinical Study Report (page 10761 of 12468, labeled as Table 11.3.7.1.3.1.1).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
* Number of subjects within the treatment group with both measurements (i.e., transaminase plus total bilirubin).

Hypersensitivity

In the ITT population, AEOSI events of hypersensitivity (Appendix 7.5) were similar between treatment arms, occurring in 1.1% (98/8280) of saxagliptin-treated subjects and 1.2% (99/8212) of subjects receiving placebo (Applicant's analysis: HR 0.98; 95% CI, 0.74 to 1.30 in favor of saxagliptin; Figure 8). However, serious hypersensitivity reactions were reported in 14 saxagliptin-treated patients compared to four in the placebo arm. An imbalance in the occurrence of angioedema (i.e., 7 vs. 1 event) was also reported, of which most of these subjects were receiving an ACEI (i.e., 6 of the saxagliptin-treated subjects, as well as the single subject receiving placebo). Published reports suggest that drug-induced angioedema may be potentiated with concurrent use of ACEIs with DPP4 inhibitors.[58,59] ACEIs are known to be associated with these events possibly through inhibition of kinins, such as bradykinin and substance P, while concurrent use of DPP4 inhibitors may further decrease the catabolism of members of the kinin system (e.g., substance P).[58,59] Of the saxagliptin-treated patients with angioedema, five were reported as SAEs, and two were reported as non-serious AEs. One of these SAEs led to discontinuation of saxagliptin, while study treatment continued for the remaining six subjects. All events resolved and no recurrent events were reported. The single event of angioedema in the placebo arm resolved with discontinuation of the ACE inhibitor. Angioedema is listed in the WARNINGS AND PRECAUTIONS section of approved saxagliptin product labeling.[1]

Bone Fracture

Bone fractures were reported in 2.9% saxagliptin-treated subjects compared to 2.9% of subjects receiving placebo (Table 42). Events were also similar between treatment arms by age ≥65 years, gender, race, renal function, and duration of diabetes. There were 21 (0.3%) subjects in the saxagliptin arm and 25 (0.3%) subjects in the placebo arm who experienced recurrent fracture events.

Table 42: Summary Table of Bone Fractures (ITT)

Fracture Occurrence	Saxagliptin (N=8280)	Placebo (N=8212)
	n (%)	
Total number of subjects with fracture events	**241 (2.9)**	**240 (2.9)**
Age ≥65 years	132/4265 (3.1)	123/4250 (2.9)
Gender		
Females	104/2755 (3.8)	108/2674 (4.0%)
Males	112/5485 (2.0)	108/5499 (2.0%)
Race		
White	202/6241 (3.2)	197/6166 (3.2)
Other	33/2039 (1.6)	39/2046 (1.9)
Renal Function		
eGFR >50 mL/min	185/6986 (2.6)	181/6930 (2.6)
eGFR ≤50 mL/min	50/1294 (3.9)	55/1282 (4.2)
Duration of Diabetes		
<10 years	75/3932 (1.9)	98/3909 (2.5)
≥10 years	160/4338 (3.7)	138/4298 (3.2)

Source: Modified from the Applicant's Clinical Study Report (pages 1221-1231 of 12468, labeled as Tables 11.3.6.7.1.3-11.3.6.7.1.8).
Abbreviations: eGFR, estimated glomerular filtration rate.

Skin Reactions

The occurrence of skin reactions in the ITT population was similar between treatment arms, with 236/8280 (2.9%) and 248/8212 (3.0%) of saxagliptin- and placebo-treated subjects, respectively, experiencing events. 'Skin ulcer' was the MedDRA preferred term reported for the coding the majority of skin reactions. For 25 (0.3%) saxagliptin-treated subjects and 32 (0.4%) placebo-treated subjects, events were coded as SAEs. Of these, a single subject in the placebo arm experienced an SAE of toxic epidermal necrolysis and Stevens-Johnson syndrome. Twelve (01%) subjects in the saxagliptin arm and 14 (0.2%) in the placebo arm had recurrent events.

6 REFERENCES

1. Onglyza [package insert]. Prinston, NJ: Bristol-Myers Squibb Company; May 2013.
2. Boulton DW, Li L, Frevert EU, et al. Influence of renal or hepatic impairment on the pharmacokinetics of saxagliptin. Clin Pharmacokinet 2011;50:253-65.
3. National diabetes statistics report, 2014. Atlanta GA: Centers for Disease Control and Prevention, 2014 (Accessed February 13, 2015, at http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf).
4. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation 2009;119:1728-35.
5. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215-22.
6. Guidance for Industry. Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. Rockville, MD: Food and Drug Administration, February, 2008. (Accessed March 22, 2013, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071624.pdf).
7. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
8. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.
9. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419-30.
10. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
11. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39.
12. Guidance for Industry. Diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Silver Spring, MD: Food and Drug Administration, December, 2008 (Accessed February 13, 2015, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf).
13. Frederich R, Alexander JH, Fiedorek FT, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. Postgrad Med 2010;122:16-27.
14. Iqbal N, Parker A, Frederich R, Donovan M, Hirshberg B. Assessment of the cardiovascular safety of saxagliptin in patients with type 2 diabetes mellitus: pooled analysis of 20 clinical trials. Cardiovasc Diabetol 2014;13:33.
15. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266.

16. Hicks KA, Hung HMJ, Mahaffey KW, et al. Standardized definitions for endpoint events in clinical trials, October, 2010. (Accessed March 3, 2015, at http://www.clinpage.com/images/uploads/endpoint-defs_11-16-2010.pdf).
17. Hicks KA, Hung HMJ, Mahaffey KW, et al. Draft Definitions for CDISC. Standardized definitions for cardiovascular and stroke endpoint events in clinical trials, August, 2014. (Accessed March 3, 2015, at http://www.cdisc.org/system/files/all/standard/Draft%20Definitions%20for%20CDISC%20August%2020,%202014.pdf).
18. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173-95.
19. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26.
20. Fadini GP, Avogaro A. Cardiovascular effects of DPP-4 inhibition: beyond GLP-1. Vascul Pharmacol 2011;55:10-6.
21. Test ID: PBNP. NT-pro B-type natriuretic peptide (BNP), serum. Rochester, MN: Mayo Clinic, 2015 (Accessed March 18, 2015, at http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/84291).
22. Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579-88.
23. Mentlein R. Dipeptidyl-peptidase IV (CD26)--role in the inactivation of regulatory peptides. Regul Pept 1999;85:9-24.
24. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. Endocr Rev 2012;33:187-215.
25. Jackson EK, Mi Z. Sitagliptin augments sympathetic enhancement of the renovascular effects of angiotensin II in genetic hypertension. Hypertension 2008;51:1637-42.
26. Marney A, Kunchakarra S, Byrne L, Brown NJ. Interactive hemodynamic effects of dipeptidyl peptidase-IV inhibition and angiotensin-converting enzyme inhibition in humans. Hypertension 2010;56:728-33.
27. Devin JK, Pretorius M, Nian H, Yu C, Billings FTt, Brown NJ. Substance P increases sympathetic activity during combined angiotensin-converting enzyme and dipeptidyl peptidase-4 inhibition. Hypertension 2014;63:951-7.
28. Ayaori M, Iwakami N, Uto-Kondo H, et al. Dipeptidyl peptidase-4 inhibitors attenuate endothelial function as evaluated by flow-mediated vasodilatation in type 2 diabetic patients. J Am Heart Assoc 2013;2:e003277.
29. Hadi HA, Suwaidi JA. Endothelial dysfunction in diabetes mellitus. Vasc Health Risk Manag 2007;3:853-76.
30. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327-35.
31. Green JB, Bethel MA, Paul SK, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. Am Heart J 2013;166:983-9 e7.
32. CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes. ClinicalTrials.gov Identifier: NCT01243424 (accessed March 10, 2015 at: https://clinicaltrials.gov/ct2/show/NCT01243424?term=carolina+and+linagliptin&rank=1).

