Bristol-Myers Squibb Company

Saxagliptin (BMS-477118)

FDA's Endocrinologic and Metabolic Drugs Advisory Committee
Briefing Document for April 2009 Meeting

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1 EXECUTIVE SUMMARY

Bristol-Myers Squibb and its development partner AstraZeneca are seeking approval for saxagliptin, a highly potent, selective, reversible, and competitive dipeptidyl peptidase 4 (DPP4) inhibitor, to improve glycemic control for patients with type 2 diabetes mellitus (T2DM). Indicated uses of saxagliptin to treat T2DM patients requested for approval include:

- monotherapy, as an adjunct to diet and exercise;
- combination therapy with metformin, a thiazolidinedione (TZD), or a sulfonylurea (SU) when the single agent alone does not provide adequate glycemic control, as an adjunct to diet and exercise; and
- initial combination therapy with metformin, when treatment with dual saxagliptin and metformin therapy is appropriate, also as an adjunct to diet and exercise.

The recommended usual clinical dose (RUCD) of saxagliptin is 5 mg once daily. A single dosage adjustment to 2.5 mg daily is recommended for patients with moderate or severe renal impairment, or end-stage renal disease (creatinine clearance [CrCl] ≤ 50 mL/min, approximately corresponding to serum creatinine levels of ≥ 1.7 mg/dL in men and ≥ 1.5 mg/dL in women).

Overview of Clinical Development Program

A total of 5346 subjects were evaluated in the saxagliptin Phase 1-3 clinical development program, including 423 in a Phase 2b dose ranging study and 4250 subjects in Phase 3 studies. In the development program, saxagliptin was studied at maximum daily doses of 400 mg (80 times the RUCD) for up to 2 weeks, 100 mg (20 times the RUCD) for up to 6 weeks, 40 mg (8 times the RUCD) and 20 mg (4 times the RUCD) for up to 12 weeks, and 10 mg (2 times the RUCD) for up to 2 years. Saxagliptin doses of 2.5 and 5 mg have also been studied for up to 2 years.

Summary of Efficacy

In subjects with T2DM, treatment with saxagliptin resulted in consistent, clinically meaningful and statistically significant reductions in glycosylated hemoglobin (A1C),

fasting plasma glucose, and postprandial plasma glucose, as well as achievement of treatment targets for A1C. Better glycemic control was consistently achieved with the 5 mg dose compared with the 2.5 mg dose. There was no incremental efficacy benefit observed with dosing of saxagliptin 10 mg compared with 5 mg. Beneficial effects were demonstrated across subgroups of demographic and baseline diabetic characteristics, confirming the applicability of the data to the broader T2DM population.

Summary of General Safety

Overall, saxagliptin was well tolerated, with a favorable adverse event profile. The main safety findings are summarized as follows:

- Saxagliptin treatment was associated with a low risk of hypoglycemia.
- Saxagliptin treatment did not lead to adverse effects in lipid parameters
- Saxagliptin treatment was associated with no or minimal differences in body weight change compared with control.
- Saxagliptin treatment did not lead to adverse effects in blood pressure or heart rate.
- The administration of some DPP4 inhibitors has been associated with skin lesions in monkeys. Overall, evaluation of the saxagliptin clinical data has not revealed any signals that correlate to the skin findings observed in monkeys and there was no evidence that saxagliptin led to an increased risk of localized edema.
- A small, non-progressive decrease in lymphocyte count was observed that was not associated with clinically meaningful infection-related adverse events.
- There was no safety signal related to drug induced liver injury, renal function, pancreatitis, or skeletal myopathy.
- There was no evidence for clinical meaningful effects on other hematology or chemistry parameters associated with saxagliptin treatment.

Summary of Cardiovascular Safety

Because cardiovascular (CV) disease is the leading cause of morbidity and mortality in patients with T2DM, CV safety was carefully evaluated in the saxagliptin development program. The assessment of CV safety in the development of treatments for T2DM has been evaluated by the FDA. In July 2008, a FDA Metabolic/Endocrine Drug Advisory Committee hearing was held to explore this issue. As a result of that meeting, FDA

released a final guidance on CV safety of T2DM drugs in December, 2008.[1] In this guidance, the Agency noted the compelling body of evidence for reduced risk of microvascular complications with improved long-term glycemic control in T2DM. Accordingly, the Agency confirmed that A1C remains an acceptable primary efficacy endpoint for approval of drugs to treat hyperglycemia in T2DM. However, T2DM is associated with an elevated risk of CV disease, and FDA determined that CV risk of treatments for T2DM should be more thoroughly addressed during drug development. The December 2008 FDA Guidance provides recommendations on how to demonstrate that new treatments for T2DM are not associated with an unacceptable CV risk. The Sponsor has used the principles outlined in the FDA guidance to assess the CV safety of saxagliptin.

Accordingly, analyses of the saxagliptin clinical data were performed to evaluate risk of CV events in the program, and the results are presented in this briefing document. The methodology applied and the results have been considered in light of the December 2008 FDA Final Guidance. The results of the comprehensive analyses do not indicate an increased CV risk associated with saxagliptin treatment.

Conclusions

Saxagliptin represents a new treatment option for T2DM, a disease with many currently available treatments, but one that is increasing in prevalence, where many patients do not achieve satisfactory glycemic control, and where current treatments are limited by tolerability and safety concerns. Compared with several of the available therapies for T2DM, saxagliptin provides an improved tolerability and safety profile with respect to hypoglycemia, weight gain, gastrointestinal AEs, heart failure, and edema. Saxagliptin provides clinically meaningful glycemic benefits, is well tolerated with no evidence of an increase in CV risk and provides a favorable benefit/risk profile when given as monotherapy, add-on therapy with metformin, TZDs, and SUs as well as in initial combination use with metformin, when treatment with dual saxagliptin and metformin therapy is appropriate.

2 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive chronic metabolic disorder caused by a combination of insulin resistance and β-cell dysfunction, resulting in hyperglycemia. It is a common disorder that leads to substantial morbidity and increased mortality rates. Data from the Diabetes Control and Complications Trial (DCCT)[2] (in type 1 diabetes) and the United Kingdom Prospective Diabetes Study (UKPDS)[3] (in type 2 diabetes) compared intensive and standard glucose management and showed a reduced risk of complications associated with improved glucose control in the intensive glucose management approach, as measured by glycosylated hemoglobin (A1C). Long-term follow-up demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up to DCCT and in the UKPDS study.[4,5] These results have established tight glucose control as a fundamental component in the management of diabetes. In spite of the availability of a number of different antihyperglycemic classes of agents, achievement of A1C targets remains suboptimal.[6] Many available treatments are associated with undesirable side effects including increased risk of hypoglycemia, weight gain, gastrointestinal adverse events, heart failure, or edema, which present barriers to their use and acceptance. Due to the progressive nature of the disease, more than one medication will be necessary for the majority of patients over time.[7] As a consequence, there remains the need to identify additional effective, safe, and well-tolerated antihyperglycemic agents to help patients achieve and sustain target glycemic levels.

Incretin hormones are gastrointestinal hormones which increase insulin secretion in response to enteral stimulation. The two primary incretin hormones are glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). These hormones contribute to the control of postprandial glucose excursions through a mechanism that is dependent on plasma glucose levels. The significance of meal ingestion for incretin-induced insulin release is illustrated in studies which compare insulin secretion after oral glucose with intravenous glucose, and showed a larger insulin response after oral glucose administration.[8]

In addition to enhanced postprandial insulin release, GLP-1 reduces glucagon release from the pancreatic α-cells, thereby decreasing hepatic glucose production.[9] This effect is also glucose-dependent, such that when plasma glucose is normal or low, the counter-regulatory response of glucagon release is not impaired.[8]

Saxagliptin is a highly potent, selective, reversible, and competitive dipeptidyl peptidase 4 (DPP4) inhibitor. DPP4 is the enzyme responsible for the inactivation of GLP-1 and GIP. By inhibiting the enzyme DPP4, saxagliptin potentiates active endogenous GLP-1 concentrations, augmenting the physiological mechanism of insulin secretion and decreasing glucagon release, thereby reducing postprandial and fasting glucose levels in patients with T2DM.

3 NONCLINICAL DEVELOPMENT

The scope of the nonclinical efficacy and safety pharmacology testing characterized saxagliptin's proposed indication for treatment of T2DM and assessed its potential for adverse pharmacologic effects on major organ systems. Based on results of in vitro and in vivo experiments, the demonstrated efficacy of saxagliptin in the treatment of T2DM is likely a result of its target activity of inhibiting DPP4 catalytic activity and increasing levels of endogenous intact GLP-1.

Saxagliptin is a highly potent, selective, reversible, and competitive inhibitor of human DPP4. It exhibits enzymological properties consistent with an extended duration of action against the DPP4 enzyme, enabling once daily dosing in humans. Saxagliptin exhibits a K_i value of 1.3 ± 0.3 nM (0.41 ng/mL), indicating very high potency (Table 1). Its major metabolite, BMS-510849, is also a competitive DPP4 inhibitor, approximately 2-fold less potent than saxagliptin in vitro with a K_i value of 2.6 ± 1 nM (0.86 ng/mL).

Table 1: Potency and Specificity of Saxagliptin and BMS-510849 as Inhibitors of Human DPP4 Compared to Related Peptidases, Determined at 37°C

	DPP4 Ki (nM)	DPP8 Ki (nM)	DPP9 Ki (nM)
Saxagliptin	1.3 ± 0.3 (12)	508 ± 174 (13) *ratio 391*	98 ± 44 (11) *ratio 75*
BMS-510849	2.6 ± 1.0 (12)	2495 ± 727 (14) *ratio 948*	423 ± 64 (12) *ratio 163*

Ratio refers to the selectivity ratio, defined as the ratio of Ki for each peptidase/Ki for DPP4 using gly-pro-pNA substrate. Values are mean ± standard deviation for (n) repeat determinations. Saxagliptin (free base) FW = 315; 1 nM = 0.315 ng/mL. BMS-510849 (free base) FW = 331; 1 nM = 0.331 ng/mL.

In vitro enzyme selectivity studies were conducted at 37^{o}C with two other DPP4-related peptidases using conditions allowing direct comparison of K_i values for the different peptidases. Saxagliptin exhibited 391-fold selectivity for DPP4 over DPP8, and 75-fold selectivity for DPP4 over DPP9 (Table 1). However, DPP4 is an extracellular enzyme, while DPP8 and DPP9 are intracellular; therefore, in vivo selectivity may be greater than that measured in vitro. The major metabolite, BMS-510849, exhibited increased selectivity ratios in favor of DPP4 over the other peptidases (948-fold over DPP8 and 163-fold over DPP9). Other studies revealed very weak or insignificant inhibition of two further DPP4-related peptidases, FAP (selectivity ratio > 4300-fold) and DPP2 (selectivity ratio > 10000-fold), by saxagliptin or BMS-510849 at room temperature.

Additional studies verified that saxagliptin and BMS-510849 had similar high potency and selectivity versus rodent and cynomolgus monkey DPP4, DPP8, and DPP9, thereby validating the use of these species in nonclinical pharmacology and safety studies.

Determination of the inhibitor:enzyme association and dissociation rate constants (k_{on} and k_{off}) showed that saxagliptin and BMS-510849 exhibit extended binding kinetics with a $t_{1/2}$ of 50 minutes and 23 minutes, respectively, for dissociation from DPP4 at 37°C. This observation is consistent with the extended duration of plasma DPP inhibition that is observed in vivo when compared to saxagliptin and its major metabolite

pharmacokinetics (see also Section 4). In addition to ~ 2 orders of magnitude less potency for inhibition of DPP8 and DPP9, saxagliptin and BMS-510849 did not have extended binding kinetics to either DPP8 or DPP9.

No issues were identified when either saxagliptin or BMS-510849 were tested in vitro at ≥ 10 μM against a panel of 21 other non-related serine proteases, 42 non-related receptors and ion channels at room temperature. Neither saxagliptin nor BMS-510849 had significant effects on human T-cell activation in a mixed lymphocyte response assay in vitro.

In humans, intact GLP-1 regulates blood glucose via at least three mechanisms: stimulation of glucose-dependent insulin secretion, delaying of gastric emptying, and inhibition of glucagon secretion. In normal rats, saxagliptin inhibited plasma DPP4 activity (ED_{50} 0.04 mg/kg 0.5 hours post dose) and increased concentrations of intact GLP-1 (ED_{50} 0.2 mg/kg 0.5 hours post dose). In insulin resistant and diabetic animal models saxagliptin (0.4 to 1.3 mg/kg) inhibited plasma DPP activity, leading to a reduction in post-prandial glucose area under the curve (AUC). In chronic dosing studies using the progressively diabetic ZDF rat model, saxagliptin (4 mg/kg) delayed development of fasting hyperglycemia and the results of oral glucose tolerance tests showed significantly improved glucose excursions.

No safety concerns for saxagliptin were identified in safety pharmacology assessments of cardiovascular, neurological, or respiratory functions. Assessments were made in rat, dog, and/or monkey with dosing durations ranging from a single-dose to repeat dosing of up to 12 months.

The pharmacokinetics and metabolism of saxagliptin were extensively evaluated in a series of studies that utilized appropriate in vitro test systems and species (ie, mouse, rat, rabbit, dog, and cynomolgus monkey) to demonstrate acceptability of these species for the safety evaluation of saxagliptin and its metabolites. Saxagliptin was rapidly absorbed following oral administration in all species including humans, and systemic exposure of saxagliptin in mouse, rat, dog, and monkey was comparable to or exceeded that in human. In mouse, rat, dog, and monkey, systemic exposure was dose-related with no apparent gender differences (except in the rat where exposure in females was higher than males) or significant accumulation after once-daily repeated dosing.

BMS-510849 was the major metabolite identified in humans and cytochrome P450 3A4/5 (CYP3A4) was identified as the major enzyme responsible for the formation of BMS-510849 from saxagliptin. While all metabolites identified in human plasma were found in mouse, rat, dog, and monkey plasma, saxagliptin was also primarily metabolized to BMS-510849 in these species, and together these compounds comprised the most abundant drug-related plasma components. Saxagliptin-derived radioactivity was rapidly and primarily excreted in human urine mainly as a mixture of saxagliptin and BMS-510849, whereas urine and feces were the primary routes of excretion in rats, dogs, and monkeys. Neither saxagliptin nor BMS-510849 induced CYP1A2, 2B6, 2C9 or 3A4 in primary human hepatocytes nor inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4/5 in pooled human liver microsomes.

The toxicity of saxagliptin was evaluated in a comprehensive battery of ICH- and GLP-compliant nonclinical toxicology studies in mice, rats, dogs, and cynomolgus monkeys at exposures comparable to or markedly higher than the therapeutic exposure. In rats, the major target organ changes were generally minimal splenic lymphoid hyperplasia, pulmonary histiocytosis, and intermittent, sporadic multi-tissue mononuclear-cell infiltrates/inflammation. Such changes were evident in the ocular accessory gland and liver in short and long-term studies and in the lung, urinary bladder, and epididymis after 104 weeks of dosing. These findings only occurred at clinically non-relevant exposures in rats (AUC ≥ 36× the RUCD [recommended usual clinical dose] of 5 mg) and were not considered adverse as they were limited in severity (never beyond mild), fully reversible, and non-progressive (no long-term histomorphologic sequelae such as lymphoproliferative or autoimmune disease or tissue injury).