33. CARMELINA: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus . ClinicalTrials.gov Identifier: NCT01897532 (accessed March 17, 2015 at: https://clinicaltrials.gov/ct2/show/NCT01897532).
34. VIVIDD: Vildagliptin in Ventricular Dysfunction Diabetes Trial. ClinicalTrials.gov Identifier: NCT00894868 (accessed March 10, 2015 at: https://clinicaltrials.gov/ct2/show/NCT00894868?term=vildagliptin+and+congestive+heart+failure&rank=1).
35. Vildagliptin shows no adverse effect on ejection fraction in diabetic patients with HF. France: European Society of Cardiology, 2013 (accessed March 20, 2015 at: http://www.escardio.org/congresses/hf2013/congress-to-you/Pages/vildagliptin-shows-no-adverse-effect-ejection-fraction-diabetic-patients-with-heart-failure.aspx).
36. Data shed light on vildagliptin in diabetes, heart failure. Thorofare, NJ: Healio Endocrine Today, 2013 (accessed March 20, 2015 at: http://www.healio.com/endocrinology/cardiometabolic-disorders/news/print/endocrine-today/%7B7cc89706-896b-4582-8c88-0851c4e100f7%7D/data-shed-light-on-vildagliptin-in-diabetes-heart-failure).
37. McMurray J. The vildagliptin in ventricular dysfunction diabetes (VIVIDD) trial. The Heart Failure Congress; May 25-28, 2013; Lisbon, Portugal. Abstract 99(available at: http://spo.escardio.org/SessionDetails.aspx?eevtid=61&sessId=10923&subSessId=0&searchQuery=/default.aspx?eevtid%3d61%26days%3d%26topics%3d%26types%3d%26rooms%3d%26freetext%3dlate%2bbreaking%2btrials%26sort%3d1%26page%3d1%26showResults%3dTrue%26nbPerPage%3d20%26scroll%3D0).
38. Chen DY, Wang SH, Mao CT, et al. Sitagliptin and cardiovascular outcomes in diabetic patients with chronic kidney disease and acute myocardial infarction: A nationwide cohort study. Int J Cardiol 2014;181C:200-6.
39. Yu OH, Filion KB, Azoulay L, Patenaude V, Majdan A, Suissa S. Incretin-based drugs and the risk of congestive heart failure. Diabetes Care 2015;38:277-84.
40. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol 2015;3:105-13.
41. Weir DL, McAlister FA, Senthilselvan A, Minhas-Sandhu JK, Eurich DT. Sitagliptin use in patients with diabetes and heart failure: a population-based retrospective cohort study. JACC Heart Fail 2014;2:573-82.
42. Kim SC, Glynn RJ, Liu J, Everett BM, Goldfine AB. Dipeptidyl peptidase-4 inhibitors do not increase the risk of cardiovascular events in type 2 diabetes: a cohort study. Acta Diabetol 2014;51:1015-23.
43. American Diabetes Association. Standards of medical care in diabetes — 2015. Diabetes Care 2015;38:S1-S93.
44. Ansorge S, Bank U, Heimburg A, et al. Recent insights into the role of dipeptidyl aminopeptidase IV (DPIV) and aminopeptidase N (APN) families in immune functions. Clin Chem Lab Med 2009;47:253-61.
45. Reinhold D, Biton A, Goihl A, et al. Dual inhibition of dipeptidyl peptidase IV and aminopeptidase N suppresses inflammatory immune responses. Ann N Y Acad Sci 2007;1110:402-9.

46. Reinhold D, Goihl A, Wrenger S, et al. Role of dipeptidyl peptidase IV (DP IV)-like enzymes in T lymphocyte activation: investigations in DP IV/CD26-knockout mice. Clin Chem Lab Med 2009;47:268-74.
47. Thompson MA, Ohnuma K, Abe M, Morimoto C, Dang NH. CD26/dipeptidyl peptidase IV as a novel therapeutic target for cancer and immune disorders. Mini Rev Med Chem 2007;7:253-73.
48. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Meyboom RH, Egberts TC, Leufkens HG. Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. Diabetes Care 2011;34:369-74.
49. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.
50. Bradley EL, 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg 1993;128:586-90.
51. Lerch MM. Classifying an unpredictable disease: the revised Atlanta classification of acute pancreatitis. Gut 2013;62:2-3.
52. Raz I, Bhatt DL, Hirshberg B, et al. Incidence of pancreatitis and pancreatic cancer in a randomized controlled multicenter trial (SAVOR-TIMI 53) of the dipeptidyl peptidase-4 inhibitor saxagliptin. Diabetes Care 2014;37:2435-41.
53. FDA drug safety communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas form incretin mimetic drugs for type 2 diabetes. Silver Spring, MD: Food and Drug Administration, March 14, 2013. (Accessed March 04, 2015, at http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm).
54. Bracci PM, Wang F, Hassan MM, Gupta S, Li D, Holly EA. Pancreatitis and pancreatic cancer in two large pooled case-control studies. Cancer Causes Control 2009;20:1723-31.
55. Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol 2012;23:2964-70.
56. Ekbom A, McLaughlin JK, Karlsson BM, et al. Pancreatitis and pancreatic cancer: a population-based study. J Natl Cancer Inst 1994;86:625-7.
57. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993;328:1433-7.
58. Brown NJ, Byiers S, Carr D, Maldonado M, Warner BA. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. Hypertension 2009;54:516-23.
59. Byrd JB, Shreevatsa A, Putlur P, et al. Dipeptidyl peptidase IV deficiency increases susceptibility to angiotensin-converting enzyme inhibitor-induced peritracheal edema. J Allergy Clin Immunol 2007;120:403-8.
60. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288-98.
61. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909.

62. Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010;33:983-90.
63. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854-65.
64. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837-53.

7 APPENDICES

7.1 Inclusion and Exclusion Criteria of SAVOR (adapted from the Clinical Protocol, pages 43-45)

Inclusion Criteria

For inclusion in the study, subjects should fulfil the following criteria:

1. Provision of informed consent prior to any study-specific procedures

2. Age ≥40 years

3. Diagnosed with T2DM based on the current American Diabetes Association guidelines

4. HbA1c ≥6.5% (based on the last measured and documented laboratory measurement in the previous 6 months)

5. High risk for a CV event defined as having either established CV disease and/or multiple risk factors:

   Established CV disease:

   - Ischemic heart disease, and/or
   - Peripheral vascular disease (e.g., intermittent claudication), and/or
   - Ischemic stroke

   Multiple Risk Factors:

   Subject must be at least 55 years old (men) and 60 years old (females) and have at least one additional risk factor (treated or non-treated) from the following:

   - Dyslipidemia (based on the last measured and documented laboratory measurement in the previous 6 months and defined as at least 1 of the following):
     - High level of low-density lipoprotein cholesterol (LDL-C), defined as >130 mg/dL (> 3.36 mmol/L)
     - Low level of high-density lipoprotein cholesterol (HDL-C), defined as <40 mg/dL (<1.04 mmol/L) for men or <50 mg/dL (<1.30 mmol/L) for women
   - Hypertension, as confirmed at the enrolment visit

- BP >140/90 mm/Hg or on a BP-lowering agent with BP >130/80 mm/Hg

- Currently smoking, as confirmed at the enrolment visit

6. Women of childbearing potential (WOCBP) must take precautions to avoid pregnancy throughout the study and for 4 weeks after intake of the last dose.

   Men participating in the study should also take precautions not to father a child while participating in the study and for 4 weeks after intake of the last dose.

   WOCBP must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to the start of study medication.

   WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥2 consecutive years).

Exclusion Criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Any conditions that, in the opinion of the Investigator, may render the subject unable to complete the study including non-CV disease (e.g., active malignancy, cardiomyopathy, cirrhosis, or chronic lung disease) with a likely fatal outcome within 5 years

2. Current or previous (within 6 months) treatment with an incretin-based therapy such as DPP4 inhibitors and or GLP-1 mimetics

3. Acute vascular (cardiac or stroke) event <2 months prior to randomization

4. Initiation of chronic dialysis and/or renal transplant and/or a serum creatinine >6.0 mg/dL

5. Pregnant or breast-feeding subjects

6. History of human immunodeficiency virus

7. Subjects being treated for severe auto immune diseases such as lupus

8. Any subject currently receiving chronic (>30 consecutive days) treatment with an oral steroid

9. Subjects with:

- Body mass index >50 kg/m^2
- Last measured HbA1c ≥12%
- Sustained BP >180/100 mm Hg
- LDL-C >250 mg/dL (> 6.48 mmol/L) (based on the last measured and documented laboratory measurement in the previous 6 months)
- Triglycerides >1000 mg/dL (>11.3 mmol/L) (based on the last measured and documented laboratory measurement in the previous 6 months)
- HDL-C <25 mg/dL (<0.64 mmol/L) (based on the last measured and documented laboratory measurement in the previous 6 months)
- Known liver function tests >3 times upper limit of normal (ULN), (based on the last measured and documented laboratory measurement in the previous 6 months)

10. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca and BMS or representative staff and/or staff at the study site)
11. Previous randomization in the present study
12. Participation in another clinical study with IP and/or intervention within 30 days prior to Visit 1
13. Individuals at risk for poor protocol or medication compliance

7.2 Endpoint Definitions for Adjudication of CV Clinical Events

The following information was adapted from the Applicant's Clinical Event Committee Charter, pages 13-24 of 45.

DEATH

Cardiovascular Death

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Sudden Cardiac Death:** refers to death that occurs unexpectedly in a previously stable subject and includes the following deaths:

    a. Witnessed and instantaneous without new or worsening symptoms

    b. Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms

    c. Witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic)

    d. Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology

    e. Unwitnessed death or other causes of death (information regarding the subject's clinical status within the week preceding death should be provided)

2. **Death due to Acute Myocardial Infarction:** death occurring up to 14 days after a documented acute myocardial infarction [verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus] and where there is no conclusive evidence of another cause of death.

    If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

    Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

3. **Death due to Heart Failure or Cardiogenic Shock:** refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death. New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

    a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a subject already receiving maximal therapy for heart failure.

    b. Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration

    c. Confinement to bed predominantly due to heart failure symptoms

    d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

    e. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

    Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

    - Cool, clammy skin or
    - Oliguria (urine output <30 mL/hour) or
    - Altered sensorium or
    - Cardiac index <2.2 L/min/m^2

    Cardiogenic shock can also be defined as SBP ≥90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour.

    The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study endpoint.

    This category will include sudden death occurring during an admission for worsening heart failure.

4. **Death due to Cerebrovascular Event** (intracranial hemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after a suspected stroke based on clinical

signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death.

Definition of Death due to Stroke: refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

5. **Death due to Other Cardiovascular Causes:** death must be due to a fully documented cardiovascular cause not included in the above categories (e.g., dysrhythmia, pulmonary embolism, or cardiovascular intervention).

Non-Cardiovascular Death

Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death and is categorized as follows:

- Pulmonary causes
- Renal causes
- Gastrointestinal causes
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome [SIRS])
- Malignancy (i.e., new malignancy, worsening of prior malignancy)
- Hemorrhage, not intracranial
- Accidental/Trauma
- Suicide
- Non-cardiovascular system organ failure (e.g., hepatic failure)
- Non-cardiovascular surgery

Presumed Cardiovascular Death

Presumed Cardiovascular Death: All deaths not attributed to the categories of cardiovascular death and not attributed to a non-cardiovascular cause, are presumed cardiovascular deaths and as such are part of the cardiovascular mortality endpoint.

ACUTE CORONARY SYNDROMES

Myocardial infarction

All myocardial infarctions (MIs) will be counted as events whether they represent the reason for the hospitalization or occurred during a hospitalization. In addition, they will be counted as events whether they occurred spontaneously or as the direct consequences of an investigation/procedure or operation. In order to meet the criteria as an endpoint, an MI must be distinct from the qualifying event (i.e., re-infarction for a subject who qualified for the study based on recent MI). The definition of MI as an endpoint will take into account whether a subject had a recent MI or has undergone revascularization with PCI or CABG surgery. In cases where both cardiac troponin and CK-MB are available (drawn at similar time points) and are discordant, biomarker criteria will be applied using cardiac troponin. The definitions of MI are as follows for the 4 clinical settings in which it may occur:

A. Spontaneous MI (normal biomarkers) - For subjects with no recent revascularization in whom biomarkers were never elevated or have been documented to return to normal after a qualifying (or recent) MI, criteria 1 & 2 or criterion 3 or criterion 4 must be met:

1. Typical cardiac biomarker rise and/or fall with the following degrees of elevation accepted as biochemical evidence of myocardial necrosis (either one or both):

    - Troponin T or I: maximal concentration greater than the MI decision limit
    - CK-MB: maximal concentration greater than the ULN

AND

2. At least 1 of the following additional supportive criteria:

    (a) Ischemic discomfort at rest lasting >10 minutes or

    (b) ECG changes indicative of ischemia (ST elevation >0.1 mV or ST depression >0.05 mV, or new T-wave inversions) OR

3. Development of new, abnormal Q waves (>30 msec in duration and >1 mm in depth) in >2 contiguous precordial leads or >2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction

OR

4. Pathologic findings of an acute MI.

B. Spontaneous MI (Elevated biomarkers) - For subjects with no recent revascularization in whom biomarkers from a qualifying (or recent) MI remain elevated, criteria 1 and 2, or criterion 3, or criterion 4 must be met:

1. Cardiac biomarker re-elevation defined as:

    (a) Increase by at least 20% of the previous value; and

    (b) Documentation that the biomarker assayed was decreasing prior to the suspected new MI;

AND

2. At least 1 of the following additional supportive criteria:

    (a) Ischemic discomfort at rest lasting >10 minutes; or

    (b) ECG changes indicative of ischemia (ST elevation >0.1 mV or ST depression >0.05 mV, or new T-wave inversions); OR

3. Development of new, abnormal Q waves (>30 msec in duration and >1 mm in depth) in >2 contiguous precordial leads or >2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction;

OR

4. New elevation of ST-segments >0.1 mV in >2 contiguous precordial or adjacent limb leads

AND

    (a) Ischemic discomfort at rest lasting >20 minutes; or

    (b) Ischemia-mediated new hemodynamic decompensation requiring pharmacologic or mechanical support; or

    (c) Angiographic evidence of acute coronary occlusion

C. Within 24 hours after PCI a subject must have EITHER:

1. CK-MB >3× ULN and, if the pre-PCI CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

OR

2. Pathologic findings of an acute MI.

Note: symptoms are not required.

D. Within 24 hours after CABG a subject must have EITHER:

1. CK-MB >5× ULN and, if the pre-CABG CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

AND

2. At least one of the following supportive criteria:

    (a) Development of new, abnormal Q waves (>30 msec in duration and >1 mm in depth) in >2 contiguous precordial leads or >2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction, or

    (b) Angiographically documented new graft or native coronary occlusion, or

    (c) Imaging evidence of new loss of viable myocardium

OR

3. Pathologic findings of an acute MI.

Note: symptoms are not required.

Note: If cardiac troponin measurements are the only cardiac biomarker data available, they may be used by the CEC, along with the ECG and clinical scenario, in the adjudication of suspected MI after revascularization (PCI or CABG).

The reviewers should also consider the clinical features (e.g., renal insufficiency), possible alternative diagnoses (e.g., pericarditis), pattern of marker release (e.g., absence of a rise and/or fall), and known sensitivity/specificity of the various cardiac markers in the adjudication of infarction, particularly when there is discordance in the results of multiple markers.

Universal Definitions of MI Criteria

Myocardial infarctions will be also be classified according to the following universal definition of MI criteria:

- Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.

- Type 2: MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.

- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by

angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

- Type 4a: MI associated with PCI.
- Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy.
- Type 5: MI associated with CABG.

ST-Segment Elevation MI versus Non-ST-segment Elevation MI

All events meeting criteria for MI* will also be classified as either ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), or unknown.

- **STEMI** – To be classified as a STEMI the event must meet all of the above criteria for myocardial infarction and one of the four criteria below.
  - New ST segment elevation at the J point in ≥2 contiguous leads, defined as: ≥0.2 mV in men (>0.25 mV in men <40 years) or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads. Subjects must have an interpretable ECG (i.e., without evidence of left ventricular hypertrophy or pre-existing left bundle branch block), or
  - New left bundle branch block
- **NSTEMI** – To be classified as a NSTEMI the event must meet all of the above criteria for myocardial infarction and not meet criteria for classification as STEMI. In order to be classified as NSTEMI there must be adequate interpretable ECG documentation associated with the event.
- **Unknown** – Events which meet criteria as specified above for MI but do not meet criteria for STEMI or NSTEMI. All cases where ECG documentation of the acute event is missing, inadequate, or uninterpretable should be classified as Unknown.

* All events adjudicated as MI will be classified as STEMI, NSTEM, or Unknown; however, it is acknowledged that a significant proportion of peri-procedural (PCI or CABG) events may have missing, inadequate or uninterpretable ECG documentation.

Unstable Angina requiring hospitalization

Unstable angina requiring hospitalization is defined as

a. No elevation in cardiac biomarkers (cardiac biomarkers are negative for myocardial necrosis)

AND

b. Clinical Presentation (one of the following) with cardiac symptoms lasting ≥10 minutes and considered to be myocardial ischemia on final diagnosis

   1. Rest angina or

   2. New-onset (<2 months) severe angina (Canadian Cardiovascular Society Grading Scale* (or CCS classification system) classification severity 2 III) AND

c. Requiring an unscheduled visit to a healthcare facility and overnight admission (does not include chest pain observation units) AND

d. At least one of the following:

   1. New or worsening ST or T wave changes on ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of LVH and LBBB:

      a. ST elevation

         New transient (known to be <20 minutes) ST elevation at the J-point in two contiguous leads with the cut-off points:

         - ≥0.2 mV in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads

         - ST depression and T-wave changes

         New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1.

   2. Evidence of ischemia on stress testing with cardiac imaging

   3. Evidence of ischemia on stress testing without cardiac imaging but with angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery or initiation/increased dosing of antianginal therapy.

   4. Angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery

Urgent Coronary Revascularization

The diagnosis of urgent coronary revascularization requires both of the two following criteria are met:

1. Ischemic chest pain (or equivalent) at rest ≥10 minutes in duration or repeated episodes at rest lasting 25 minutes considered to be myocardial ischemia upon final diagnosis

AND

2. Prompting hospitalization and percutaneous coronary revascularization within 7 days of symptoms or surgical coronary revascularization within 14 days of symptoms.