In dogs, the major finding was gastrointestinal toxicity characterized by bloody/mucoid feces (AUC multiple of 19× the RUCD) and enteropathy (AUC multiple of 580× the RUCD). Clinical correlates to the bloody/mucoid feces observed in dogs have not been associated with saxagliptin in human clinical trials.

In monkeys, major target organ changes included reversible, erosive and/or ulcerative skin lesions with scab formation, splenic lymphoid hyperplasia and multi-tissue mononuclear-cell infiltrates/inflammation (AUC multiple of ≥ 7× the RUCD). Healing of erosive skin lesions occurred with continued dosing. Edema has neither been observed in the monkey with saxagliptin at AUC exposures up to 120× the RUCD nor in any other

nonclinical species at any dose evaluated. Similar to the rat, splenic lymphoid hyperplasia and mononuclear-cell infiltrates/inflammation were considered reflective of exaggerated pharmacology in monkeys. Further, mononuclear-cell infiltrates/inflammation may be an exacerbation of background changes commonly observed in monkeys.[10] The AUC at the no-observable-effect level (NOEL) for the skin and microscopic changes was 1 to 3× the RUCD. The underlying mechanism(s) for these changes is currently unknown, but to date there have been no clinical correlates for similar skin lesions observed in humans treated for up to 2 years with saxagliptin at twice the RUCD.

Saxagliptin was not genotoxic based on the weight of evidence from a battery of genotoxicity studies and was not carcinogenic in rodents at large exposure multiples relative to the RUCD (up to 1210× in mice and 368× [males] to 2303× [females] in rats). With the exception of delayed ossification in the rat (maternal AUC multiple of 1560×), all reproductive/developmental toxicities were observed at maternally toxic doses, supporting the conclusion that saxagliptin is not a selective developmental toxicant.

The cardiovascular (CV) system was evaluated in a comprehensive series of nonclinical studies. In vitro, neither saxagliptin nor its major metabolite, BMS-510849, had significant effects on hERG/IKr currents or Purkinje fiber action potential duration at concentrations equivalent to Cmax exposures 394× or 210× the RUCD, respectively. In vivo, no adverse CV findings (ECG or hemodynamic changes) were observed in rats, dogs (including telemetry), or monkeys following oral dosing at Cmax exposures up to 619×, 750× and 120× the RUCD, respectively. Based on the nonclinical CV assessments, there was no predicted human CV safety concern.

Given that several immunoregulatory functions have been attributed to DPP4,[11, 12, 13, 14] comprehensive investigations of the effect of saxagliptin on immune endpoints in nonclinical studies were conducted. No inhibition of T-cell activation at therapeutic levels was observed in in vitro assessments using human lymphocytes (CD26/CD3-dependent T-cell activation or mixed-lymphocyte response). The IC50 of saxagliptin for inhibition of CD26/CD3-dependent human T-lymphocyte activation was 1000× that of the IC50 of the DPP4 enzyme catalytic activity. In addition to standard clinical and anatomical pathology, several immunotoxicity assessments were conducted in nonclinical repeat-dose studies (eg, peripheral blood lymphocyte and splenocyte phenotyping, serum

immunoglobulin [IgG and IgM] levels, antinuclear antibodies, reactive antibodies to red blood cells and/or or platelets, T- and/or B-cell dependent immune responses, and immune mediator/cytokine analyses). Elevations in serum IgG and IgM were consistently demonstrated in all species, but no phenotypic changes in peripheral blood or splenic lymphocytes were noted. Futhermore, no antinuclear antibodies or reactive Ig to erythrocytes or platelets were noted in monkeys and no impairments of T- or B-lymphocyte dependent immune responses were detected in rats. Collectively, the comprehensive nonclinical evaluation of immunologic endpoints after saxagliptin administration suggested no potential adverse effect on the immune system in humans.

In conclusion, results of the nonclinical pharmacology and safety testing program were predictive of the demonstrated efficacy and low potential for adverse side effects of saxagliptin in clinical trials. There were no nonclinical findings that preclude the safe administration of saxagliptin to humans.

4 CLINICAL PHARMACOLOGY

The pharmacokinetics of saxagliptin and its major pharmacologically active metabolite, BMS-510849, have been well characterized. Saxagliptin was:

- rapidly absorbed after oral administration, with maximum plasma concentrations usually attained within 2 hours after dosing
- extensively absorbed following an oral dose in humans, as demonstrated by mass balance and metabolic profiling data
- eliminated mainly via renal pathway (~ 76% of dose) as saxagliptin and metabolites with renal excretion as the primary elimination pathway for BMS-510849
- metabolized primarily by CYP3A
- shown to have dose proportional kinetics beyond the saxagliptin therapeutic dose range
- shown to have no appreciable accumulation upon repeated once-daily dosing at doses up to 400 mg once daily (ie, 80 times the RUCD) for up to 2 weeks

There is no need for dose modification of saxagliptin based on food or drug-drug interactions. Food had no meaningful effect on saxagliptin pharmacokinetics, and no clinically meaningful drug-drug interaction has been identified in the saxagliptin clinical

development program that would require a dose adjustment for either saxagliptin or the other drug. Drug-drug interaction studies were conducted with the following compounds: metformin (hOCT1 and hOCT2 substrate), glyburide (CYP2C9 substrate), pioglitazone (CYP2C9 [major] and CYP3A4 [minor] substrate), digoxin (P-gp substrate), simvastatin (CYP3A4 substrate), diltiazem (substrate and moderate inhibitor of CYP3A4), ketoconazole (substrate and potent inhibitor of CYP3A4), omeprazole (substrate of CYP2C19 [major], CYP3A4 [minor] and P-gp), aluminum hydroxide + magnesium hydroxide + simethicone combination, rifampin (potent inducer of CYP3A4), and famotidine (inhibitor of hOCT1, hOCT2 and hOCT3).

T2DM, body mass index (BMI), weight, gender, age, race, hepatic impairment, and mild renal insufficiency had no clinically meaningful effects on the pharmacokinetics of saxagliptin or BMS-510849.

Renal excretion was the primary elimination pathway for systemic saxagliptin and its metabolites, including BMS-510849. Based on renal clearance values, saxagliptin appeared to undergo active renal excretion, whereas BMS-510849 only appeared to be filtered. In subjects with mild renal insufficiency (CrCl 50 - 80 mL/min), AUC values of saxagliptin and BMS-510849 following administration of a single 10 mg dose of saxagliptin were 16% and 67% higher, respectively, compared with AUC values in healthy subjects with normal renal function. These differences are not considered to be clinically meaningful, and no dosage adjustment is proposed in subjects with mild renal impairment. In subjects with moderate (CrCl 30 to 50 mL/min) or severe renal impairment (CrCl < 30 mL/min), AUC values for saxagliptin and BMS-510849 were generally greater than 2-fold higher than the AUC values in healthy subjects. Because of the increased exposure, saxagliptin 2.5 mg is the dose proposed in patients with moderate, severe, or end-stage renal disease requiring hemodialysis. This dosing regimen is designed to maintain systemic exposures to saxagliptin and BMS-510849 within the 10 mg once daily long-term safety experience, while providing a glycemic-control benefit similar to that attained with 5 mg in subjects with normal renal function.

5 CLINICAL DEVELOPMENT PROGRAM

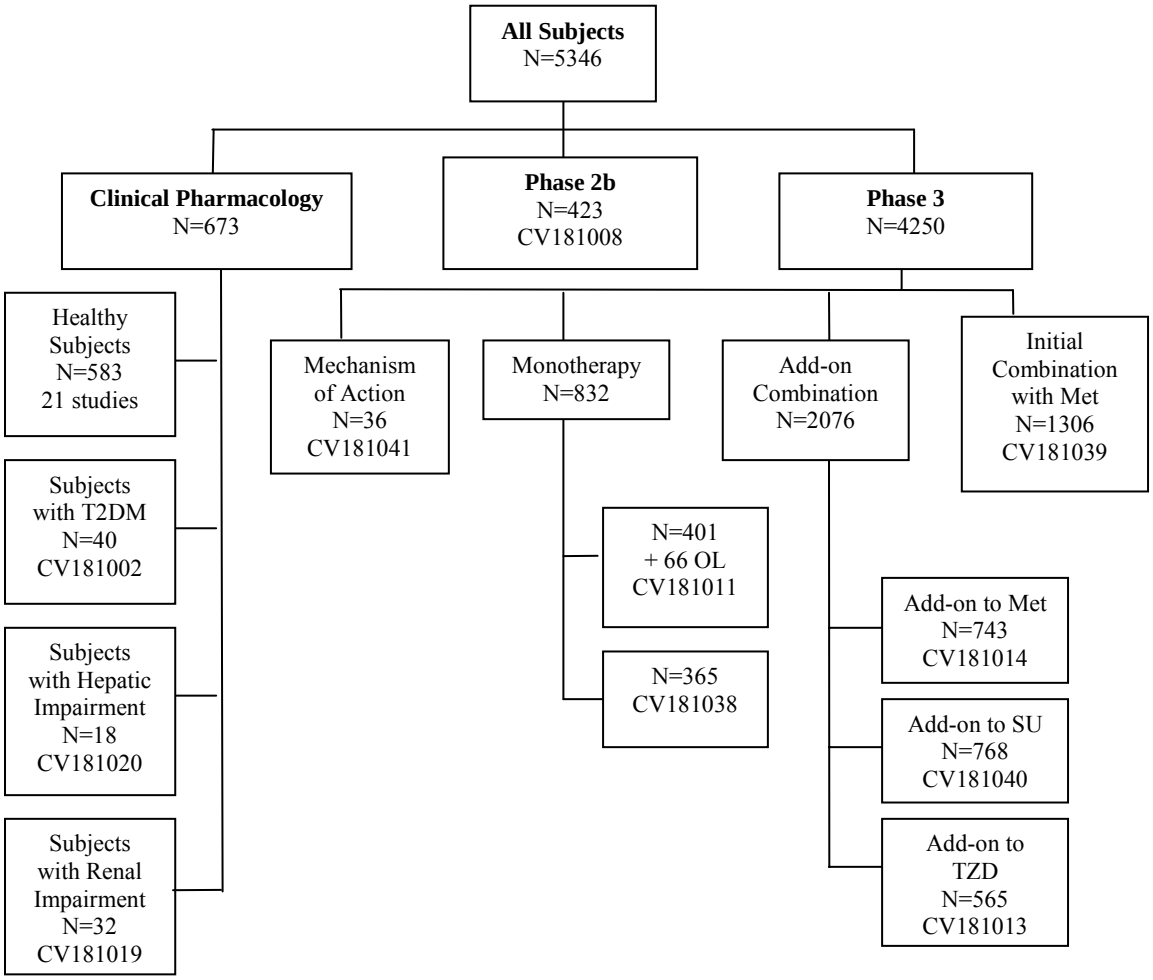
5.1 Overview

A total of 5346 subjects were evaluated in the saxagliptin Phase 1-3 clinical development program, including 423 in a Phase 2b dose ranging study and 4250 subjects in Phase 3 studies (Figure 1). In these studies, saxagliptin was studied at maximum daily doses of 400 mg (80 times the RUCD) for up to 2 weeks, 100 mg (20 times the RUCD) for up to 6 weeks, 40 mg (8 times the RUCD) and 20 mg (4 times the RUCD) for up to 12 weeks, and 10 mg (2 times the RUCD) for up to 2 years.

The Phase 2b and Phase 3 worldwide clinical development program in T2DM included eight studies in which 4607 subjects were randomized and treated, with an additional 66 subjects receiving non-randomized open-label (OL) saxagliptin 10 mg monotherapy in Study CV181011. Of the 4607 randomized and treated subjects, 3356 received double-blind saxagliptin. The eight Phase 2b/3 studies included one 12-week Phase 2b dose-finding study, one 12-week Phase 3 mechanism of action study with a 104 week long-term (LT) period, and six Phase 3 studies with 24-week short-term (ST) treatment periods and LT periods of 52-182 additional weeks. Treatment assignments were blinded to the investigators, subjects, and site personnel, during the LT treatment periods. The LT treatment periods were ongoing at the time of the submission of the New Drug Application (NDA), as agreed with the FDA at the pre-NDA meeting. Data from these LT treatment periods were included in the NDA and in the 120 Day Update of Clinical Safety Report.

In the six pivotal Phase 3 studies (also referred to as the Core Phase 3 studies), 4148 subjects with T2DM were randomized and received study drug, 3021 of whom were treated with saxagliptin. At the time of the NDA filing, a total of 1364 subjects had received saxagliptin for ≥ 50 weeks, including 328 who had received saxagliptin 10 mg, twice the RUCD. The 120 Day Update of Clinical Safety Report includes a total of 2236 subjects who had received saxagliptin for ≥ 50 weeks.

Figure 1: Saxagliptin Clinical Development Program and Number of Subjects Treated with Saxagliptin or Comparator

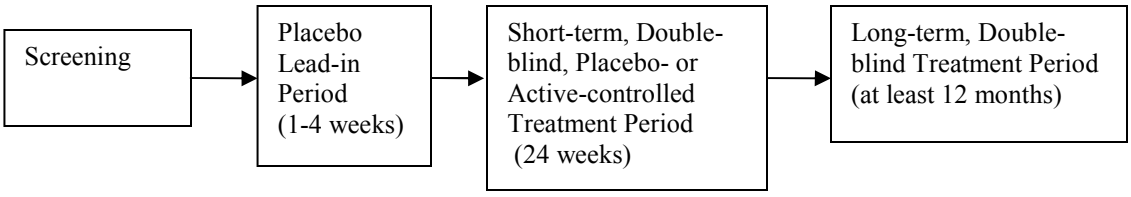


Abbreviations: Met = metformin; OL = open-label; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

All controlled studies in subjects with T2DM used a randomized, double-blind design. An overview of the Core Phase 3 study designs is provided in Figure 2. The primary assessment point for all Core Phase 3 studies was at 24 weeks. Subjects were then eligible to remain on randomized treatment and continue into a controlled LT extension of at least 12 months to provide additional safety and efficacy experience. The Core Phase 3 studies incorporated strict rescue criteria to permit additional glucose lowering treatment in the event that individual subjects experienced poor glycemic control during either the ST or LT period of each study. Glycemic rescue therapy never included the

addition of saxagliptin or other DPP4 inhibitors (sitagliptin or vildagliptin) to subjects treated with placebo or active control at any time in any study. This restriction assured the ability to make valid comparisons of safety data among subjects treated with saxagliptin compared with other non-DPP4 based standard of care diabetes therapies or placebo over ST + LT study periods of up to 128 weeks.

Figure 2: Core Phase 3 Study Design Overview



Extensive safety monitoring continued throughout the Phase 3 program. At the start of Phase 3, an independent Data Monitoring Committee (DMC) was established to periodically review the accumulating saxagliptin safety data. To complement standard safety monitoring practices, a targeted program to collect information and evaluate events of special interest was also implemented.

Inclusion and exclusion criteria were instituted to enable evaluation of a wide-range of subjects with T2DM while optimizing subject safety. The accrual of safety experience, the characterization of the clinical profile of saxagliptin, and review of the data by the DMC during Phase 3 allowed for relaxation of exclusion criteria to enable safe study of a broader patient population (ie, exclusion criteria related to lymphocytes and platelets). The studies included men and women with T2DM between the ages of 18 to 77 years with baseline C-peptide $\geq$ 1 ng/mL and BMI $\leq$ 40 kg/m^2 ($\leq$ 45 kg/m^2 in the add-on to TZD study). A1C inclusion criteria at subject screening were 7%-10% in the monotherapy and add-on to metformin studies, 7%-10.5% in the add-on to TZD study, 7.5%-10% in the add-on to SU study, and 8%-12% in the initial combination study with metformin. The lower limits for A1C were set slightly higher in the add-on to SU study

and the initial combination study to avoid possible hypoglycemia and in the initial combination study to target a population most in need of initial combination therapy.