CEREBROVASCULAR EVENTS

Stroke

Stroke is defined as an acute focal neurological deficit of sudden onset,

(a) that is not reversible within 24 hours or results in death (in <24 hrs) and is not due to an identifiable non-vascular cause (i.e., brain tumor, trauma), or

(b) that resolves in <24 hrs and is accompanied by clear evidence of a new stroke on cerebral imaging

Stroke will be sub-classified into one of the following 4 groups:

Non-hemorrhagic Cerebral Infarction - Stroke without focal collections of intracerebral blood on a brain imaging. This category will be sub-classified into suspected embolic vs other.

Non-hemorrhagic Infarction with Hemorrhagic Conversion - Cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. Hemorrhagic conversion usually occurs on the cortical surface. Hemorrhagic conversion in the deeper brain requires evidence of nonhemorrhagic infarction in the same vascular territory.

Microhemorrhages evident on gradient echoMRI, whether in the cortex or deep brain structures, are not considered to be consistent with a hemorrhagic conversion endpoint.

Primary Hemorrhagic

Intracerebral Hemorrhage - Stroke with focal collections of intracerebral blood seen on a brain image (CT or MRI) or a postmortem examination, not likely to represent hemorrhagic conversion. Primary hemorrhages cause hematomas which are usually easily discriminated by their subcortical location and rounded or elliptical shape. Microhemorrhages incidentally discovered on brain imaging in the absence of associated symptoms will not be considered to be a primary intracranial hemorrhage endpoint.

Subarachnoid hemorrhage - High density fluid collection in subarachnoid space on brain images or blood in the subarachnoid space on autopsy

Uncertain - Any stroke without brain image (CT or MRI) or autopsy documentation of type, or if tests are inconclusive

Subdural hematoma will not be classified as a stroke but will be classified as a bleeding event (intracranial hemorrhage).

Intracerebral microhemorrhages will be classified in a separate category for analysis. Microhemorrhage is defined as rounded foci of <10mm that appear hypointense and that are distinct from other causes of signal loss on gradient-echo MRI sequences (e.g. vascular flow voids, leptomeningeal hemasidarosis, or non-hemorrhagic subcortical mineralization).

Transient ischemic attack is defined by:

(a). an acute focal neurological deficit ending lasting <24 hours, and not due to an identifiable non-vascular cause (i.e., brain tumor, trauma), and

(b). absence of new infarct on brain imaging (if obtained)

HEART FAILURE REQUIRING HOSPITALIZATION

Heart Failure (HF) requiring hospitalization is defined as an event that meets the following criteria:

a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available).

AND

b. Clinical manifestations of heart failure including at least one of the following:

New or worsening

- dyspnea
- orthopnea
- paroxysmal nocturnal dyspnea
- edema
- pulmonary basilar crackles

- jugular venous distension
- new or worsening third heart sound or gallop rhythm, or
- radiological evidence of worsening heart failure.

AND

c. Additional/Increased therapy

1. Initiation of intravenous diuretic, inotrope, or vasodilator therapy

2. Up-titration of intravenous therapy, if already on therapy

3. Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

   Biomarker results (e.g., brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

CORONARY REVASCULARIZATION PROCEDURE

A coronary revascularization procedure is defined as either coronary artery bypass graft surgery (CABG) or a percutaneous coronary intervention (PCI) (e.g., angioplasty, coronary stenting) that required or prolonged hospitalization. CABG is defined as the successful placement of at least one conduit with either a proximal and distal anastomosis or a distal anastomosis only. PCI is defined as successful balloon inflation with or without stenting and the achievement of a residual stenosis <50%. The balloon inflation and/or stenting could have been preceded by device activation (e.g., angiojet, directional coronary atherectomy, or rotational atherectomy).

7.3 Definitions for Adjudication of Pancreatitis Events

The following information was adapted from the Applicant's Clinical Event Committee Charter, pages 25-26 of 45.

The diagnosis, severity, and concomitant risk factors were adjudicated for all cases of suspected pancreatitis.

Diagnosis:

1. Definite Acute Pancreatitis (must have 2 out of the following 3 criteria):
    a. Typical abdominal pain (e.g., unremitting pain)
    b. Enzymes - serum amylase and/or lipase >3 UNL
    c. Abnormal imaging consistent with acute pancreatitis

2. Possible Acute Pancreatitis
    a. Atypical abdominal symptoms (without clear alternative diagnosis) plus at least one of the following criteria:
        i. Enzymes - serum amylase and/or lipase >3 UNL
        ii. Abnormal imaging consistent with acute pancreatitis
        iii. Past history of pancreatitis

3. Chronic pancreatitis based on medical history and /or cross sectional imaging

4. Unlikely to be pancreatitis (None of the above definitions)

Severity (only assessed for Definite or Possible Acute Pancreatitis):

Severe: Single or multi organ failure >48 hours duration or death or
Non-severe: All other cases

Risk factors:

Risk factors for pancreatitis identified (select all applicable)

- Gallstones
- Alcohol
- Hypertriglyceridemia
- Hypercalcemia
- ERCP
- Postoperative
- Trauma
- Concomitant drugs
- Renal failure
- Inflammatory bowel disease
- Cancer
- Open label GLP1 mimetics or DPP4 inhibitors
- Recent Viral Disease
- Other _____specify_____

7.4 Clinical Events Adjudication

Adjudication Committee for Cardiovascular Events:

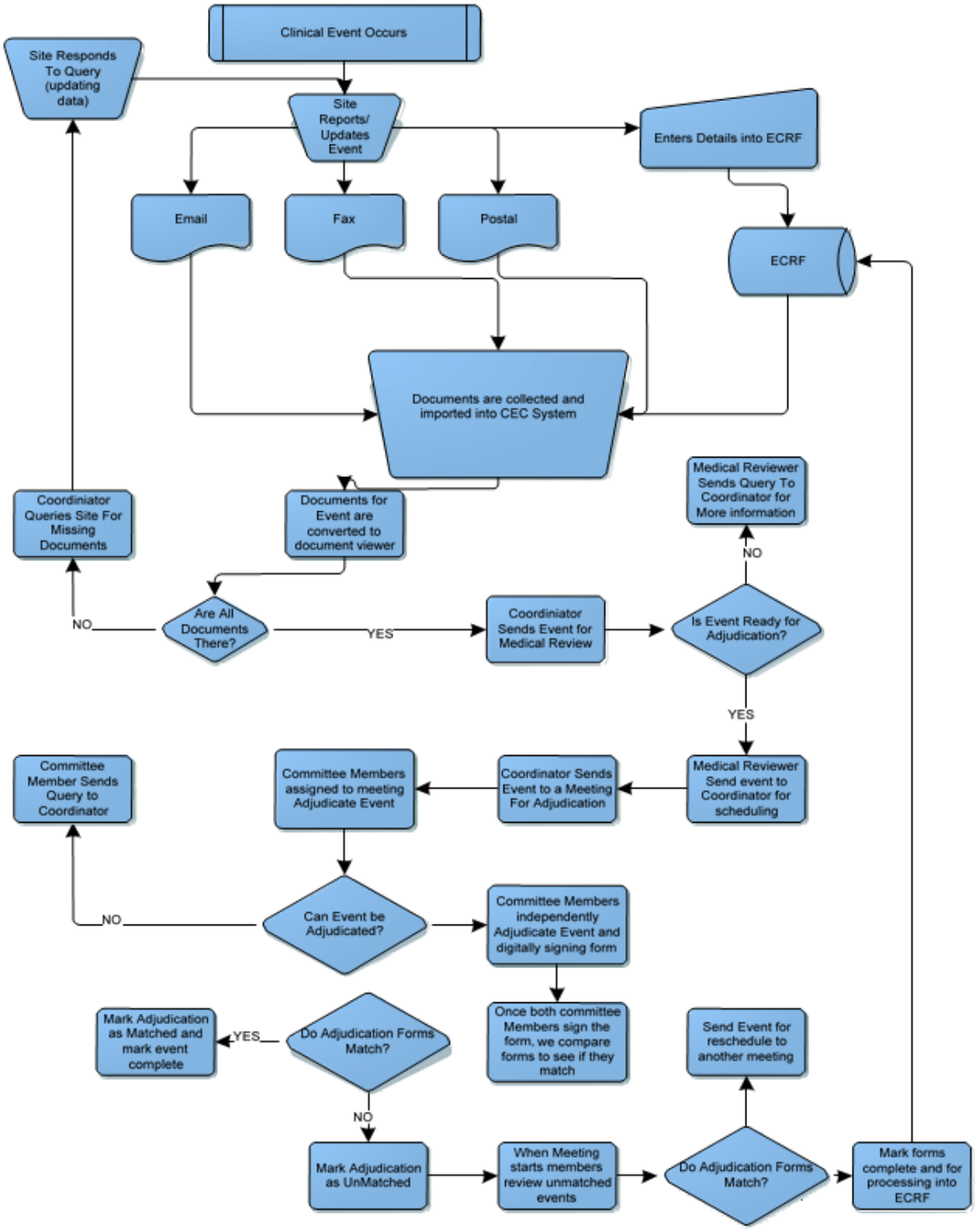
The Applicants, in conjunction with academic leadership (i.e., the Thrombolysis in Myocardial infarction [TIMI] Study Group and Hadassah Medical Organization), selected an independent Data Monitoring Committee (DMC), an independent and blinded (i.e., unaware of subject identification or treatment assignment) Clinical Event Adjudication Committee (CEC), and Executive and Steering Committees to provide study oversight and/or assess the safety and efficacy data and decide when stopping rules were met. The CEC was tasked with adjudication of events of the primary efficacy and safety variables and the events of the secondary efficacy variables, as well as events of pancreatitis throughout the study. This committee was comprised of specialists in CV and pancreatic medicine. A schematic of the adjudication process is presented in Figure 9 below.

The following events endpoints (triggered by systematic queries of the electronic case report form [eCRF]) were adjudicated by the CEC (i.e., by two members independently):

- Death (CV or presumed CV; non-CV)
- Coronary Ischemic Events (MI [non-procedural, peri-percutaneous coronary invention, peri-coronary artery bypass graft surgery]; unstable angina leading to hospitalization)
- Cerebrovascular Events (stroke [non-hemorrhagic, hemorrhagic,])
- Heart failure leading to hospitalization
- Hospitalization for coronary revascularization
- Pancreatitis (acute, chronic)

If the two adjudicators did not match, the event was sent for reschedule at another CEC meeting. Additionally, 5% of all adjudicated events were reviewed by another pair of adjudicators to determine if there were differences between the adjudications that require action.

Figure 9: Adjudication Process Overview



Source: Reproduced from the Applicants' Clinical Events Adjudication Committee Charter (page 10 of 45).

7.5 Criteria for Identifying Adverse Events of Special Interests (AEOSI)

The following are the prespecified lists of MedDRA Preferred Terms (Version 12.0; subject to updates) and/or criteria that were used to identify the AEOSI (adapted from the Clinical Study Report, Appendix I, pages 146-164):

Decrease in Lymphocyte Counts:
Lymphopenia, Lymphocyte count decreased, Lymphocyte percentage decreased, B-lymphocyte count decreased, T-Lymphocyte count decreased, CD4 lymphocytes decreased, CD8 lymphocytes decreased.

Decrease in Thrombocyte Counts:
Autoimmune Thrombocytopenia, Haemolytic uraemic syndrome, Idiopathic thrombocytopenic purpura, Platelet count decreased, Platelet destruction increased, Platelet production decreased, Plateletcrit decreased, Thrombocytopenia, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura.

Severe Infections:
All MedDRA PTs in the SOC of infections and infestations and meet the regulatory criteria for seriousness (e.g., hospitalization).

Opportunistic Infections:
Acute pulmonary histoplasmosis, Adrenal gland tuberculosis, Arthritis fungal, Atypical mycobacterial infection, Atypical mycobacterial lymphadenitis, Atypical mycobacterium pericarditis, Bacillary angiomatosis, Bartonellosis, Biliary tract Infection cryptosporidial, Biliary tract infection fungal, Bone tuberculosis, Bovine tuberculosis, Bronchitis fungal, Candida osteomyelitis, Candida pneumonia, Candida sepsis, Cerebral fungal infection, Cerebral toxoplasmosis, Chronic pulmonary histoplasmosis, Coccidioides encephalitis, Coccidioidomycosis, Congenital tuberculosis, Conjunctivitis tuberculous, Cryptococcal cutaneous infection, Cryptococcal fungaemia, Cryptococcosis, Cryptosporidiosis infection, Cutaneous coccidioidomycosis, Cutaneous tuberculosis, Cytomegalovirus antigen positive, Cytomegalovirus chorioretinitis, Cytomegalovirus colitis, Cytomegalovirus duodenitis, Cytomegalovirus enteritis, Cytomegalovirus enterocolitis, Cytomegalovirus gastritis, Cytomegalovirus gastroenteritis, Cytomegalovirus gastrointestinal infection, Cytomegalovirus hepatitis, Cytomegalovirus infection, Cytomegalovirus mononucleosis, Cytomegalovirus mucocutaneous ulcer, Cytomegalovirus myelomeningoradiculitis, Cytomegalovirus myocarditis, Cytomegalovirus oesophagitis, Cytomegalovirus pancreatitis, Cytomegalovirus pericarditis, Cytomegalovirus proctocolitis, Cytomegalovirus syndrome, Cytomegalovirus test positive, Cytomegalovirus urinary tract infection, Cytomegalovirus viraemia, Disseminated cryptococcosis, Disseminated cytomegaloviral infection, Disseminated tuberculosis, Ear tuberculosis, Encephalitis cytomegalovirus, Encephalitis fungal, Endocarditis candida, Endocarditis histoplasma, Enterocolitis fungal, Epididymitis tuberculous, Extrapulmonary tuberculosis, Eye infection toxoplasmal, Female genital tract tuberculosis, Fungal abscess central nervous system, Fungal cystitis, Fungal endocarditis, Fungal oesophagitis, Fungal peritonitis,

Fungal retinitis, Fungal rhinitis, Fungal sepsis, Gastritis fungal, Gastroenteritis cryptococcal, Gastroenteritis cryptosporidial, Gastrointestinal fungal infection, Hepatic candidiasis, Hepatic infection fungal, Hepatitis toxoplasmal, Herpes oesophagitis, Herpes sepsis, Herpes simplex hepatitis, Herpes simplex visceral, Herpes zoster disseminated, Herpes zoster infection neurological, Herpes zoster multi-dermatomal, Histoplasmosis, Histoplasmosis cutaneous, Histoplasmosis disseminated, Isosporiasis, JC virus infection, Joint tuberculosis, Listeria encephalitis, Listeria sepsis, Listeriosis, Lower respiratory tract infection fungal, Lymph node tuberculosis, Lymphadenitis fungal, Male genital tract tuberculosis, Meningitis candida, Meningitis coccidioides, Meningitis cryptococcal, Meningitis fungal, Meningitis herpes, Meningitis histoplasma, Meningitis listeria, Meningitis toxoplasmal, Meningitis tuberculous, Mycobacterial infection, Mycobacterium abscessus infection, Mycobacterium avium complex immune restoration disease, Mycobacterium avium complex infection, Mycobacterium chelonei infection, Mycobacterium fortuitum infection, Mycobacterium kansasii infection, Mycobacterium kansasii pneumonia, Mycobacterium marinum infection, Mycobacterium ulcerans infection, Myocarditis toxoplasmal, Necrotising fasciitis fungal, Neurocryptococcosis, Oesophageal candidiasis, Oesophageal tuberculosis, Opportunistic infection, Osteomyelitis fungal, Pancreatitis fungal, Pericarditis fungal, Pericarditis histoplasma, Pericarditis tuberculous, Peritoneal tuberculosis, Pneumocystis jiroveci infection, Pneumocystis jiroveci pneumonia, Pneumonia cryptococcal, Pneumonia cytomegaloviral, Pneumonia fungal, Pneumonia toxoplasmal, Presumed ocular histoplasmosis syndrome, Progressive multifocal leukoencephalopathy, Prostatitis tuberculous, Pulmonary tuberculoma, Pulmonary tuberculosis, Pyelonephritis fungal, Renal tuberculosis, Retinitis histoplasma, Salmonella bacteraemia, Salmonella sepsis, Salpingitis tuberculous, Silicotuberculosis, Sinusitis fungal, Spleen tuberculosis, Splenic infection fungal, Systemic candida, Thyroid tuberculosis, Toxoplasmosis, Tuberculoma of central nervous system, Tuberculosis, Tuberculosis bladder, Tuberculosis gastrointestinal, Tuberculosis liver, Tuberculosis of central nervous system, Tuberculosis of eye, Tuberculosis of genitourinary system, Tuberculosis of intrathoracic lymph nodes, Tuberculosis of peripheral lymph nodes, Tuberculosis serology test positive, Tuberculosis test positive, Tuberculosis ureter, Tuberculous abscess central nervous system, Tuberculous laryngitis, Tuberculous pleurisy, Tuberculous tenosynovitis, Tubo-ovarian abscess, Urine cytomegalovirus positive.

Hypersensitivity Reactions:

Allergic oedema, Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Angioedema, Auricular swelling, Bronchial oedema, Circumoral oedema, Conjunctival oedema, Drug hypersensitivity, Endotracheal intubation, Epiglottic oedema, Eye oedema, Eye swelling, Eyelid oedema, Face oedema, Gastrointestinal oedema, Genital swelling, Gingival oedema, Gingival swelling, Gleich's syndrome, Hereditary angioedema, Hypersensitivity, Idiopathic urticaria, Intubation, Laryngeal dyspnea, Laryngeal obstruction, Laryngeal oedema, Laryngospasm, Laryngotracheal oedema, Lip oedema, Lip swelling, Nasal oedema, Oedema genital, Oedema mouth, Oedema mucosal, Oral allergy syndrome, Orbital oedema, Oropharyngeal spasm, Oropharyngeal swelling, Palatal oedema, Penile oedema, Penile swelling, Periorbital oedema, Pharyngeal oedema, Scrotal oedema, Scrotal swelling, Small bowel angioedema, Stridor, Swelling face, Swollen tongue, Throat tightness, Tongue oedema, Tracheal obstruction, Tracheal oedema, Tracheostomy, Type I hypersensitivity, Urticaria,

Urticaria cholinergic, Urticaria chronic, Urticaria popular, Vaginal oedema, Vaginal swelling, Visceral oedema, Vulval oedema

Liver Abnormalities:
Laboratory criteria included ALT or AST elevated ≥3x ULN and total bilirubin >2x ULN.