Subjects were excluded if they had a significant history of CV events within 6 months, or CHF (NYHA Stage III or IV or LVEF ≤ 40%), as were immunocompromised individuals (such as having undergone organ transplantation or diagnosed with human immunodeficiency virus) and subjects with abnormal hepatic, renal, and hematological function. While subjects with recent CV events were excluded, the Phase 2b/3 Pooled Population included subjects at increased risk of CV events as described in Section 7.5.5.

5.2 Selection of Doses for Evaluation in Phase 3

In the Phase 3 program, saxagliptin doses of 2.5, 5, and 10 mg administered once daily were evaluated to fully characterize the efficacy, safety, and benefit/risk profile of saxagliptin within the dose-response range established in Phase 2. In addition, the potential usefulness of titration of saxagliptin as monotherapy, using a starting dose of 2.5 mg, was examined. The rationale for selecting the dose range and dosing interval for Phase 3 was based on an integrated assessment of efficacy, pharmacodynamic, and safety data generated from subjects exposed to saxagliptin in Phase 1 and 2b studies. The main conclusions from the integrated assessment were the following:

- The largest effect on glycemic control was generally seen at a dose of 5 or 10 mg, with no apparent increase in efficacy at doses higher than 10 mg.
- The largest effect to inhibit plasma DPP4 at trough was seen at a dose of 10 mg, with no apparent increase in inhibition at doses higher than 10 mg.
- Significant inhibition of plasma DPP4 activity was seen at the trough of the dosing interval, ie, 24 hours after dosing of saxagliptin 2.5, 5, and 10 mg.
- Saxagliptin doses in the range of 2.5 to 10 mg were associated with potentiation of postprandial GLP-1 and reduction in excursion of postprandial glucagon.
- No dose-limiting toxicity was observed. A modest dose-related reduction of absolute lymphocyte count was observed that was most apparent at doses of saxagliptin greater than or equal to 20 mg. This effect was reversible upon discontinuation of study drug.

Clinically meaningful and statistically significant decreases in A1C, fasting serum glucose, and postprandial serum glucose were seen at all doses in the Phase 2b study;

numerically greater reductions in A1C and fasting serum glucose were seen with the 5 mg dose. Thus, saxagliptin 5 mg served as the anchor dose in the Phase 3 program. The saxagliptin 10 mg dose was studied to provide additional safety information at a higher dose and to assess if incremental efficacy of a higher dose would be observed during long-term treatment beyond 12 weeks or in other settings besides monotherapy. The saxagliptin 2.5 mg dose was included to explore the lower end of the dose range.

6 CLINICAL EFFICACY

Data establishing the clinical efficacy of saxagliptin are based on six Core Phase 3 studies: two monotherapy placebo-controlled studies, three add-on placebo-controlled studies (add-on to TZD, SU, and metformin, respectively), and one active-controlled study where saxagliptin was given as initial treatment in combination with metformin. The key results of these studies are:

- Treatment with saxagliptin resulted in consistent, clinically meaningful and statistically significant reductions in A1C, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG), as well as achievement of treatment targets for A1C.
- Better glycemic control was consistently achieved with the 5 mg dose compared with the 2.5 mg dose. There was no incremental efficacy benefit observed with dosing of saxagliptin 10 mg compared with 5 mg.
- Beneficial effects were demonstrated across subgroups of demographic and baseline diabetic characteristics, confirming the applicability of the data to the broader T2DM population.
- Saxagliptin treatment was associated with sustained glycemic control relative to the comparator.

6.1 Methodology

The primary endpoint in the Core Phase 3 program was the change in A1C from baseline to Week 24. The three following secondary efficacy endpoints assessed at Week 24 were common to all six Core Phase 3 studies:

- change from baseline in FPG
- therapeutic glycemic response, defined as proportion of subjects achieving A1C < 7.0%
- change from baseline in AUC from 0 to 180 minutes for PPG response to an oral glucose tolerance test (OGTT)

Data collected after rescue and initiation of additional oral anti-diabetic therapy were not utilized in any efficacy analyses presented in this document. To be included in an analysis at any specific time point, the subject must have had a post-baseline measurement for the time point. If the subject received rescue medication, that measurement must have been taken before rescue.

The primary endpoint analysis results were considered statistically significant differences in adjusted mean change from baseline from control at $\alpha = 0.027$ for CV181038, CV181013, CV181040 and CV181039 and $\alpha = 0.019$ for CV181011 and CV181014 (applying Dunnetts adjustment). Secondary endpoints were tested at $\alpha = 0.05$ (applying a sequential testing procedure).

6.2 Short-term Efficacy

The efficacy of saxagliptin was established in a broad range of subjects with T2DM, enabling analyses in representative subpopulations. The range of endpoints in the studies also enabled examination of saxagliptin's mechanism of action, which provided further context and understanding of saxagliptin's glucose lowering effect. All efficacy endpoints were analyzed up to the time of rescue therapy, if needed. If a subject was rescued, the efficacy value obtained most recently prior to rescue was carried forward for analysis (ie, Last Observation Carried Forward [LOCF] method).

To provide context to the presentation of efficacy results in this section, Table 2 shows the number of randomized and treated subjects (randomized subjects data set) in the Phase 2b and Core Phase 3 studies.

Table 2: Number of Randomized and Treated Subjects in the Phase 2b and Core Phase 3 Studies

Study	Saxagliptin 2.5 mg	Saxagliptin 5 mg	Saxagliptin 10 mg	Placebo
Monotherapy				
-008*	55	47	63	67
-011	102	106	98	95
-038**	74	74	NA	74
Add-on combination				
+TZD (-013)	195	186	NA	184
+SU (-040)	248	253	NA	267
+MET (-014)	192	191	181	179
	Saxagliptin 5 mg + Metformin	**Saxagliptin 10 mg + Metformin**	**Saxagliptin 10 mg**	**Metformin**
Inital Comb. (-039)	320	323	335	328

* Includes subjects in the saxagliptin 2.5, 5, 10 mg, and placebo groups from the 0-40 mg cohort. Number of randomized and treated subjects in the saxagliptin 20, 40, 100 mg, and the placebo groups of the 0-100 mg cohort were 54, 52, 44, and 41, respectively (not shown in the table).
** Includes subjects in the saxagliptin 2.5 mg QAM, 5 mg QAM,and placebo groups. Number of randomized and treated subjects in the saxagliptin 2.5/5 mg titration group and the 5 mg PM group were 71 and 73, respectively (not shown in the table).

In subjects with T2DM, treatment with saxagliptin for 24 weeks consistently provided clinically relevant and statistically significant improvements in A1C. Improvement was achieved both in fasting and postprandial glucose levels, and was compatible with improved β-cell function.

Table 3 summarizes results from placebo-controlled Phase 2b/3 studies of saxagliptin given as monotherapy and as combination treatment added on to metformin, TZD or an SU. Statistically significantly larger reductions from baseline in A1C were seen across all studies in the saxagliptin treatment groups compared with control (Table 3 and Figures 3 and 4). Treatment with 5 mg saxagliptin led to placebo-subtracted adjusted mean changes in A1C that ranged from -0.40% to -0.83%. The saxagliptin 5 mg groups achieved greater reductions from baseline in A1C than the saxagliptin 2.5 mg groups in five of the six studies. There was no evidence for improved efficacy at 10 mg compared with 5 mg.

Table 3: A1C, FPG, and PPG AUC Difference [95%CI] from Placebo in Adjusted Mean Change from Baseline at Week 24, Phase 2b and Placebo-controlled Phase 3 Studies

Parameter / Study	Saxagliptin 2.5 mg	Saxagliptin 5 mg	Saxagliptin 10 mg
A1C (%)			
Monotherapy -008*	-0.45 [-0.78, -0.13]	-0.63 [-0.97, -0.29]	-0.54 [-0.85, -0.23]
Monotherapy -011	-0.62 [-0.90, -0.33]	-0.64 [-0.93 -0.36]	-0.73 [-1.02, -0.44]
Monotherapy -038**	-0.45 [-0.74, -0.16]	-0.40 [-0.69, -0.12]	-
Add-on-to TZD (-013)	-0.36 [-0.57, -0.15]	-0.63 [-0.84, -0.42]	-
Add-on-to SU (-040)	-0.62 [-0.78, -0.45]	-0.72 [-0.88, -0.56]	-
Add-on to MET (-014)	-0.73 [-0.92, -0.53]	-0.83 [-1.02, -0.63]	-0.72 [-0.91, -0.52]
FPG (mg/dL)			
Monotherapy -008*	-13.66 [-25.80, -1.51]	-24.49 [-36.90, -12.07]	-18.72 [-30.21, -7.22]
Monotherapy -011	-20.60 [-31.47, -9.72]	-14.73 [-25.50, -3.97]	-22.81 [-33.79, -11.84]
Monotherapy -038**	-14.7 [-27.2, -2.3]	-14.0 [-26.4, -1.6]	-
Add-on-to TZD (-013)	-11.6 [-19.7, -3.4]	-14.5 [-22.7, -6.3]	-
Add-on-to SU (-040)	-7.7 [-14.3, -1.1]	-10.3 [-16.9, -3.8]	-
Add-on to MET (-014)	-15.55 [-22.55, -8.55]	-23.28 [-30.29, -16.27]	-21.74 [-28.81, -14.68]
PPG AUC (mg*min/dL)			
Monotherapy -008*	-1295 [-2129, -462]	-1680 [-2587, -772]	-1904 [-2690, -1117]
Monotherapy -011	-6221 [-9570, -2872]	-6249 [-9546, -2952]	-7437 [-10798, -4076]
Monotherapy -038**	-4927 [-8416, -1437]	-5130 [-8630, -1630]	-
Add-on-to TZD (-013)	-5159 [-7333, -2985]	-6579 [-8826, -4333]	-
Add-on-to SU (-040)	-5492 [-7122, -3862]	-6195 [-7807, -4584]	-
Add-on to MET (-014)	-5599 [-7894, -3305]	-6294 [-8606, -3983]	-4845 [-7153, -2537]

*The duration of study CV181008 was 12 weeks, all other studies were of 24 weeks duration. In study CV181008, fasting serum glucose was analyzed (FPG in the other studies), and PPG AUC (0-60 min) was measured after a mixed meal [PPG AUC (0-180 min) was measured after an OGTT in the other studies].
** In study CV181038, data from the saxagliptin 2.5 mg AM (without titration) and 5 mg AM groups are shown.

Figure 3: A1C Adjusted Mean Changes from Baseline (95%CI) at Week 24 (LOCF) - Phase 3 Monotherapy Studies

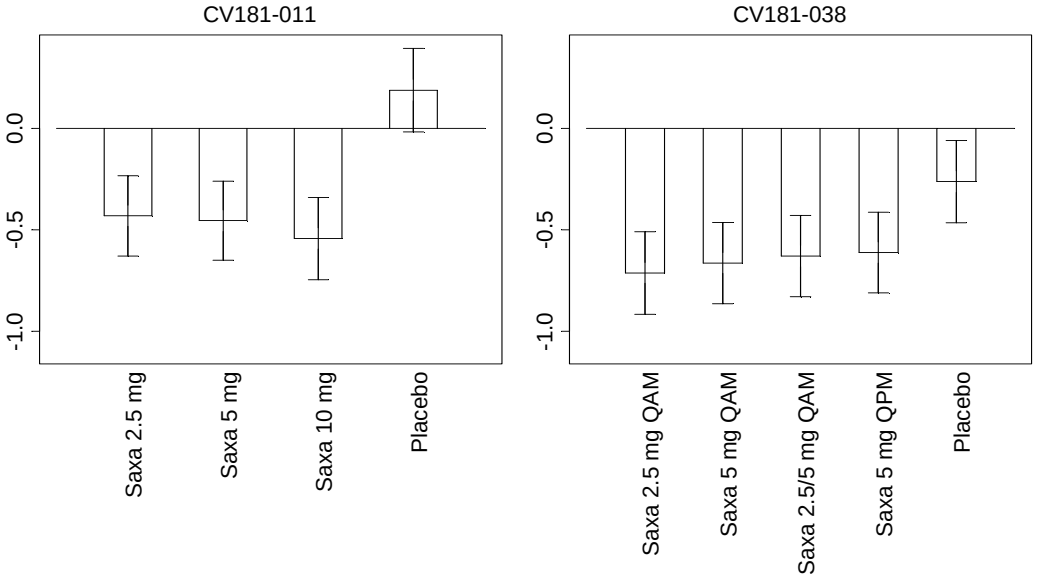
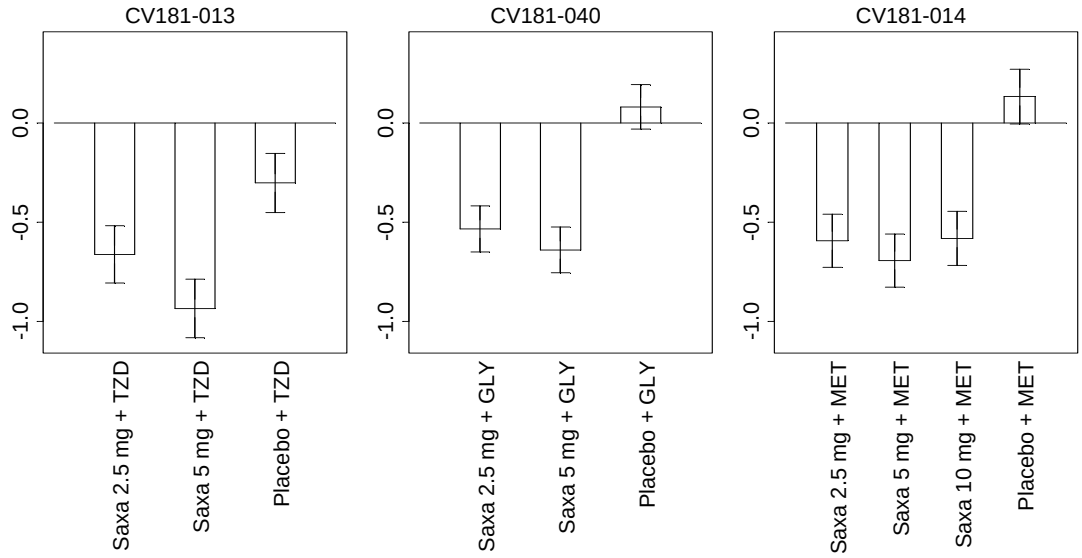
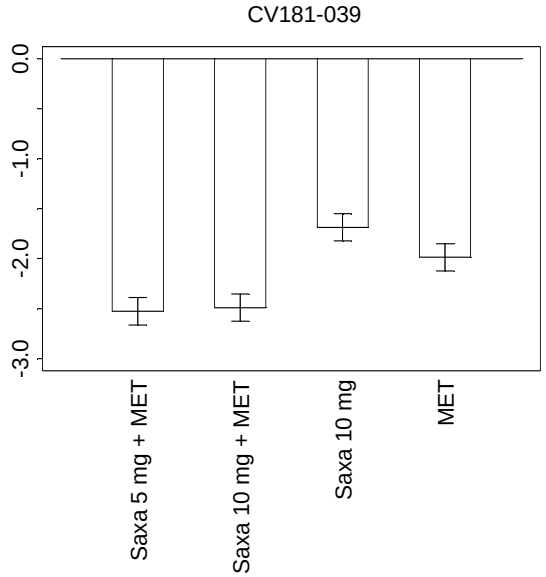


Figure 4: A1C Adjusted Mean Changes from Baseline (95%CI) at Week 24 (LOCF) - Phase 3 Add-on Combination Therapy Studies



As expected, the reduction in A1C was largest in the initial combination study with metformin, which included a treatment naive population with a higher baseline A1C compared with the other studies in the program (Figure 5). The adjusted mean change from baseline in A1C was -2.53% in the saxagliptin 5 mg + metformin group and -2.49% in the saxagliptin 10 mg + metformin group, with the largest mean reduction observed in subjects in the pre-defined subgroups with baseline A1C ≥ 9% to < 10% (-2.49% in the saxagliptin 5 mg + metformin group) and ≥ 10% (-3.33% in the saxagliptin 5 mg + metformin group). In the saxagliptin 5 mg + metformin group, the difference (95% confidence interval [CI]) in adjusted mean change from baseline was -0.54% (-0.73, -0.35) when compared with metformin monotherapy and -0.84% (-1.03, -0.65) when compared with saxagliptin 10 mg monotherapy. These differences were statistically significant. Similar decreases in A1C were observed for the saxagliptin 10 mg + metformin group when compared with saxagliptin and metformin monotherapy.

Figure 5: A1C Adjusted Mean Changes from Baseline (95%CI) at Week 24 (LOCF) - Phase 3 Initial Combination Study CV181039



Reductions in FPG were observed consistently across all studies (Table 3). In the initial combination with metformin study, the adjusted mean change from baseline (95% CI) in FPG was -59.8 (-64.4, -55.2) and -62.2 (-66.8, -57.7) mg/dL in the saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin groups, respectively, compared with -30.9 (-35.5, -26.4) and -47.3 (-51.9, -42.8) mg/dL in the saxagliptin 10 mg and metformin monotherapy groups, respectively. The differences between the saxagliptin + metformin combination therapy groups and the monotherapy groups were statistically significant. The impact of treatment with saxagliptin on FPG provided clinical evidence for improvement in basal β-cell function as also indicated by increases in HOMA-2β. The proportion of subjects who achieved the pre-specified glycemic goal of A1C < 7% was larger in the saxagliptin treatment groups compared with the control groups. As was observed for the primary efficacy endpoint, the greatest effect on the endpoints of FPG and the proportion of subjects who achieved A1C < 7% was most frequently seen at the 5 mg saxagliptin dose compared with 2.5 mg, without evidence for improved efficacy at 10 mg beyond that seen for 5 mg. Despite the high A1C at baseline in the initial combination study, ranging from a mean of 9.4% to 9.6%, the proportion of subjects who achieved the glycemic goal of A1C < 7% at 24 weeks was 60.3% and 59.7% in the saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin groups as compared with 32.2% and 41.1% for the saxagliptin, and metformin groups, respectively. The proportion of subjects who achieved A1C reductions ≥ 0.7% was similarly greater in subjects who received saxagliptin 5 mg compared with 2.5 mg in all studies except CV181038.

There was a decrease from baseline to Week 24 in PPG AUC (Table 3) and in the PPG levels measured at 120 minutes after a standard OGTT in the saxagliptin treatment groups compared with placebo. Greater decreases in PPG AUC were seen at the 5 mg saxagliptin dose compared with 2.5 mg in all studies, without evidence for improved efficacy at 10 mg beyond that seen at 5 mg. In the initial combination with metformin study, the adjusted mean change from baseline (95% CI) in PPG AUC was -21080 (-22723, -19437) and -21336 (-23044, -19628) mg*min/dL in the saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin groups, respectively, compared with -16054 (-17677, -14430) and -15005 (-16689, -13322) mg*min/dL in the saxagliptin 10 mg and metformin monotherapy groups, respectively. The differences between the saxagliptin + metformin combination therapy groups and the monotherapy groups were statistically significant.

The reduction in PPG AUC in conjunction with increases in insulin and C-peptide concentrations during a standard OGTT provides clinical evidence for the effect of saxagliptin on improving β-cell function. These findings are consistent with the proposed mechanism of action of saxagliptin, which is to enhance incretin action leading to augmentation of glucose-dependent insulin secretion. Improvement in glucose sensing by the α-cells may also have contributed to this observation[15], as demonstrated by a greater decrease from baseline in postprandial glucagon concentrations at Week 24, an effect reported for other incretin mimetics and DPP4 inhibitors.[16,17] There was a numerical decrease in mean postprandial glucagon AUC and a numerical increase in mean postprandial insulin AUC in the saxagliptin treatment groups compared with the control groups in all Core Phase 3 studies.

Based on evaluations of A1C reduction in multiple subgroup populations, treatment with saxagliptin consistently demonstrated a beneficial antihyperglycemic effect across subgroups of demographic and baseline diabetes characteristics (eg, age, gender, race). There were clinically meaningful reductions in A1C for monotherapy and combination therapy groups regardless of age, comparing subjects < 65 and ≥ 65 years. While the number of subjects ≥ 75 years was low (1.4% of subjects in the Core Phase 3 studies), the A1C reductions were comparable to the younger age groups. Saxagliptin-treatment led to greater reductions in A1C from baseline for subgroups with higher baseline A1C, typical of drugs used for the treatment of diabetes.

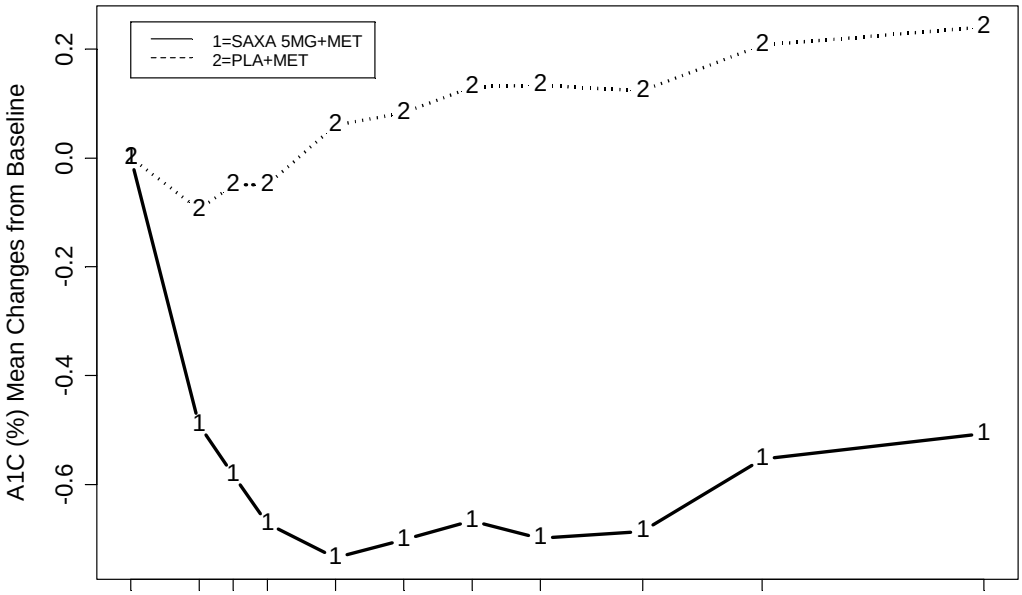
6.3 Long-term Efficacy

Interim analyses were performed on the efficacy results from ongoing LT extensions of the six Core Phase 3 studies. Because glycemic parameters would be affected by the addition of rescue therapy, efficacy results obtained after the initiation of rescue treatment were not included in any efficacy analyses.

In the interim analyses of the LT data from all Phase 3 studies, treatment with saxagliptin was associated with a greater reduction in A1C when compared with the control group. For example, the placebo-subtracted adjusted mean change (95% CI) from baseline in A1C at Week 50 in the saxagliptin 5 mg treatment group was -0.74% (-0.95, -0.54) in the add-on to metformin study based on LOCF analysis (see Figure 6). Although the shape of

the A1C concentration curves varied, a difference relative to control persisted in all studies.

Figure 6: A1C Mean Changes from Baseline (LOCF) During ST + LT Treatment Period, Add-on to Metformin Study CV181014



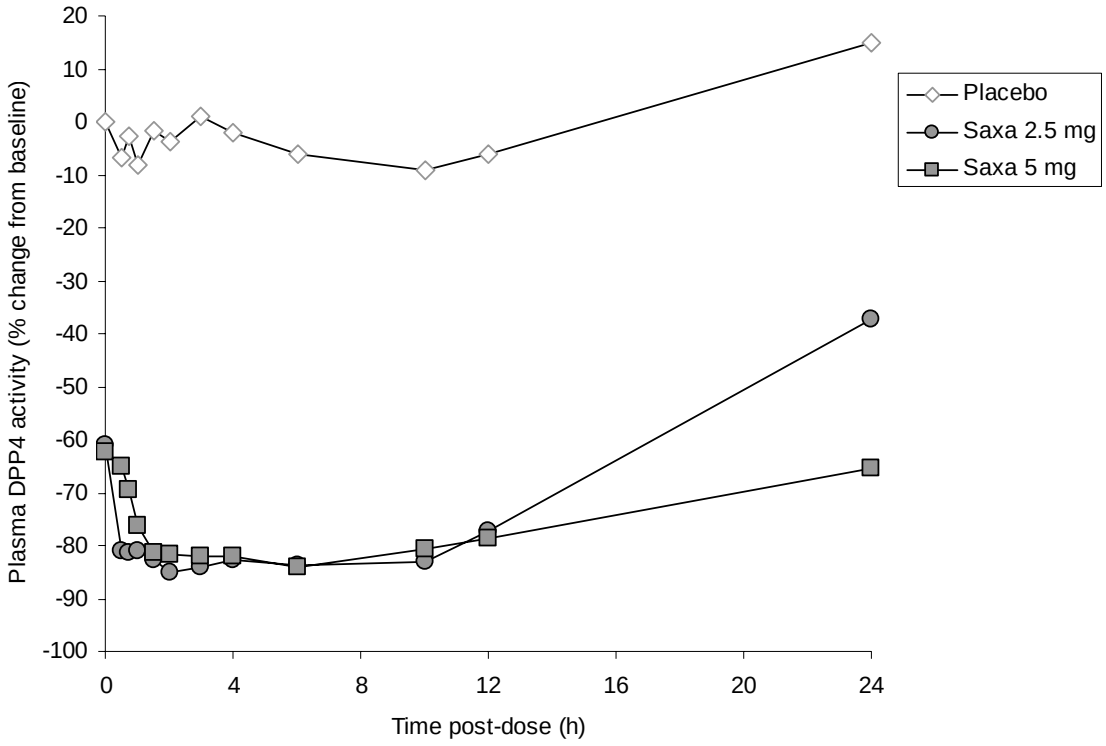
Number of subjects:										
SAXA 5MG(LOCF):	191	178	187	187	187	187	187	187	187	187
SAXA 5MG(obs):	191	174	173	167	163	150	144	137	122	100
PLA(LOCF):	179	165	175	175	175	175	175	175	175	175
PLA(obs):	179	162	148	139	132	122	110	106	74	59

6.4 Relevance and Applicability of Efficacy Data for Dosing

The efficacy results from the eight clinical studies in the saxagliptin Phase 2b/3 program in over 4600 subjects support the oral dose of saxagliptin 5 mg once daily in a wide range of subjects with T2DM, in either monotherapy, add-on combination therapy with metformin, a TZD, a SU, or initial combination therapy with metformin. Based on consistency and magnitude of glycemic effect, saxagliptin 5 mg once daily is the optimal dose. This is a fixed dose regimen with no need for titration.

In the Phase 1 and Phase 2b studies, administration of saxagliptin 5 mg was associated with greater inhibition of plasma DPP4 activity at the trough of the dosing interval compared with 2.5 mg (Figure 7). Clinically meaningful and statistically significant decreases in A1C, fasting serum glucose, and postprandial serum glucose were also seen at all doses in the Phase 2b study; the greatest numerical reductions in A1C and fasting serum glucose were seen with the 5 mg dose.

Figure 7: Mean Steady-state Plasma DPP4 Inhibition Following Once Daily Doses of 2.5 or 5 mg Saxagliptin or Placebo in Subjects with T2DM



Data from study CV181002 (Multiple ascending dose study in subjects with T2DM), n=6 or 7

There was no evidence that the 10 mg saxagliptin dose offered any incremental glycemic benefits to those observed with the 5 mg dose. Subjects in the saxagliptin 5 mg groups consistently achieved better glycemic control than the subjects who received saxagliptin 2.5 mg. In all studies except for CV181038 (where the adjusted mean change from

baseline [95% CI] to Week 24 in A1C was -0.66% [-0.86, -0.46] for the saxagliptin 5 mg group and -0.71% [-0.92, -0.51] for the 2.5 mg group), the saxagliptin 5 mg group consistently demonstrated greater decreases from baseline in A1C than the saxagliptin 2.5 mg group; the magnitude of difference in A1C change from baseline favoring the 5 mg over the 2.5 mg dose ranged from 0.02% to 0.26%. A post-hoc pooled analysis was performed for A1C reduction from baseline including the saxagliptin 2.5 and 5 mg groups in the Phase 2b monotherapy study (CV181008) and the two Phase 3 monotherapy studies (CV181011 and the QAM groups in CV181038). A1C inclusion criteria in these studies were similar. In this assessment, where the timepoint of A1C evaluation, as well as the time of saxagliptin dosing, were uniform across the pooled studies, a greater A1C reduction from baseline at 12 weeks was observed in the 5 mg QAM group (-0.72%) compared with the 2.5 mg QAM group (-0.61%); the placebo-subtracted values (95% CI) were -0.61% (-0.78, -0.45) and -0.51% (-0.67, -0.35), respectively. Accordingly, there is consistent evidence for a superior glycemic benefit at the 5 mg saxagliptin dose, whether studied as monotherapy or in combination treatment with metformin, SU, or TZD.

There were larger decreases from baseline in FPG in the saxagliptin 5 mg group than in the saxagliptin 2.5 mg groups in all of the add-on combination studies. In addition, there was a greater reduction from baseline in PPG AUC for the saxagliptin 5 mg groups compared with the 2.5 mg groups in all Phase 2b/3 studies. PPG AUC, a measure of the primary mechanism of action for saxagliptin, aligns with the primary endpoint of A1C lowering, and supports the conclusion that saxagliptin 5 mg per day is the optimal dose.

7 CLINICAL SAFETY

Saxagliptin was well tolerated in all clinical trials at once daily doses of up to 400 mg (80 times the RUCD) for up to 2 weeks, 100 mg (20 times the RUCD) for up to 6 weeks, 40 mg (8 times the RUCD) and 20 mg (4 times the RUCD) for up to 12 weeks and 10 mg (2 times the RUCD) for up to 2 years. Overall, in the extensive Phase 2b/3 program in 3422 subjects treated with saxagliptin, the safety profiles of saxagliptin 2.5 mg and 5 mg were generally comparable. The majority of reported adverse events (AEs) were of mild intensity and did not require treatment discontinuation. The safety profile was generally

consistent when saxagliptin was given as monotherapy, as add-on combination treatment to metformin, SU, or TZD, and as initial therapy in combination with metformin.