Criteria by AE submissions included a combination of at least one of PT from the Transaminase Elevation **AND** the Bilirubin Elevation or Jaundice lists:

- Transaminase Elevation: Alanine aminotransferase abnormal, Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Gamma-glutamyltransferase abnormal, Gamma-glutamyltransferase increased, Hepatic enzyme abnormal, Hepatic enzyme increased, Hepatic function abnormal, Hypertransaminasaemia, Liver function test abnormal, Mitochondrial aspartate aminotransferase increased, Transaminases abnormal, Transaminases increased.

- Bilirubin Elevation or Jaundice: Hyperbilirubinaemia, Icterus index increased, Jaundice, Jaundice cholestatic, Jaundice hepatocellular, Ocular icterus, Yellow skin, Bilirubin conjugated abnormal, Bilirubin conjugated increased, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Urine bilirubin increased, Urobilin urine present.

Fracture:
Fracture events were identified by searching PTs using the text string ‘fracture’ and excluding ‘tooth fracture.’

Pancreatitis:
Cullen's sign, Hereditary pancreatitis, Ischaemic pancreatitis, Oedematous pancreatitis, Pancreatic abscess, Pancreatic haemorrhage, Pancreatic necrosis, Pancreatic phlegmon, Pancreatic pseudocyst, Pancreatic pseudocyst drainage, Pancreatitis, Pancreatitis acute, Pancreatitis chronic, Pancreatitis haemorrhagic, Pancreatitis necrotizing, Pancreatitis relapsing, Pancreatorenal syndrome.

Skin Reactions:
Anal erosion, Anal ulcer, Anal ulcer haemorrhage, Anorectal ulcer, Auditory meatus external erosion, Diabetic neuropathic ulcer, Diabetic ulcer, Epidermal necrosis, Eyelid erosion, Fungating wound, Genital erosion, Genital ulceration, Infected skin ulcer, Lip erosion, Lip ulceration, Nasal necrosis, Nasal septum ulceration, Nasal ulcer, Neuropathic ulcer, Nipple ulceration, Penile necrosis, Penile ulceration, Scab, Scrotal ulcer, Skin erosion, Skin necrosis, Skin ulcer, Skin ulcer excision, Skin ulcer haemorrhage, Testicular necrosis, Vulval ulceration, Vulvar erosion, Vulvovaginal ulceration.

Renal Abnormalities:
Identified by a doubling of creatinine levels development of end-stage renal disease (e.g., dialysis or renal transplantation) and/or by the following PTs:

- Acute prerenal failure, Anuria, Azotaemia, Continuous haemodiafiltration, Dialysis, Haemodialysis, Nephropathy toxic, Oliguria, Peritoneal dialysis, Renal failure, Renal failure acute, Renal impairment, Renal transplantation.

7.6 Key Regulatory Actions and Dates for Saxagliptin and SAVOR

Key Regulatory Actions

Date	Meetings / Submission Types / Regulatory Actions	Comments
07/31/2009	NDA 22350 (ONGLYZA) Approval	• Saxagliptin (ONGLYZA) tablets are approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. A postmarketing CVOT would be required to exclude a 30% excess risk of MACE (i.e., PMR 1493-6).
10/8/2009	Protocol Submission	• The initial protocol for SAVOR was submitted to IND 63634 (saxagliptin). • Protocol approved 11/23/2010.
03/25/2010	SAP Submission	• The Agency reached agreement 03/19/2012.
11/05/2010	NDA 200678 (KOMBIGLYZE XR) Approval	• Saxagliptin/metformin extended-release tablets (KOMBIGLYZE XR) are approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate.
03/18/2011	Protocol Amendment	• The planned enrollment of 12000 subjects at 700 study sites (based on the assumption of a 2.8% annual event rate) was increased to 16500 at 900 sites (based on the observed annual event rate of 1.8%) to maintain PMR timelines. • The Agency reached agreement 04/23/2011.
11/18/2011	Protocol Amendment	• All-cause mortality endpoint was included in the formal prespecified hierarchical testing of the efficacy endpoint. • The Agency reached agreement 03/19/2012.
02/28/2014	sNDA Submission	• sNDAs 22350/S-14 and 200678/S-13, which requested to include the efficacy and safety findings of SAVOR in product labeling for ONGLYZA and KOMBIGLYZE XR, respectively, were submitted. • Original PDUFA date: 12/28/2014
01/26/2015	Transfer of Obligation	• Sponsorship of NDA 22350 transferred from Bristol-Myers Squibb to AstraZeneca.

Source: Derived from the Applicant's Clinical Study Report.
Abbreviations: CVOT, cardiovascular outcomes trial; NDA, New Drug Application; PDUFA, Prescription Drug User Fee Act; PMR, postmarketing requirement; SAP, statistical analysis plan; SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded; sNDA, supplemental New Drug Application; and XR, extended-release.

7.7 Clinical Narrative

Please note that the following narrative was reproduced verbatim from the Applicant's submission. It contains many spelling and abbreviation variants, reflective of varying usage across a multinational program.

[D1680C00003] / E1931023 / Czech Republic / (b) (6) / Randomization code 12840

Investigational product:	Saxagliptin
Age/Sex/Race/Ethnicity:	64/Male/White/Not applicable
Days on investigational product:	603
Started investigational product:	(b) (6)
Stopped investigational product:	(b) (6)
Death:	Non-cardiovascular Death
SAE:	Pulmonary sarcoidosis (PT: Pulmonary sarcoidosis)
SAE:	Hyperglycemia (PT: Hyperglycaemia)
SAE:	Cholecystolithiasis (PT: Cholelithiasis)
SAE:	Supraventricular tachycardia. (PT: Supraventricular tachycardia)
SAE:	Congestive heart failure (PT: Cardiac failure congestive)
SAE:	Respiratory failure (PT: Respiratory failure)
Serious AEoSI [Severe infection]:	Pneumonia (PT: Pneumonia)
Serious AEoSI [Severe infection]:	Subfrenical abscess (PT: Subdiaphragmatic abscess)
Non-Serious AEoSI [Pancreatitis]:	Pancreatitis (PT: Pancreatitis)
DAE:	N/A

AEoSI = Adverse Event of Special Interest, identified via investigator assessment (tick box in eCRF) according to pre-specified criteria

(i) Clinical Summary

The information in this narrative is derived principally from checkboxes and free responses on the CRF, supplemented by adjudication package information, if applicable.

The patient's medical history provided at the time of enrolment ((b) (6), Day 1) included the following diagnoses: HbA1c >6.5% in the previous 6 months, current smoker, dyslipidemia, hypertension (with documented BP >140/>90 mmHg on both measurements at baseline), and diabetes mellitus, type II. At enrolment, it was noted that the patient did not have an established vascular disease. At enrolment, it was also noted that the patient had the following cardiovascular risk factors: hypertension, dyslipidemia, and current smoker. At baseline, the patient was receiving cardiovascular medications in the following drug classes: angiotensin converting enzyme inhibitor, beta-blocker, calcium antagonist, diuretics, and statin; and the following diabetes medication: metformin hydrochloride.

The baseline physical examination did not show any abnormal findings. The baseline ECG showed an abnormal finding (AV block i.gr).

On (b) (6) (Day 425), the patient developed an event of Pulmonary sarcoidosis (PT: Pulmonary sarcoidosis). The event met SAE criteria on (b) (6) (Day 603). This was a serious event because it was an important medical event. The investigator became aware of the event on (b) (6) (Day 608).

The investigator reported the following: symptoms and course, "Cough. Dyspnoe". diagnostic investigations and results, "CT lungs [redacted]:Advanced pulmonary fibrosis with condenso. Pulmonary node with a diameter of 9 mm in the S10 to the right. The border width of the pulmonary blood vessels without evidence of embolis" treatment of AE, "Medrol, Ecobec" and other comments, "The patient was a longtime smoker.".

The patient experienced the following serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after the event: Respiratory failure (PT: Respiratory failure), Subfrenical abscess (PT: Subdiaphragmatic abscess), Congestive heart failure (PT: Cardiac failure congestive), Pneumonia (PT: Pneumonia), Pancreatitis (PT: Pancreatitis), Supraventricular tachycardia (PT: Supraventricular tachycardia), Cholecystolithiasis (PT: Cholelithiasis), and Hyperglycemia (PT: Hyperglycaemia).