7.1 Safety Background

7.1.1 Safety Monitoring in Phase 3 Studies

The safety of saxagliptin was evaluated extensively throughout the Phase 3 program. Standard safety monitoring included evaluation of AEs, laboratory parameters, and vital signs. In addition, at the start of the Phase 3 clinical development program, an independent Data Monitoring Committee (DMC) was established. The DMC periodically reviewed the accumulating saxagliptin safety data, including findings from the six Core Phase 3 studies. The DMC has allowed all studies in the saxagliptin Phase 3 program under its review to continue at all doses under evaluation and has not required any modifications. Based on ongoing review of Phase 3 data, the DMC approved relaxation of protocol-specified discontinuation criteria for decreased lymphocyte and platelet count.

To complement standard safety monitoring practices, an extensive program to monitor and collect information on events of special interest was implemented. Events were identified as being of special interest based on findings observed in the saxagliptin non-clinical and Phase 1 and 2b programs, safety-related concerns reported for other DPP4 inhibitors, and theoretical considerations related to the mechanism of action of DPP4 inhibitors. The events of interest included: (1) events related to skin lesions; (2) selected infections (eg, events related to herpes simplex virus or Mycobacterium tuberculosis); (3) decreased lymphocyte counts; (4) decreased platelet counts; and (5) events of localized edema. Monitoring activities included ongoing identification of events and deployment of supplemental case report forms (CRFs) to gather additional information. Algorithms were developed to guide investigators in managing subjects with decreases in lymphocyte or platelet counts or findings related to liver function test abnormalities and creatine kinase (CK) elevation. In addition, special CRFs were also used throughout the Phase 3 program to acquire details of all reported events of hypoglycemia.

7.1.2 Methods

7.1.2.1 Populations

Safety data from the following populations are presented:

1) **Study Level Populations**: Includes presentation of data from each of the six Core Phase 3 studies including the five placebo-controlled studies (two monotherapy [CV181011 and CV181038], add-on to metformin [CV181014], add-on to SU [CV181040], and add-on to TZD [CV181013]) and one active-controlled study (initial combination with metformin [CV181039]).
2) **Placebo-controlled Pooled Safety Population**: Includes pooled subject data from the five placebo-controlled pivotal Phase 3 studies (two monotherapy [CV181011 and CV181038], add-on to metformin [CV181014], add-on to SU [CV181040], and add-on to TZD [CV181013]).
3) **Phase 2b/3 Pooled Population**: Includes the Phase 2b study CV181008, six Core Phase 3 studies (see above), and one Phase 3 mechanism of action study (CV181041).

The Study Level Populations enabled evaluation of potential safety signals for saxagliptin administered under different treatment conditions (ie, as monotherapy, as add-on combination to either metformin, TZD, or SU, or as initial combination with metformin). The Placebo-controlled Pooled Safety Population allowed for integration of small numerical imbalances within each placebo-controlled study population data set. This pooling approach facilitated recognition of potential small signals and provided increased precision of AE rates through adding datasets common among saxagliptin-treated subjects compared with placebo-treated subjects. Finally, the Phase 2b/3 Pooled Population incorporated the controlled experience for all eight Phase 2b/3 studies, enabling comprehensive evaluation of relatively infrequent events (eg, deaths).

The experience from the 10 mg OL cohort of monotherapy Study CV181011 is not included in tabular presentations due to its uncontrolled nature; thus, the analyses that follow are reflective of the controlled Phase 2b/3 experience. The safety findings in the open-label cohort were qualitatively similar to the findings in the double-blind cohort of Study CV181011.

The demographic and baseline disease characteristics of the Phase 2b/3 Pooled Population are shown in Table 4. The shorter mean duration of T2DM in the saxagliptin 10 mg treatment group is a reflection of the study of the 10 mg dose in one monotherapy and the initial combination study, where mean duration of T2DM at study entry was shorter than in the add-on combination studies. The 10 mg dose was not studied in two of the three add-on combination studies.

Table 4: Demographic and Baseline Disease Characteristics, Phase 2b/3 Pooled Population

		Saxa 2.5 mg N = 937	Saxa 5 mg N = 1269	Saxa 10 mg N = 1000	All Saxa (a) N = 3356	Control (b) N = 1251
Age,	Mean (SD) years	54.6 (10.0)	53.7 (10.3)	52.7 (10.7)	53.6 (10.3)	53.9 (10.6)
Race,	White, n (%)	650 (69.4)	902 (71.1)	775 (77.5)	2456 (73.2)	889 (71.1)
	Non-white, n (%)	287 (30.6)	367 (28.9)	225 (22.5)	900 (26.8)	362 (28.9)
Gender,	Male, n (%)	444 (47.4)	625 (49.3)	495 (49.5)	1659 (49.4)	620 (49.6)
	Female, n (%)	493 (52.6)	644 (50.7)	505 (50.5)	1697 (50.6)	631 (50.4)
Duration of T2DM						
	Mean (SD) years	5.1 (5.2)	4.1 (5.1)	2.5 (3.6)	3.8 (4.8)	4.1 (5.0)
Duration of T2DM Categories						
	≥ 5 years, n (%)	386 (41.2)	400 (31.5)	193 (19.3)	1005 (29.9)	388 (31.0)
	≥ 10 years, n (%)	150 (16.0)	145 (11.4)	53 (5.3)	356 (10.6)	151 (12.1)
A1C						
	Mean (SD) %	8.1 (0.99)	8.5 (1.18)	9.0 (1.42)	8.5 (1.26)	8.4 (1.23)
A1C Categories						
	< 8%, n (%)	444 (47.4)	455 (35.9)	260 (26.0)	1253 (37.3)	486 (38.8)
	≥ 8% - < 9%, n (%)	302 (32.2)	412 (32.5)	249 (24.9)	996 (29.7)	381 (30.5)
	≥ 9%, n (%)	190 (20.3)	397 (31.3)	488 (48.8)	1097 (32.7)	383 (30.6)
CrCl	≤ 80 mL/min, n (%)	158 (16.9)	241 (19.0)	147 (14.7)	560 (16.7)	238 (19.0)
	> 80 mL/min, n (%)	779 (83.1)	1027 (80.9)	853 (85.3)	2795 (83.3)	1013 (81.0)

Table 4: Demographic and Baseline Disease Characteristics, Phase 2b/3 Pooled Population

	Saxa 2.5 mg N = 937	Saxa 5 mg N = 1269	Saxa 10 mg N = 1000	All Saxa (a) N = 3356	Control (b) N = 1251
At least one diabetes-related microvascular complication*, n (%)	181 (19.3)	216 (17.0)	130 (13.0)	547 (16.3)	219 (17.5)

(a) Includes 20, 40 and 100 mg experience from CV181008
(b) Includes metformin monotherapy from CV181039
* Microvascular complication includes: retinopathy, neuropathy, nephropathy, and microalbuminurea.

7.1.2.2 Datasets

Safety analyses were performed on the following datasets:

1) **ST excluding rescue**: 24-week data from the ST treatment period, excluding data collected after the initiation of rescue therapy. This dataset avoided the issue of confounding by rescue treatment.
2) **ST including rescue:** Data through 24 weeks, regardless of rescue. This dataset addressed imbalances in exposure to blinded study medication across treatment groups. As noted previously, no subject randomized to placebo or active control metformin monotherapy was ever rescued for the purpose of maintaining necessary glycemic control with saxagliptin or another DPP4 inhibitor.
3) **ST + LT data including rescue**: Data collected through the interim database lock from both the ST period of study and LT extension including data collected after the initiation of rescue therapy. Analyses of these interim databases were performed on ST + LT data at the time of: 1) data cutoff for the NDA (NDA Database) and 2) data cutoff for the 120 Day Update of Clinical Safety Report (120 Day Database). These datasets provide the most complete longitudinal experience available for analysis and are used extensively for evaluation of infrequent adverse events.

7.2 Exposure

A total of 5346 subjects were studied in the saxagliptin Phase 1-3 clinical program, of which 4042 subjects received saxagliptin. In the Phase 2b/3 program, which included eight studies in total, 3422 subjects received saxagliptin, including 66 subjects who received OL saxagliptin 10 mg in Study CV181011, and 1251 received placebo or control

treatment. Overall, 937, 1269, and 1066 subjects received saxagliptin at doses of 2.5 mg, 5 mg, and 10 mg, respectively, once daily. There is substantial exposure beyond the 24-week ST treatment period, including exposure beyond 102 weeks of continued dosing (Table 5). Approximately one-third of exposure on saxagliptin was accrued at a dose of 10 mg, which is two-times the proposed usual clinical dose of 5 mg.

Table 5: Extent of Exposure in ST + LT Periods (Including Rescue) in the NDA and the 120 Day Database, Phase 2b/3 Pooled Population

	Number of Subjects				
Weeks	**Saxa 2.5 mg[a] N = 937**	**Saxa 5 mg[a] N = 1269**	**Saxa 10 mg[b] N = 1066**	**All Saxa[c] N = 3422**	**Control[d] N = 1251**
Exposure in the NDA					
≥ 24	773	1038	831	2642	942
≥ 50	512	524	328	1364	463
≥ 76	193	200	215	608	152
≥ 102	72	80	114	266	66
Exposure in the 120-Day Update of Clinical Safety					
≥ 24	773	1046	836	2655	945
≥ 50	660	879	697	2236	784
≥ 76	361	393	260	1014	288
≥ 102	145	149	177	471	110

[a] Saxa 2.5 mg includes subjects titrated to 5 or 10 mg from CV181038 and the Saxa 5 mg includes subjects titrated to 10 mg from CV181038.

[b] Includes exposure from the saxagliptin 10 mg OL group in Study CV181011 (N = 66).

[c] Includes saxagliptin 20 mg (N = 54), saxagliptin 40 mg (N = 52), saxagliptin 100 mg (N = 44) groups in Study CV181008 and saxagliptin 10 mg OL group in CV181011.

[d] Includes exposure from the placebo group (N = 41) of the 0, 100 mg cohort (Study CV181008) and the metformin monotherapy group (N = 328) from the initial combination study (CV181039).

The exposure for the Saxa 5 mg + Met and Saxa 10 mg + Met treatment groups from CV181039 includes exposure to saxagliptin only (not metformin).

Abbreviations: LT = long-term; Met = Metformin; OL = open-label; Saxa = saxagliptin; ST = short-term.

At the time of the 120 Day Update of Clinical Safety the total number of subjects in the Phase 2b/3 Pooled Population exposed to saxagliptin (2.5 mg, 5 mg, or 10 mg) for

≥ 50 weeks included 652 subjects treated with saxagliptin monotherapy, 902 subjects treated with saxagliptin in combination with metformin (the add-on combination study and the initial combination study), 407 subjects treated with saxagliptin added on to SU, and 275 subjects treated with saxagliptin added on to TZD.

The ICH guidance for industry (E1A)[18] recommends a total exposure of at least 1,500 subjects (300 to 600 for 6 months, 100 for 1 year) for the safety assessment of chronically administered drugs developed for the treatment of non-life-threatening conditions. In the February 2008 Draft Guidance for Diabetes Mellitus, the FDA recommended that exposures exceeding these recommendations should be used for products developed for the treatment of T2DM, given the large and growing size of the population with T2DM and the increasing complexity of treatment regimens.[19] At the time of submission of the marketing application for products intended for the treatment of T2DM, the FDA Draft Diabetes Mellitus Guidance recommendation was that 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 to the investigational product for 18 months or more.

The December 2008 FDA Final Guidance on evaluating CV risk in new antidiabetic therapies to treat T2DM additionally commented that controlled trials will need to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term CV risk (eg, minimum 2 years) for these chronically used therapies.[1]

Table 6 shows the extent of exposure to saxagliptin in the Phase 2b/3 Pooled Population program in light of the ICH and FDA guidelines. In each instance, the saxagliptin program has met or exceeded exposure guidelines provided by ICH and FDA, and, in addition, includes substantial experience beyond 2 years of continuous dosing.

Table 6: Extent of Exposure to Saxagliptin in the Phase 2b/3 Pooled Population

Exposure	ICH Guidance*	FDA Guidance*	Saxagliptin ST + LT NDA Database	Saxagliptin ST+ LT 120 Day Database
Total	1500	2500	3422	3422
≥ 1 year (1)	100	1300 - 1500	1364	2236
≥ 18 months (2)	NA	300 - 500	608	1014
≥ 2 years (3)	NA	NA	266	471

* Sources: FDA Draft Guidance for Diabetes Mellitus[19] and ICH E1 Guideline[18]

(1) ≥ 50 weeks

(2) ≥ 76 weeks

(3) ≥ 102 weeks

Unless otherwise specified, the safety findings described below are based on exposure up to 24 weeks in duration, with a focus on the saxagliptin 5 mg once daily dose.

7.3 Adverse Events

Saxagliptin was well tolerated as monotherapy and in combination with other oral antihyperglycemic agents. The overall frequency of subjects with (AEs) (including AEs of hypoglycemia) in subjects treated with saxagliptin 5 mg was similar to placebo (72.2% compared with 70.6%), based on an analysis of the Placebo-controlled Pooled Safety Population up to Week 24 including rescue (Table 7). The clinical AE profile for the saxagliptin 2.5 mg and 5 mg doses was similar.

Analyses of the LT extensions of the Core Phase 3 studies, which included data up to 128 weeks in duration, did not reveal any unexpected events or emergent safety signals when compared with analyses of the respective short-term (24-week) study periods. The overall clinical AE profile based on exposure up to 128 weeks was consistent with that observed at 24 weeks.

In general, the clinical AE profile of saxagliptin did not differ consistently within major subgroups, including by gender, age (< 65 and ≥ 65 years), race, ethnicity, BMI, duration of diabetes, and degree of renal insufficiency.

Table 7: Overall Summary of Adverse Events During Double-blind Period up to Week 24, Regardless of Rescue (NDA Database), Placebo-controlled Pooled Safety Population

	Number (Percent) of Subjects				
	Saxa 2.5 mg N = 882	**Saxa 5 mg N = 882**	**Saxa 10 mg N = 279**	**All Saxa N = 2043**	**Placebo N = 799**
At least one AE	635 (72.0)	637 (72.2)	214 (76.7)	1486 (72.7)	564 (70.6)
Deaths	2 (0.2)	0	0	2 (<0.1)	2 (0.3)
At least one SAE	31 (3.5)	30 (3.4)	7 (2.5)	68 (3.3)	27 (3.4)
At least one related* SAE	2 (0.2)	1 (0.1)	0	3 (0.1)	1 (0.1)
Discontinuations due to SAEs	5 (0.6)	2 (0.2)	3 (1.1)	10 (0.5)	5 (0.6)
Discontinuations due to AEs	19 (2.2)	29 (3.3)	11 (3.9)	59 (2.9)	14 (1.8)

* Investigator assessment of relationship.

7.4 Deaths, Serious Adverse Events, and Adverse Events Leading to Discontinuation

There were a total of 4 deaths reported in the Placebo-controlled Pooled Safety Population, up to Week 24 regardless of rescue, two in the saxagliptin group and two in the placebo group (Table 7). In an analysis of all Phase 2b/3 studies [ie, based on the Phase 2b/3 Pooled Population (NDA Database)], a total of 16 deaths were reported in the ST + LT treatment period including rescue; 2 subjects (0.2%) each in the saxagliptin 2.5 and 5 mg groups, 3 subjects (0.3%) in the saxagliptin 10 mg group, 5 subjects (0.5%) treated with placebo, and 4 subjects (1.2%) treated with metformin. There was one additional death in a subject with a history of hepatic impairment who received saxagliptin in a clinical study evaluating the pharmacokinetics of saxagliptin in subjects with hepatic impairment (CV181020). This was a 46-year-old female who died as a result

of multi-organ failure (Child Pugh Class C) 40 days after a single dose of saxagliptin 10 mg. The investigator characterized the event as unrelated to saxagliptin.

The frequency of serious adverse events (SAEs) was generally comparable between the saxagliptin and control groups throughout the six Core Phase 3 studies (ie, saxagliptin given as monotherapy, as add-on combination treatment to metformin, TZD and SU, or as initial combination therapy with metformin). In the Placebo-controlled Pooled Safety Population, the proportion of subjects with SAEs was 3.4% in subjects who received saxagliptin 5 mg and 3.4% in subjects who received placebo (Table 7). SAEs were uncommon in all studies, and there was no predominance of any single, specific SAE associated with saxagliptin treatment. SAEs considered to be related to study drug or leading to discontinuation were infrequent in subjects who received saxagliptin and occurred at rates generally comparable to that of placebo (Table 7).

The frequency of AEs leading to discontinuation of study drug was generally low for all treatment groups in the Core Phase 3 studies. In the Placebo-controlled Pooled Safety Population, the overall frequency of AEs leading to discontinuation of study drug was comparable between the saxagliptin 2.5 mg (2.2%) and placebo (1.8%) groups, but was greater for subjects in the saxagliptin 5 mg (3.3%) and 10 mg (3.9%) groups (Table 7). In the active-controlled initial combination study with metformin, the frequency of discontinuation due to AEs was comparable for each saxagliptin treatment group (2.4% for saxagliptin 10 mg monotherapy; 2.5% for saxagliptin 5 mg + metformin; and 2.2% for saxagliptin 10 mg + metformin) as compared with the metformin monotherapy group (3.4%). The most frequently reported AEs (> 1 subject, based on Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]) leading to study discontinuation, which were numerically higher in subjects who received saxagliptin compared with placebo were: lymphopenia, blood CK increased, blood creatinine increased, nausea, and eye pain. Rates of discontinuation for rash were similar in subjects who received saxagliptin and placebo, whereas the rate of discontinuation for AEs of weight increased, depression, and angina pectoris were higher in subjects who received placebo compared with saxagliptin. The most common AEs leading to discontinuation from study in the metformin monotherapy group were related to gastrointestinal disorders.

7.5 Cardiovascular Safety

Cardiovascular disease is the leading cause of morbidity and mortality in subjects with T2DM. CV safety was therefore carefully evaluated in the saxagliptin development program. A comprehensive set of analyses was performed in light of the recent (December 2008) FDA Final Guidance on evaluating CV risk in new antidiabetic therapies to treat T2DM.[1] The December 2008 FDA guidance provides recommendations on how to demonstrate that new treatments for T2DM are not associated with an unacceptable CV risk.

In this Guidance, the Agency recommended that Sponsors compare the incidence of important CV events occurring with the investigational agent to the incidence of the same types of events occurring with the control group by calculating a point estimate and 95% confidence interval (95% CI) for the estimated risk ratio. The point estimate represents the value most consistent with available data for the risk ratio while the 95% CI represents the range that would contain the true risk ratio 95% of the time. The Agency indicated that pre-marketing data showing an upper bound of the 95% CI between 1.3 and 1.8 would support approval; a post-marketing trial generally would be needed in this circumstance to show that the upper bound is < 1.3. Pre-marketing data showing an upper bound < 1.3 would support approval; a post-marketing trial may not be necessary in this circumstance. The Agency noted that a point estimate of 1.5 would not be reassuring, even if the upper bound of the 95% CI was < 1.8.

The FDA indicated that important CV events include cardiovascular mortality, myocardial infarction, and stroke, but could also include other events (eg, hospitalization for acute coronary syndrome and urgent revascularization procedures). This evaluation could be accomplished through a meta-analysis of Phase 2 and 3 clinical trials (including all placebo-controlled trials, add-on trials, and active-controlled trials) that were appropriately designed to enable integration. Sponsors were advised to consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase.

The FDA requested specific analyses of CV events in separate communications to the Sponsor. The Sponsor performed these analyses, and the results are presented in Section 7.5.2.

The Sponsor has also provided additional assessments of CV events in the saxagliptin program. Results of these analyses are presented in Section 7.5.4. The Sponsor has conducted these assessments in accordance with the principles described in the guidance document. Because the guidance was issued after the submission of the saxagliptin NDA, analyses of most CV events were conducted retrospectively. In addition, CV events were not prospectively adjudicated in the saxagliptin Phase 2b/3 program. Nonetheless, the assessment of SAEs and AEs performed according to standards of clinical trial conduct and Good Clinical Practice can identify major and significant CV events across the clinical trial program to allow a comprehensive assessment of the CV safety. The timeline for the saxagliptin clinical development program, the issuance of the FDA guidance, and the analyses of CV events in the saxagliptin program is summarized below:

July 2005:	• End of Phase 2 Meeting: FDA provided guidance to Sponsor on design of Phase 3 studies. • Sponsor implemented the Agency's recommendations for the Phase 3 clinical development program.
November 2007:	• Pre-NDA meeting: FDA requested longer duration of exposure in Phase 3 studies. • Sponsor delayed NDA submission to accommodate FDA request to provide increased exposure.
June 2008:	• Sponsor analyzed Acute Cardiovascular Events in the saxagliptin clinical program. • Sponsor submitted NDA to FDA.
July 2008:	• FDA held Advisory Committee on CV safety of treatments for T2DM.
September 2008:	• FDA requested Sponsor to analyze Major Adverse Cardiovascular Events (MACE) in saxagliptin clinical program. • Sponsor retrospectively defined and analyzed MACE in the NDA database.
October 2008:	• Sponsor submitted Day 120 Update of Clinical Safety Report to the FDA.
December 2008:	• Sponsor updated analyses of MACE based on the Day 120 Update database. • FDA issued Guidance to Sponsors on evaluation CV risk in new therapies for T2DM

January 2009:
- FDA provided definitions and methods of analysis for MACE to the Sponsor.
- Sponsor analyzed MACE retrospectively as instructed by FDA.

The regulatory environment regarding assessment of CV safety evolved during the saxagliptin development program. The Sponsor responded to requests from the FDA to provide increased duration of exposure and to provide additional analyses of the saxagliptin CV safety profile. In order to provide longer duration of exposure with an enhanced safety database, the Sponsor delayed the submission of the saxagliptin NDA.

The CV safety experience was evaluated using a range of different endpoints and methods to ensure that findings were consistent throughout. This is consistent with safety-signal detection methodology.

Taken together, these analyses provide a comprehensive evaluation of CV risk in the Phase 2b/3 saxagliptin clinical database. The results do not indicate an increased CV risk associated with saxagliptin treatment, and are consistent with the benign CV safety profile of saxagliptin in nonclinical species.

7.5.1 Analyses of Cardiovascular Events Defined by the FDA - Methods

The US FDA requested CV-related analyses based on correspondence received on September 12, 2008 and on January 11, 2009.

The Agency requested that CV events be listed by type (eg, "ischemia-related") using Standardized MedDRA Queries (SMQs, a way of standardizing search queries across different safety databases). In response, AEs in the MedDRA System Organ Class (SOC) Cardiac Disorders were sub-categorized into four mutually exclusive categories based on SMQs as follows:

1) "ischemic heart disease" (SMQ code 20000043),
2) "cardiac failure" (SMQ code 20000004),
3) "cardiac arrhythmias" (SMQ code 20000049), and
4) "other" for those AEs not found in the 3 SMQ categories.

The AE preferred terms (PTs) in these SMQs were reviewed for clinical consistency. Three PTs were added to the "cardiac failure" SMQ (diastolic dysfunction, left ventricular dysfunction, and ventricular hypokinesia), based on the perspective that these PTs were appropriate and relevant to the "cardiac failure" classification.

FDA further requested analyses of the following two endpoints:

1) **SMQ MACE** - a composite endpoint of CV death, and all PTs in the SMQ for "Myocardial Infarction" and "Central Nervous System Haemorrhages and Cerebrovascular Accidents". A list of the PTs in the SMQ MACE is provided in Appendix 1.
2) **Custom MACE** - a composite endpoint of CV death and MedDRA PTs indicative of MACE (specific list provided by FDA is included in Appendix 2).

The Agency permitted CV deaths, identified by clinical review of all deaths, to be included in both SMQ MACE and Custom MACE. Further, the Agency requested that analyses of SMQ MACE and Custom MACE be based on the randomized, double-blind, controlled short-term periods for all completed Phase 2 and Phase 3 trials as well as the randomized, controlled periods including data past the primary A1C efficacy measurement (ie, ST+LT including experience collected after the initiation of rescue therapy). The results presented below are comprised of the ST + LT analysis dataset, using the 120 Day Database, because it provides the most complete longitudinal experience for analysis; results based on the ST period of these studies were qualitatively consistent with those presented for the ST + LT period.

The Agency also requested summaries of the incidence of SMQ MACE and Custom MACE events, incidence ratio, incidence difference, incidence rate, incidence rate ratio and incidence rate difference (with corresponding 95% CIs). See Section 7.5.3 and Appendix 7 for detailed statistical methods.

7.5.2 Analyses of Cardiovascular Events Defined by the FDA - Results

The number of subjects with at least one AE in the cardiac disorders SOC and the number of subjects with at least one AE for each SMQ category for the Phase 2b/3 Pooled Population is shown in Table 8.

The overall proportion of subjects with Cardiac Disorders AEs was 4.9% in the All Saxa group and 5.7% in the Comparator group (the Comparator Group included placebo or metformin monotherapy, see Table 8). The numerical difference in proportions was primarily accounted for by the lower proportion of subjects with Ischemic Heart Disease AEs in saxagliptin treated subjects (All Saxa: 1.3%, Comparator: 1.9%). There were generally comparable proportions of subjects with AEs in the All Saxa and Comparator treatment groups in the other 3 categories. There was no evidence for a dose-response relationship.

Table 8: Summary of Cardiac Disorders by SMQ Event Type During ST + LT Treatment Period (120 Day Database), Phase 2b/3 Pooled Population

	Saxa 2.5 mg N=937 n (%)	Saxa 5 mg N=1269 n (%)	Saxa 10 mg N=1000 n (%)	All Saxa N=3356 n (%)	Comparator N=1251 n (%)
Total Subject with an Event	53 (5.7)	63 (5.0)	48 (4.8)	164 (4.9)	71 (5.7)
Ischaemic Heart Disease	14 (1.5)	17 (1.3)	12 (1.2)	43 (1.3)	24 (1.9)
Cardiac Failure	8 (0.9)	7 (0.6)	5 (0.5)	20 (0.6)	7 (0.6)
Cardiac Arrhythmias	32 (3.4)	36 (2.8)	31 (3.1)	99 (2.9)	37 (3.0)
Other	9 (1.0)	8 (0.6)	6 (0.6)	23 (0.7)	7 (0.6)

Summaries of the overall incidence of SMQ MACE and Custom MACE in the Phase 2b/3 Pooled Population and in each study are included in Tables 9 and 10.

The events identified by the approach using SMQ MACE differed from those using Custom MACE. In particular, the number of events identified using Custom MACE was substantially fewer than those identified using SMQ MACE. The incidence of SMQ MACE and Custom MACE (Tables 9 and 10) provide some insight into the basis for this difference.

The approach based on SMQ MACE (Table 9) led to identification of 141 subjects; in contrast, only 40 subjects were identified based on the Custom MACE approach (Table 10). Of the difference of 101 subjects, the majority (88) are accounted for by the presence of a single MedDRA Preferred Term ("blood creatine phosphokinase increased") in the SMQ MACE list. The Custom MACE definition is therefore likely to

be more selective for MACE events, given the inclusion of the PT for "blood creatine phosphokinase increased" in the SMQ MACE list. The list of PTs provided by the FDA to define Custom MACE (Appendix 2), while not identical to the list of PTs proposed by the Sponsor to define Primary MACE (Appendix 4), identifies almost the same cohort of subjects with purported MACE events as identified by the Sponsor's definition (for details, see Section 7.5.4.3 and Appendix 6). As a consequence, estimates of hazard or incidence ratios are similar when using either the Sponsor's Primary MACE definition or the FDA's Custom MACE definition.

Table 9: Incidence of SMQ MACE During ST + LT Treatment Period (120 Day Database) by Dose of Saxagliptin

Population	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa n/N (%)	Comparator n/N (%)
Pooled P2b/3	28/937 (3.0)	37/1269 (2.9)	30/1000 (3.0)	100/3356 (3.0)	41/1251 (3.3)
Monotherapy					
(-008)*	1/55 (1.8)	3/47 (6.4)	0	9/315 (2.9)	1/108 (0.9)
(-011)	0	4/106 (3.8)	2/98 (2.0)	6/306 (2.0)	4/95 (4.2)
(-038)	3/145 (2.1)	1/146 (0.7)	NA	4/291 (1.4)	2/74 (2.7)
(-041)	NA	0	NA	0	1/16 (6.3)
Add-on combination					
+Met (-014)	6/192 (3.1)	6/191 (3.1)	9/181 (5.0)	21/564 (3.7)	6/179 (3.4)
+SU (-040)	9/248 (3.6)	11/253 (4.3)	NA	20/501 (4.0)	12/267 (4.5)
+TZD (-013)	9/195 (4.6)	10/186 (5.4)	NA	19/381 (5.0)	4/184 (2.2)
Initial comb. (-039)	NA	2/320 (0.6)	19/658 (2.9)	21/978 (2.1)	11/328 (3.4)

* In CV181008, 5 MACE events occurred in subjects who received saxagliptin doses >10 mg.

Table 10: Incidence of Custom MACE During ST + LT Treatment Period (120 Day Database) by Dose of Saxagliptin

Population	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa n/N (%)	Comparator n/N (%)
Pooled P2b/3	6/937 (0.6)	6/1269 (0.5)	11/1000 (1.1)	23/3356 (0.7)	17/1251 (1.4)
Monotherapy					
(-008)	0	0	0	0	0
(-011)	0	2/106 (1.9)	0	2/306 (0.7)	1/95 (1.1)
(-038)	0	0	NA	0	0
(-041)	NA	0	NA	0	0
Add-on combination					
+Met (-014)	1/192 (0.5)	1/191 (0.5)	4/181 (2.2)	6/564 (1.1)	4/179 (2.2)
+SU (-040)	2/248 (0.8)	1/253 (0.4)	NA	3/501 (0.6)	6/267 (2.2)
+TZD (-013)	3/195 (1.5)	1/186 (0.5)	NA	4/381 (1.0)	1/184 (0.5)
Initial comb. (-039)	NA	1/320 (0.3)	7/658 (1.1)	8/978 (0.8)	5/328 (1.5)

Summaries of the incidence rate ratios of SMQ MACE and Custom MACE, for the Phase 2b/3 Pooled Population and by study, combined across doses of saxagliptin are provided in Figures 8 and 9, respectively.