The patient was treated with Medrol, Syntophyllin, and Ambrobene.

The outcome of the event was reported as "not resolved". The patient was receiving study medication at the onset of the event. The investigator considered the event to be causally unrelated to study treatment.

On [redacted] (Day 461), the patient developed an event of Cholecystolithiasis (PT: Cholelithiasis). The event met SAE criteria on [redacted] (Day 521). This was a serious event because it prolonged a pre- existing hospitalization. The investigator became aware of the event on [redacted] (Day 532).

The investigator reported the following: symptoms and course, "Cholecystolithiasis was found upon hospitalization for a different event hyperglycemia" diagnostic investigations and results, "Ultrasound abdomen, laboratory tests. Ultrasound abdomen: Gall-bladder with a few stones the size of up to 3 inches"". treatment of AE, "Retrograde endoscopy gall and the extraction of the stone [redacted] and [redacted] with drain exchange". and other comments, "without symptoms. The basic cause of gallstones for has not been found. The patient had no previous history of this condition. This event continue until death, patient died [redacted].

The patient experienced the following serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after the event: Respiratory failure (PT: Respiratory failure), Subfrenical abscess (PT: Subdiaphragmatic abscess), Congestive heart failure (PT: Cardiac failure congestive), Pneumonia (PT: Pneumonia), Pancreatitis (PT: Pancreatitis), Supraventricular tachycardia (PT: Supraventricular tachycardia), and Hyperglycemia (PT: Hyperglycaemia).

The patient was treated with nitrofurantoin.

The outcome of the event was reported as "not resolved". The patient was receiving study medication at the onset of the event. The investigator considered the event to be causally unrelated to study treatment.

On [redacted] (Day 521), the patient developed an event of Hyperglycemia (PT: Hyperglycaemia). The event met SAE criteria on [redacted] (Day 521). This was a serious event because the patient was hospitalized from [redacted] (Day 521) to [redacted] (Day 528). The investigator became aware of the event on [redacted] (Day 532).

The investigator reported the following: symptoms and course, "14 days hyperglycemia. No symptoms, the patient had only hyperglycemia the domestic measurement" diagnostic investigations and results, "Laboratory tests. Glycemia 26 mmol/l, CBC: leukocytes 14,4 otherwise standard"; treatment of AE, "The patient were planted diabetes medications and insulin treatment was started" and other comments, "The patient had only hyperglycemia the domestic measurement.".

The patient received treatment for this diabetes complication. The patient's treatment regimen for diabetes was increased by addition of insulin for >=3 months.The patient experienced the following serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after the event: Supraventricular tachycardia (PT: Supraventricular tachycardia).

The patient was treated with insulin.

The outcome of the event was reported as "resolved". The patient was receiving study medication at the onset of the event. The investigator considered the event to be causally unrelated to study treatment.

On [redacted] (Day 532), the patient developed an event of Supraventricular tachycardia (PT: Supraventricular tachycardia). The investigator became aware of the event on [redacted] (Day 532). The event met SAE criteria on [redacted] (Day 532). This was a serious event because the patient was hospitalized from [redacted] (Day 532) to [redacted] (Day 535).

The investigator reported the following: symptoms and course, "Rapid pulse. Ischaemic heart disease- arrhythmia form - atrial flutter"; diagnostic investigations and results, "ECG: atrial flutter 2:1, 145/min. QRS 0.08, flatly negative T in III, aVF, V3, RTG of lungs without progression"; treatment of AE, "Digoxin parenteraly, Clexane, Cardilan, Cordarone, Warfarine"; and other comments, "In the history of tachycardia has not been recorded.".

The patient experienced the following serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after the event: Pancreatitis (PT: Pancreatitis) and Hyperglycemia (PT: Hyperglycaemia).

The patient was treated with digoxin, Clexane, warfarin, Cordarone, and Cardilan.

The outcome of the event was reported as "resolved". The patient was receiving study medication at the onset of the event. The investigator considered the event to be causally unrelated to study treatment.

On [redacted] (Day 549), the patient developed an event of Pancreatitis (PT: Pancreatitis). It was considered to be an adverse event of special interest defined in Appendix I of the Study Protocol.

The investigator reported the following: symptoms and course, "Diagnostic test were performed to find out cause of elevated liver enzymes. No symptoms. Abdominal pain [redacted] - suspected exacerbation of pancreatitis- ruled out"; diagnostic investigations and results, "Endosono diagnostic - [redacted] (scheduled test due to elevated liver enzymes, result: chronical pancreatitis, lab test - elevated liver enzymes - [redacted]". treatment of AE, "Lab test [redacted] liver enzymes normal, S-amylaza normal, only CRP 386,1 mg/l. URL limit 10,0 mg/l" and other comments, "Pancreatitis was not known prior to the subject enrollment to the study.".

The patient did not experience any signs or symptoms related to this event. According to the CRF checkbox, no intervention was needed. The patient did not experience any complications as a consequence of the event. The patient had no relevant medical history or previous episodes of pancreatitis. The patient had no current/past history of alcohol use or drinking alcohol prior to the event. The patient was on other medications that may cause pancreatitis. The patient possessed risk factors for pancreatitis. There were no other potential causes for the event.

The event was referred to the Clinical Event adjudication Committee and adjudicated as: a chronic pancreatitis based on medical history and/or sectional imaging. The reported risk factors were gallstones. The following information was reported within the adjudication package: “[The patient’s] S-amylaza [were] 10.14…[and] 1,76…Amylaza v moci [was] 11,72”; “US - endoscopy…[done on] [redacted]…[concluded that]…the finding corresponds to chronic pancreatitis in the head and body of the pancreas”. “Personal history [included] type-2 diabetes mellitus”. “[Upon admission, the patient had] sudden onset of shortness of breath…his glycemia was 26”. “Ultrasound of the upper section of the abdomen [revealed]…cholecystolithiasis”. “Surgery consultation [showed]…cholecystolithiasis, suspected pancreas irritation - clinically silent”. “Conservative approach [was recommended]”. “[The] patient’s clinical status improved, problems disappeared”. “He was discharged to home care”. “[Per Protocol of Daily Clinic report], [diagnoses were] dyslipidemia - mixed type; cholecystolithiasis - ERCP with EPT and extraction of a concrement ([redacted]), - ERCP with exchange of a drain ([redacted]); [and] chronic pancreatitis.”.

A table showing the time-course of changes in the clinical laboratory values relevant to this event can be found at the conclusion of this clinical summary.

The patient experienced the following serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after the event: Pneumonia (PT: Pneumonia), Congestive heart failure (PT: Cardiac failure congestive), Subfrenical abscess (PT: Subdiaphragmatic abscess), and Respiratory failure (PT: Respiratory failure).

The outcome of the event was reported as "not resolved". The patient was receiving study medication at the onset of the event. The investigator considered the event to be causally unrelated to study treatment.

On (b) (6) (Day 576), the patient developed an event of Pneumonia (PT: Pneumonia). The event met SAE criteria on (b) (6) (Day 580). This was a serious event because the patient was hospitalized from (b) (6) (Day 580) to (b) (6) (Day 589). The investigator became aware of the event on (b) (6) (Day 590).

The investigator reported the following: symptoms and course, "Deterioration of the breath, irritating cough"; diagnostic investigations and results, "RTG- advanced fibrotic changes bilateral, non- homogenous infiltrates, inflammation, LABS: CRP 171,5, cultivation from sputum: Haemophilus,"; treatment of AE, "Antibiotics: Doxybene, Amoksiklav"; and other comments, "Patient has diagnoses sarkoidosis II.-III. degree in (b) (6) (b) (6) ".

This was not an opportunistic infection. The infection was not herpes zoster. The patient had no relevant medical history or previous episodes of the event. There were other potential causes for the event.

The patient experienced the following serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after the event: Congestive heart failure (PT: Cardiac failure congestive).

The patient was treated with Doxybene and Amoksiklav.

The outcome of the event was reported as "resolved". The patient was receiving study medication at the onset of the event. The investigator considered the event to be causally unrelated to study treatment.

A table showing the time-course of changes in the clinical laboratory values potentially relevant to this event can be found at conclusion of this clinical summary.

On (b) (6) (Day 580), the patient developed an event of Congestive heart failure (PT: Cardiac failure congestive). The investigator became aware of the event on (b) (6) (Day 597). The event met SAE criteria on (b) (6) (Day 597) and also was identified as a potential clinical endpoint by the investigator. This was a serious event because it was an important medical event. The investigator reported the following: symptoms and course, "Oedema of lower limbs". diagnostic investigations and results, "BNP 580, ultrasonography vessels of lower limbs phlebotrombosis not confirmed". treatment of AE, "Indap, Lusopress discontinued, Furon started.".