Figure 8: Stratified Analyses of Incidence Rate Ratio of FDA-Defined SMQ MACE

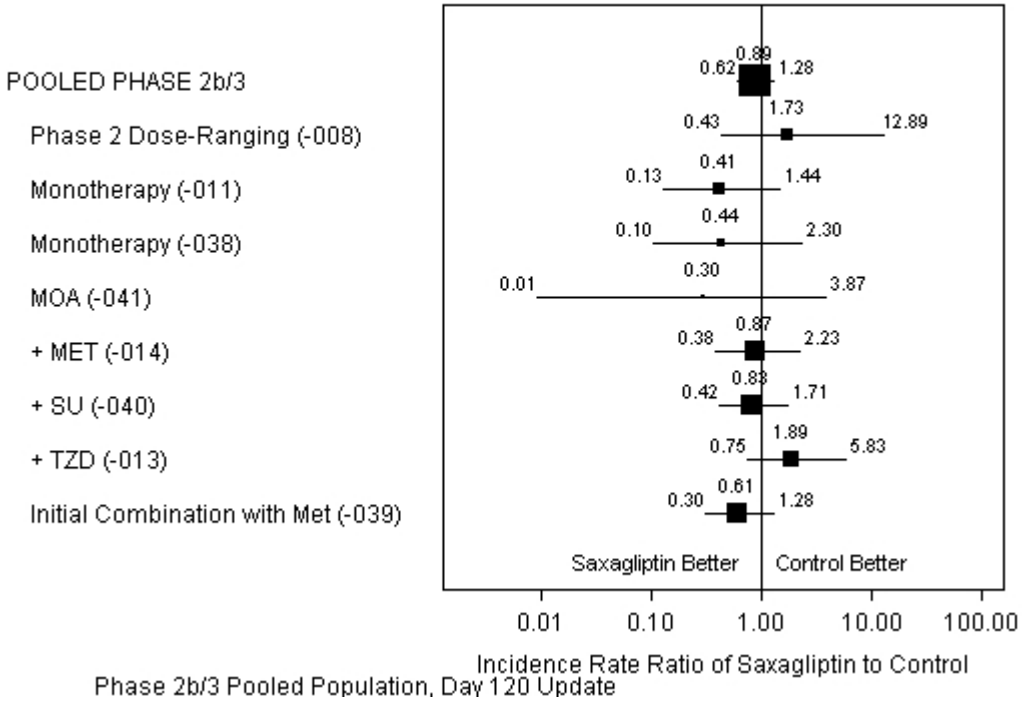
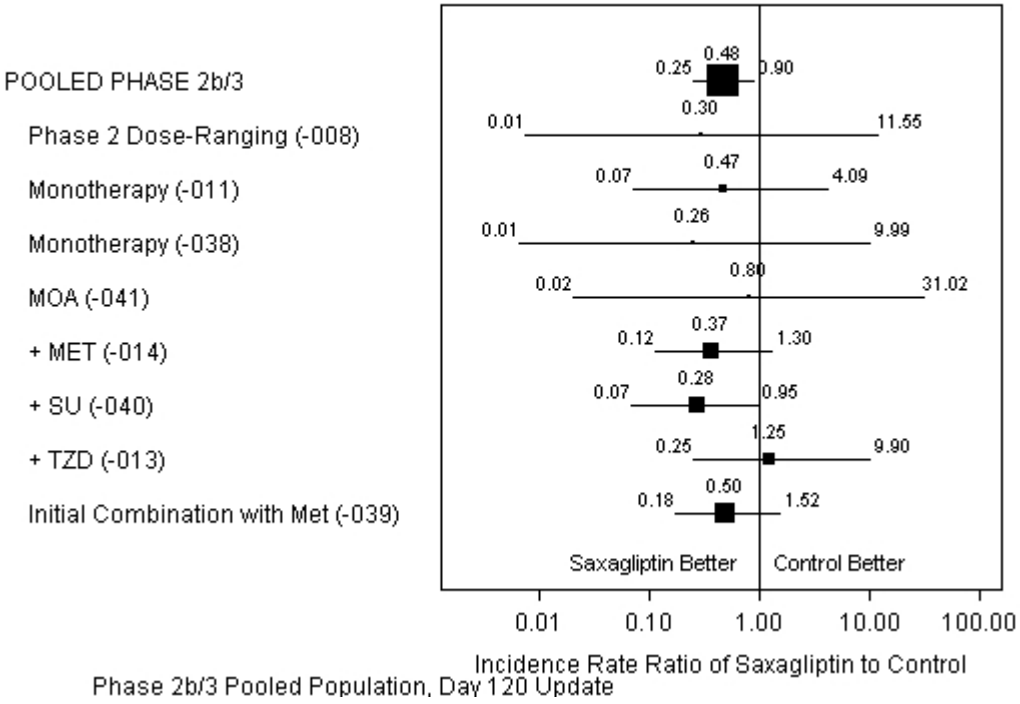


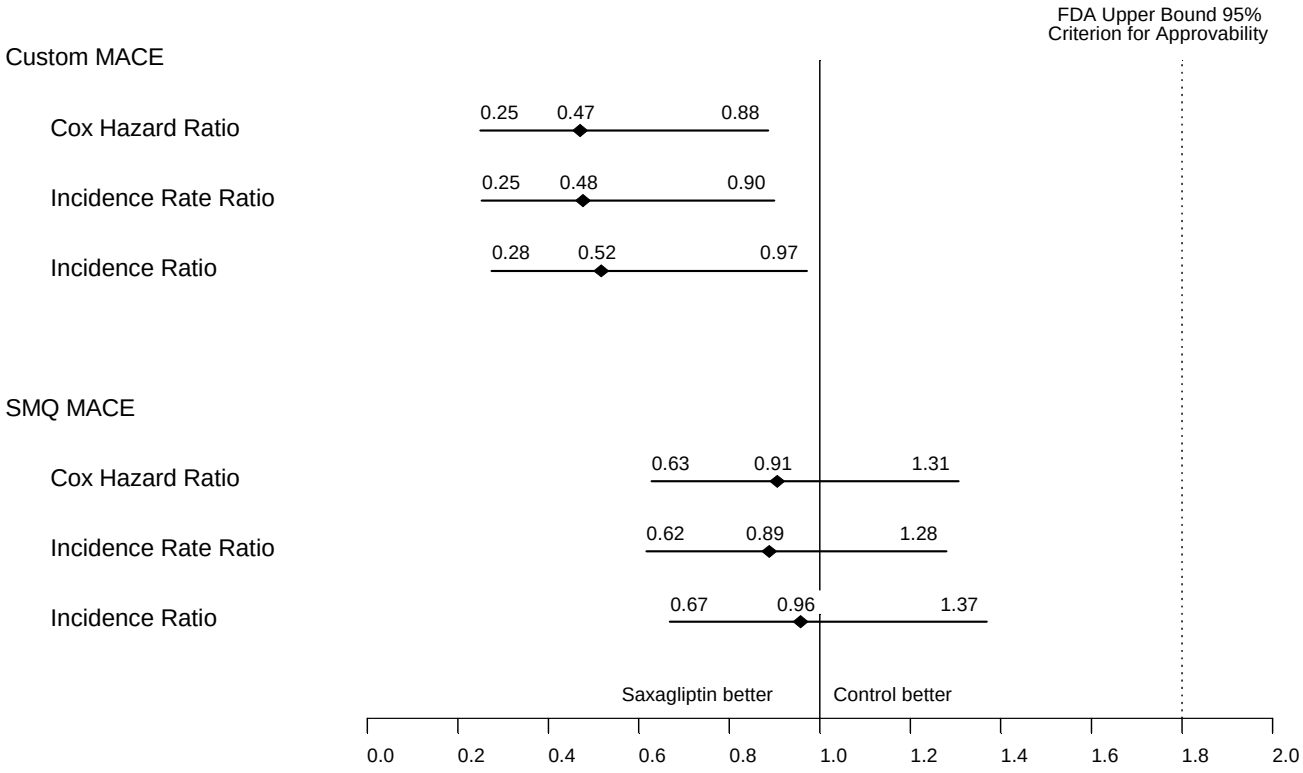
Figure 9: Stratified Analyses of Incidence Rate Ratio of FDA-Defined Custom MACE



7.5.2.1 Summary of FDA-Defined Analyses of Cardiovascular Events

Overall, comprehensive analyses of MACE events based on those defined by the Agency, including both a broader inclusive SMQ MACE analysis and a more selective Custom MACE analysis, demonstrated consistency of results. There was no evidence for an increase in CV risk with saxagliptin use and there was no evidence for a dose-response relationship for saxagliptin doses of 2.5 through 10 mg. In each pooled assessment, the point estimate of the relative risk was always < 1 (range: 0.47 - 0.96), with the upper 95% confidence limit < 1.4 (range: 0.88 - 1.37) (Figure 10). In each pooled analysis, the point estimates of the relative risk and the upper bounds of the 95% confidence limit were lower for saxagliptin in the more selective Custom MACE analysis compared with the broader, inclusive assessment of SMQ MACE.

Figure 10: Stratified Analyses of FDA-Defined Custom MACE and SMQ MACE



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7.5.3 Analyses of Cardiovascular Events Defined by the Sponsor - Methods

7.5.3.1 Populations and Datasets

CV events were evaluated in the Study Level Populations and Phase 2b/3 Pooled Population. For description of the populations, see Section 7.1.2.1. The presentation of CV safety focuses on the ST + LT dataset including experience following rescue therapy in the 120 Day Database. This dataset was selected as it provides the most complete longitudinal experience available for analysis.

7.5.3.2 Endpoints and Ascertainment of Events

A range of complementary CV events was examined in order to provide a comprehensive evaluation of the CV safety of saxagliptin. The wide-range of outcomes and analytical methods were specifically intended to assess whether results were consistent and not unique to any single endpoint or analytic method. CV events included broad assessments of overall cardiac safety as well as more specific evaluations focused on Major Adverse Cardiovascular Events (MACE). MedDRA PT lists were developed to objectively ascertain CV events. All deaths in the program were clinically reviewed to identify any CV-related deaths which may not have been specifically identified through the MedDRA preferred term lists.

Cardiovascular outcomes were examined as follows: 1) Overall Cardiac Adverse Events, defined using the MedDRA SOC Cardiac Disorders; 2) Acute Cardiovascular Events, defined using a MedDRA PT list for CV AEs considered acute, ischemic and clinically relevant, specified before unblinding five of the seven Phase 3 databases; and 3) Primary MACE (ie, AEs of myocardial infarction [MI], stroke, or CV-death), defined using a MedDRA PT list selective for these events and supplemented by clinical review of all deaths. A secondary analysis of MACE (Secondary MACE) included all deaths. Lists of PTs for Acute Cardiovascular Events and Primary/Secondary MACE are included in Appendix 3 and 4, respectively. A list of all deaths is included in Appendix 5. Details on the events and the ascertainment of events are described in Appendix 6.

7.5.3.3 Analytical Methods

Tables are presented by saxagliptin dose, all saxagliptin, and comparator. The proportion of subjects with a CV event identified using: 1) the SOC Cardiac Disorders; 2) the MedDRA preferred term list for Acute Cardiovascular Events; 3) the Primary MACE PT list supplemented by clinical review of deaths; and 4) the Secondary MACE PT list including all deaths, were summarized. Time to first MACE was calculated using a weighted Kaplan-Meier estimate, applied to the all saxagliptin and all control groups. A point estimate and 95% CI for relative risk of Primary MACE, Secondary MACE, and Acute Cardiovascular Events were calculated using three different analytic methods. Those methods (Cox proportional hazards regression model, incidence rate ratio, and incidence ratio) are described in detail in Appendix 7.

7.5.4 Analyses of Cardiovascular Events Defined by the Sponsor - Results

7.5.4.1 Overall Cardiac Adverse Events

The proportion of subjects with AEs in the SOC Cardiac Disorders was similar in all treatment groups in each individual study and in the pooled populations (Table 11). The results do not suggest a dose-response relationship.

Table 11: Cardiac Disorders (MedDRA SOC) AEs (120 Day Database) Phase 2b/3 Pooled Population and Phase 2b and 3 Studies

Population	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa* n/N (%)	Comparator** n/N (%)
Pooled P2b/3	53/937 (5.7)	63/1269 (5.0)	48/1000 (4.8)	164/3356 (4.9)	71/1251 (5.7)
Monotherapy					
(-008)	1/55 (1.8)	0	0	1/315 (0.3)	3/108 (2.8)
(-011)	6/102 (5.9)	8/106 (7.5)	7/98 (7.1)	21/306 (6.9)	5/95 (5.3)
(-038)	11/145 (7.6)	2/146 (1.4)	NA	13/291 (4.5)	1/74 (1.4)
(-041)	NA	0	NA	0	2/16 (12.5)
Add-on combination					
+Met (-014)	14/192 (7.3)	14/191 (7.3)	13/181 (7.2)	41/564 (7.3)	14/179 (7.8)
+SU (-040)	14/248 (5.6)	15/253 (5.9)	N/A	29/501 (5.8)	14/267 (5.2)
+TZD (-013)	7/195 (3.6)	13/186 (7.0)	N/A	20/381 (5.2)	13/184 (7.1)
Initial comb. (-039)	NA	11/320 (3.4)	28/658 (4.3)	39/978 (4.0)	19/328 (5.8)

* Includes 20-40 mg and 100 mg experience from CV181008
** Includes metformin monotherapy from CV181039

7.5.4.2 Acute Cardiovascular Events

A total of 61 subjects in the Phase 2b/3 Pooled Population were identified as having an Acute Cardiovascular Event, 38 (1.1%) in the All Saxa group and 23 (1.8%) in the Comparator group (Table 12). There was no evidence for an increased risk of Acute Cardiovascular Events in the saxagliptin groups compared with the control groups (Table 12). There was also no evidence for a dose-response relationship with Acute Cardiovascular Events for saxagliptin doses of 2.5 through 10 mg.

Table 12: Acute Cardiovascular Events (120 Day Database) Phase 2b/3 Pooled Population and Phase 2b and 3 Studies

Population	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa* n/N (%)	Comparator** n/N (%)
Pooled P2b/3	14/937 (1.5)	10/1269 (0.8)	14/1000 (1.4)	38/3356 (1.1)	23/1251 (1.8)
Monotherapy					
(-008)	0	0	0	0	0
(-011)	0	2/106 (1.9)	0	2/306 (0.7)	2/95 (2.1)
(-038)	2/145 (1.4)	0	NA	2/291 (0.7)	2/74 (2.7)
(-041)	NA	0	NA	0	1/16 (6.3)
Add-on combination					
+Met (-014)	2/192 (1.0)	2/191 (1.0)	4/181 (2.2)	8/564 (1.4)	3/179 (1.7)
+SU (-040)	6/248 (2.4)	2/253 (0.8)	NA	8/501 (1.6)	7/267 (2.6)
+TZD (-013)	4/195 (2.1)	3/186 (1.6)	NA	7/381 (1.8)	2/184 (1.1)
Initial comb. (-039)	NA	1/320 (0.3)	10/658 (1.5)	11/978 (1.1)	6/328 (1.8)

* Includes 20-40 mg and 100 mg experience from CV181008
** Includes metformin monotherapy from CV181039

7.5.4.3 Major Adverse Cardiovascular Events

A total of 41 subjects in the Phase 2b/3 Pooled Population were identified as having a Primary MACE, 23 (0.7%) in the All Saxa group and 18 (1.4%) in the Comparator group (Table 13). Primary MACE (defined by the Sponsor) and Custom MACE (defined by the FDA) identified almost the identical set of subjects, and differ by only one subject. Thus, all analyses or Primary MACE are similar to the analyses of Custom MACE (see Section 7.5.2). There was no evidence for an increased risk of Primary MACE in the saxagliptin groups compared with the control groups. There was also no evidence for a dose-response relationship with Primary MACE for saxagliptin doses of 2.5 through 10 mg.