The event was referred to the Clinical Event adjudication Committee and adjudicated as: a hospitalization for heart failure. The patient did not die as a consequence of the protocol-defined HF hospitalization. The following information was reported within the adjudication package: "[Medical history included] former smoker since January 2012, previously smoked 10-12 cigarettes daily…[and previous hospitalization] on (b) (6) [in which patient] was discharged from the Medical department [with]…atrial flutter". "The patient was…admitted for shortness of breath [and] irritative cough". "[Complaints of the patient upon admission were] approx. 4 days of deteriorated breathing, irritative cough…initial saturation 63% on oxygen, increase to 89%". "[Findings included] short of breath…[and] breathing with crepitations bilaterally at the base". "Laboratory examination has shown elevation of CRP, BNP - antibiotic therapy…B Natriurel peplid 580…[and] CRP 171.5.";"Radiology examination…[on] (b) (6)… [of] lungs in PA view…[revealed] obvious non-homogeneous infiltrate in the middle and lower lung fields, more on the

right - progress during the underlying disease with very probable inflammatory contribution. Blunt contours of the diaphragm, on the right side there is smaller effusion; fuzzy contours of the heart shadow, which is wider to both directions". "Radiology examination…[on] (b) (6) …[of] lungs in PA view…[revealed] inflammatory infiltrates bilaterally in mild regression". "Radiology examination…[on] (b) (6) …[of] lungs in the posterior anterior view…[revealed] mild hypertrophy of the left ventricle, heart shadow…contours are rather blunt…[and] irregular significant thickening of insterstitium bilaterally with honeycomb pattern."; "Probable progression of the finding, inflammatory superposition, contribution of congestion in pulmonary circulation…Sudden development of swelling of the right lower limb around the ankle…The patient is cardiopulmonary compensated at discharge…He has n complaints". "[Diagnoses were] pneumonia within the terrain of fibrous disease of the lungs…atrial fibrillation and flutter…[and] right-sided cardiac subcompensation". "[Per] Protocol of Daily Clinic [form]…[diagnoses were] ischemic heart disease - silent nonO ischemia in the anteroseptal area…arrhythmic form (flutter) - currently persistent reverse to SA…swelling of the lower limb of mixed etiology…incipient right sided heart failure.".

The patient experienced the following serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after the event: Respiratory failure (PT: Respiratory failure), Subfrenical abscess (PT: Subdiaphragmatic abscess), and Pneumonia (PT: Pneumonia).

The patient was treated with Godasal and Furon.

The outcome of the event was reported as "not resolved". The patient was receiving study medication at the onset of the event. The investigator considered the event to be causally unrelated to study treatment.

On (b) (6) (Day 601), the patient developed an event of Subfrenical abscess (PT: Subdiaphragmatic abscess). The event met SAE criteria on (b) (6) (Day 601). This was a serious event because the patient was hospitalized on (b) (6) (Day 601). The investigator became aware of the event on (b) (6) (Day 608).

The investigator reported the following: symptoms and course, "Abdominal pain (b) (6) . diagnostic investigations and results, " (b) (6) -in (b) (6) hospital were performed ultrasonic diagnostic + CT (results: liquids perihepatal and subphrenical, cholecystolithiasis, advanced lung fibrosis with inflammation superposition"; treatment of AE, "CT biopsy (collection of liquid above liver segment S4). Antibiotics - no further details in discharge summary available"; and other comments, "Lab test (liver enzymes normal, only CRP 386,1 mg/l, URL 10 mg/l).There may be possible connection with previous pneumonia SAE no.10".

This was not an opportunistic infection. The type of organism was unknown. No diagnostic test was performed. The infection was not herpes zoster. The patient had no relevant medical history or previous episodes of the event. There were other potential causes for the event.

The patient experienced the following serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after the event: Respiratory failure (PT: Respiratory failure).

The patient was treated with antibiotics.

The outcome of the event was reported as "not resolved". The patient was receiving study medication at the onset of the event. The investigator considered the event to be causally unrelated to study treatment.

A table showing the time-course of changes in the clinical laboratory values potentially relevant to this event can be found at conclusion of this clinical summary.

On (b) (6) (Day 603), the patient developed an event of Respiratory failure (PT: Respiratory failure). The event met SAE criteria on (b) (6) (Day 603). This was a serious event because it resulted in death. The investigator became aware of the event on (b) (6) (Day 608).

The investigator reported the following: symptoms and course, "progressive dysponea"; diagnostic investigations and results, "none"; treatment of AE, "mechanical ventilation, Synthophyllin, Ambrobene, Solu-medrol"; and other comments, "sarkoidosis in the stage of lung fibrosis, permanent corticosteroids treatment".

The event was referred to the Clinical Event adjudication Committee and adjudicated as: a non- cardiovascular death (pulmonary failure). The following information was reported within the adjudication package: “[The patient was hospitalized] due to chronic pancreatitis”. “Complaints have already lasted for one week”. “[The patient reported] abdominal pain in the area of the epigastrium”. “[On] (b) (6) …cardiopulmonary resuscitation was initiated…due to progressing shortness of breath, cyanosis, and subsequent…asystole…after drainage of the subphrenic abscess”. “He was connected to artificial pulmonary ventilation”. “Attempt to restore functional blood circulation during cardiopulmonary resuscitation was not successful”. “Resuscitation was terminated”. “Diagnoses [were] subphrenic abscess…acute respiratory failure…sarcaidossis of the lungs in a stage of pulmonary fibrosis…[and] chronic ischemic heart disease, unspecified”. There were no serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after this event.

The patient was treated with Syntophyllin, Ambrobene, Furosemide, Solu-Medrol, and Clexane.

The outcome of the event was reported as "fatal". The patient was receiving study medication at the onset of the event. The investigator considered the event to be causally unrelated to study treatment.

On (b) (6) (Day 603), the patient died. The time of death was (b) (6) .

The investigator reported that the most likely cause of death was non-cardiovascular death. This was an event of respiratory failure (not due to infection). The death was related to the AE/SAE of Respiratory failure (PT: Respiratory failure).

The patient experienced the following serious adverse events, discontinuations due to adverse event, or adverse events of special interest starting within 14 days prior to and 7 days after the event: Subfrenical abscess (PT: Subdiaphragmatic abscess). The patient was receiving study medication at the time of death. An autopsy was not performed.

All deaths were reviewed by the TIMI CEC. Death classification is non-cardiovascular death (pulmonary failure).

7.8 Summary Table of the Literature Related to All-Cause Mortality Reported in Diabetes CVOTs

Table 43: Association between HbA1c Reduction and All-Cause Mortality in Type 2 Diabetes Clinical Trials

Study	Design	Population	Intervention	Median Follow-Up (yr)	Mean HbA1c % (Change from Baseline %)*	All-Cause Mortality
SAVOR	**RDBPC**	**N=16,492; mean age: 65 yr** **Diabetes duration: 10 yr** **Established CVD: 78%** **Baseline HbA1c: 8.0%**	**Saxagliptin** **Placebo**	**2.1**	**7.7 (-0.3)** **7.9**	**256/8240** **204/8173** **HR 1.23 (1.02, 1.47)†**
ACCORD[8,61,62]	ROL (double 2x2 factorial)	N=10,251, mean age: 62 yr Diabetes duration: 10 yr Established CVD: 35% Baseline HbA1c: 8.3%	Intensive antidiabetic therapy Standard antidiabetic therapy	3.4	6.4 (-1.01) 7.5	283/5128 232/5123 HR 1.22 (1.01-1.46) Percent with events/yr decreased from 1.92 to 1.67 with follow-up.
VADT [11]	ROL	N=1,791, mean age: 60 yr Diabetes duration: 10 yr Established CVD: 14% Baseline HbA1c: 9.4%	Intensive antidiabetic therapy Standard antidiabetic therapy	5.6	6.9 (-1.16) 8.4	102/892 95/899 HR 1.07 (0.81-1.42) With diabetes duration over 21 years: HR 1.977 (1.77, 3.32)
ADVANCE[10]	ROL (2x2 factorial)	N=11,140, mean age: 66 yr Diabetes duration: 8 yr Established CVD: 32% Baseline HbA1c: 7.5%	Intensive antidiabetic therapy Standard antidiabetic therapy	5	6.5 (-0.72) 7.2	498/4828 533/4741 HR 0.93 (0.83, 1.06)
UKPDS[60,63,64]	ROL	N=3,867, mean age: 53 yr Diabetes duration: 8 yr Established CVD: 2% Baseline HbA1c: 7.1%	Intensive antidiabetic therapy Standard antidiabetic therapy	10	7.0 (-0.66) 7.9	123/2729 53/1138 HR 0.96 (0.70, 1.33)

Source: Adapted from Turnbull FM, et al. (2009)[60]and the respective references included in the table.[8,10,11,61-64]
*Comparator-subtracted mean change in HbA1c from baseline.
†On-treatment plus 7-day post-treatment window (mITT-FDA).
Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CVD, established cardiovascular disease; FRC, factorial, randomized, controlled; RDBPC, randomized, double-blind, placebo-controlled; ROL, randomized, open-label, UKPDS, united Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial; and yr, year.