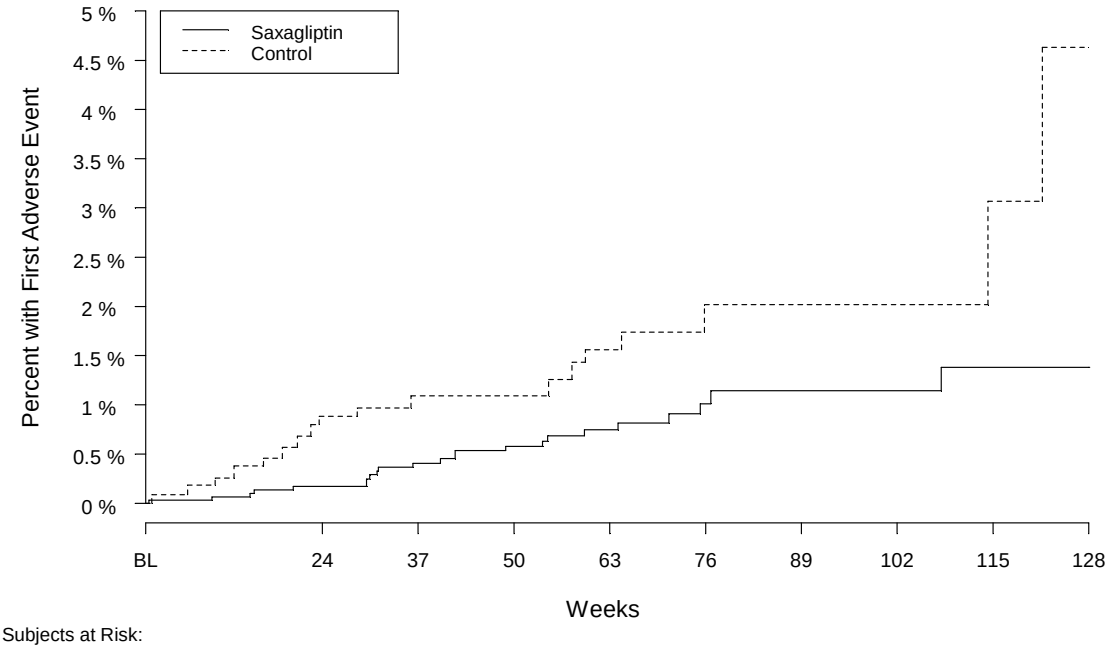
Table 13: Summary of Primary MACE (120 Day Database) Phase 2b/3 Pooled Population and Phase 2b and 3 Studies

Population	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa* n/N (%)	Comparator** n/N (%)
Pooled P2b/3	6/937 (0.6)	6/1269 (0.5)	11/1000 (1.1)	23/3356 (0.7)	18/1251 (1.4)
Monotherapy					
(-008)	0	0	0	0	0
(-011)	0	2/106 (1.9)	0	2/306 (0.7)	1/95 (1.1)
(-038)	0	0	NA	0	1/74 (1.4)
(-041)	NA	0	NA	0	0
Add-on combination					
+Met (-014)	1/192 (0.5)	1/191 (0.5)	4/181 (2.2)	6/564 (1.1)	4/179 (2.2)
+SU (-040)	2/248 (0.8)	1/253 (0.4)	NA	3/501 (0.6)	6/267 (2.2)
+TZD (-013)	3/195 (1.5)	1/186 (0.5)	NA	4/381 (1.0)	1/184 (0.5)
Initial comb. (-039)	NA	1/320 (0.3)	7/658 (1.1)	8/978 (0.8)	5/328 (1.5)

* Includes 20-40 mg and 100 mg experience from CV181008
** Includes metformin monotherapy from CV181039

The time to onset of first Primary MACE in the Phase 2b/3 Pooled Population is shown in Figure 11. The data in Figure 11 indicate no increased risk of Primary MACE for saxagliptin-treated subjects during both the short-term and long-term periods of the clinical studies.

Figure 11: Time to Onset of First Primary MACE - Weighted Kaplan Meier Estimate for Cumulative Proportion During ST + LT Treatment Period (120-Day Database) - Phase 2b/3 Pooled Population



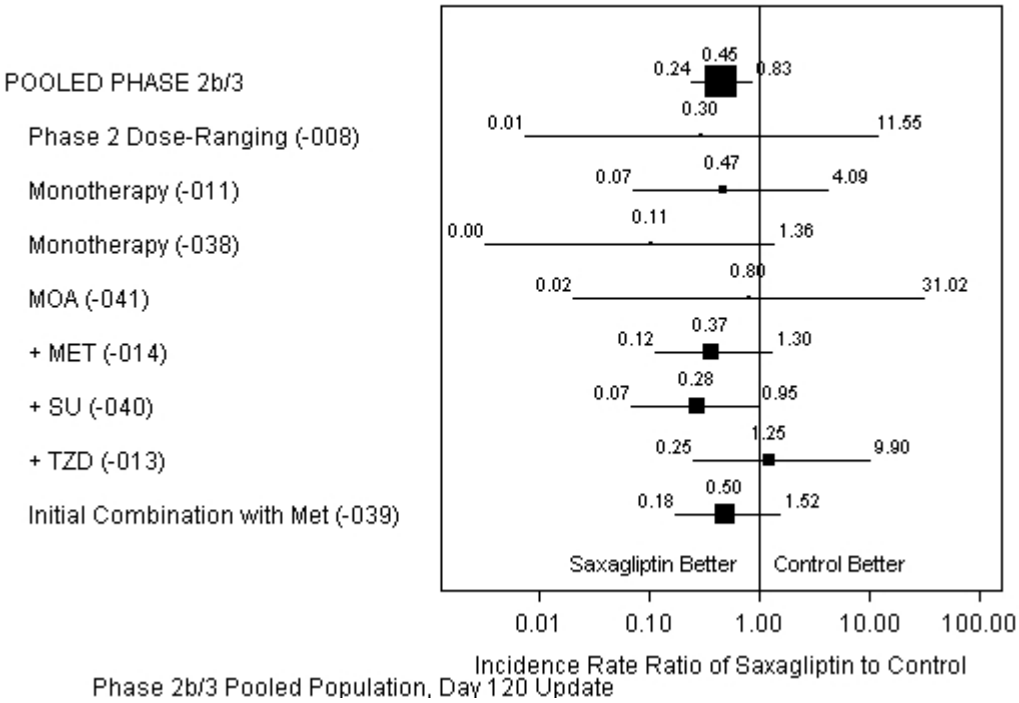
Subjects at Risk:

Saxagliptin:	3356	2615	2419	2209	1638	994	498	436	373	197
Control:	1251	935	860	774	545	288	144	123	102	57

Fatal outcomes were assessed in the Phase 2b/3 Pooled Population (120 Day Database). The frequency of CV deaths was 0.2% (7/3356) in subjects treated with saxagliptin and 0.8% (10/1251) in subjects in the control group. For all cause mortality, the frequency was 0.3% (10/3356) in subjects treated with saxagliptin and 1.0% (12/1251) in subjects in the control group.

For the Phase 2b/3 Pooled Population, the overall incidence rate ratio based on a stratified Mantel-Haenszel approach (95% CI) for Primary MACE was 0.45 (0.24, 0.83). The results were consistent across the studies (Figure 12).

Figure 12: Stratified Analyses of Incidence Rate Ratio of Sponsor-Defined Primary MACE (120 Day Database) Phase 2b/3 Pooled Population and Phase 2b and 3 Studies

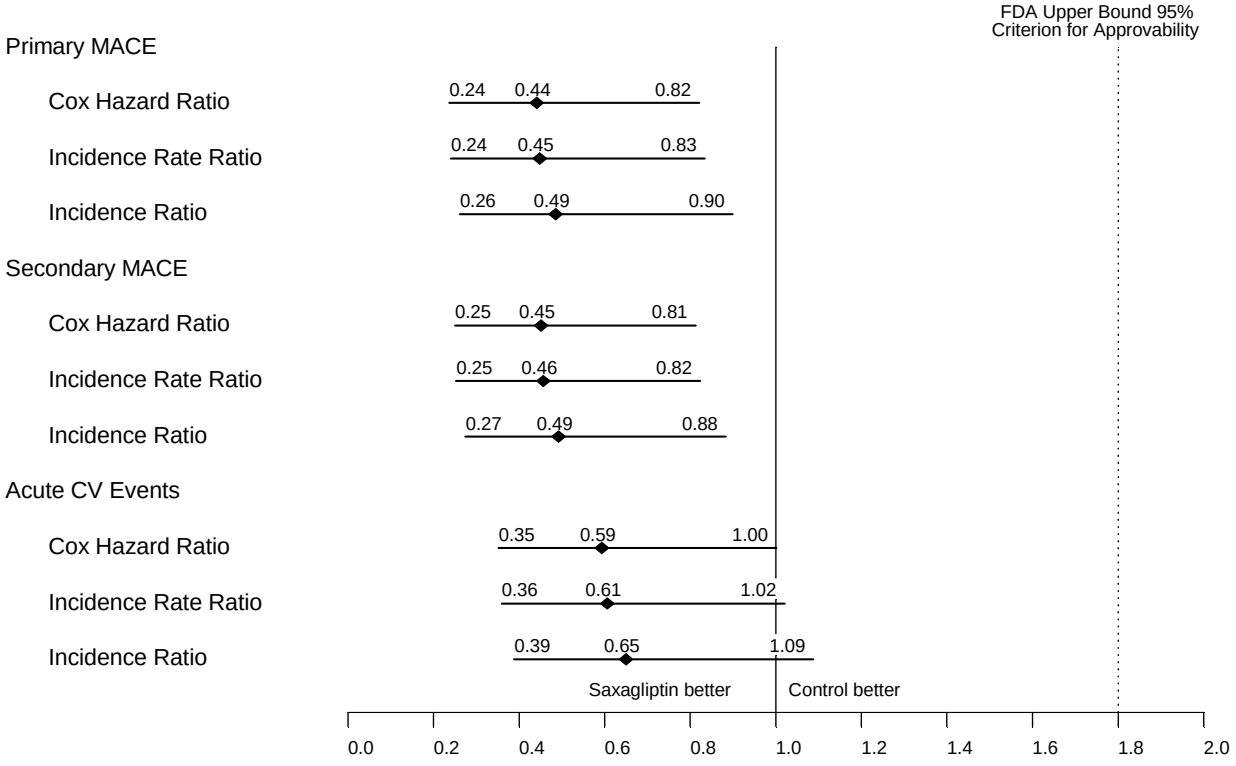


7.5.4.4 Summary of Sponsor-Defined Analyses of Cardiovascular Events

Hazard ratios and corresponding 95% CI for saxagliptin and comparator using the Cox Proportional Hazards model, as well as incidence rate ratios, and incidence ratios with corresponding 95% CI using the Mantel-Haenszel approach are summarized in Figure 13 for the endpoints Primary MACE, Secondary MACE, and Acute Cardiovascular Events. In all analyses of the Phase 2b/3 Pooled Population, the point-estimates of the ratios were less than 1 (range: 0.44 - 0.65). In addition, in all analyses, the upper-bound of the 95% CI was < 1.1 (range: 0.81 - 1.09).

Based on this comprehensive set of analyses designed for signal detection of CV events in the saxagliptin program, there was no indication for an increase in CV risk with saxagliptin use or any indication of a CV safety-related signal. There was no evidence for imbalance in event frequency when looking at overall cardiac events. Results were consistent across specific study settings (ie, monotherapy, add-on combination treatment, and initial combination treatment), and there was no evidence for a dose-response relationship for saxagliptin doses of 2.5 through 10 mg.

Figure 13: Stratified Analyses of Sponsor-defined Cardiovascular Endpoints (120 Day Database) Phase 2b/3 Pooled Population



Phase 2b/3 Pooled Population
Day 120 Update

7.5.5 Cardiovascular Risk Factors in the Phase 2b/3 Pooled Population

As recommended in the FDA Guidance on evaluating CV risk in new antidiabetic therapies, the Sponsor assessed the risk ratio for CV events in the Phase 2b/3 Pooled Population. While these analyses provide evidence that saxagliptin is not associated with increased CV risk in T2DM, it is important to evaluate the following questions:

- Did the Phase 2b/3 Pooled Population include subjects who were at risk of CV Events to assure safety in the broad population of patients with T2DM who may receive saxagliptin therapy?
- Was there evidence of increased CV risk when saxagliptin was used in subsets of subjects who were at increased risk of CV Events?

To address the first question, the Sponsor assessed the baseline CV risk profile of the Phase 2b/3 Pooled Population. A total of 569 subjects had clinically evident CV disease upon entry to the Phase 2b/3 studies, defined as a history of myocardial infarction, congestive heart failure, hospitalization for unstable angina pectoris, stable angina pectoris, prior percutaneous coronary intervention, prior coronary artery bypass surgery, coronary artery disease, cerebrovascular disease, or peripheral vascular disease (Table 14). While T2DM is a well-recognized risk factor for CV events, the majority (≥ 80%) of subjects enrolled in the Phase 2b/3 studies had at least one additional risk factor for CV events (including prior history of hypertension, hypercholesterolemia, smoking, or first degree relative with premature coronary heart disease). Approximately 15% of subjects were elderly (≥ 65 years of age). The data in Table 14 indicate that the Phase 2b/3 program included a substantial number of subjects at increased risk for CV events.

Table 14: Cardiovascular Risk Factors at Baseline in the Phase 2b/3 Pooled Population

	Saxa 2.5 mg N = 937	Saxa 5 mg N = 1269	Saxa 10 mg N = 1000	All Saxa (a) N = 3356	Control (b) N = 1251
History of cardiovascular disease*, n (%)	118 (12.6)	150 (11.8)	118 (11.8)	404 (12.0)	165 (13.2)
At least one other cardiovascular risk factor (in addition to T2DM), n (%)	777 (82.9)	1015 (80.0)	803 (80.3)	2724 (81.2)	1035 (82.7)
Hypertension, n (%)	519 (55.4)	655 (51.6)	510 (51.0)	1750 (52.1)	688 (55.0)
Hypercholesterolemia**, n (%)	471 (50.3)	565 (44.5)	353 (35.3)	1475 (44.0)	566 (45.2)
Smoking history, n (%)	383 (40.9)	449 (35.4)	393 (39.3)	1301 (38.8)	471 (37.6)
First degree relative with premature coronary heart disease, n (%)	190 (20.3)	248 (19.5)	186 (18.6)	677 (20.2)	265 (21.2)
Gender					
Male, n (%)	444 (47.4)	625 (49.3)	495 (49.5)	1659 (49.4)	620 (49.6)
Female, n (%)	493 (52.6)	644 (50.7)	505 (50.5)	1697 (50.6)	631 (50.4)
Age Categories					
< 65 years, n (%)	783 (83.6)	1084 (85.4)	854 (85.4)	2850 (84.9)	1058 (84.6)
≥ 65 years, n (%)	154 (16.4)	185 (14.6)	146 (14.6)	506 (15.1)	193 (15.4)

(a) Includes 20, 40 and 100 mg experience from CV181008
(b) Includes metformin monotherapy from CV181039
* CV history includes: previous MI, congestive heart failure, hospitalized for unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass graft, coronary artery disease, cerebrovascular disease, or peripheral vascular disease.
** Includes mixed dyslipidemia.

To further evaluate the CV risk in the Phase 2b/3 population, the incidence rates for the different CV events (shown in Table 15) were compared with the incidence rates for MACE in the ACCORD study, a large, recently conducted global study of CV events in patients with T2DM.[20] The incidence rates in the control group in the saxagliptin Phase 2b/3 population ranged from 13.1 to 31.9 events per 1000 patient years (Table 15).

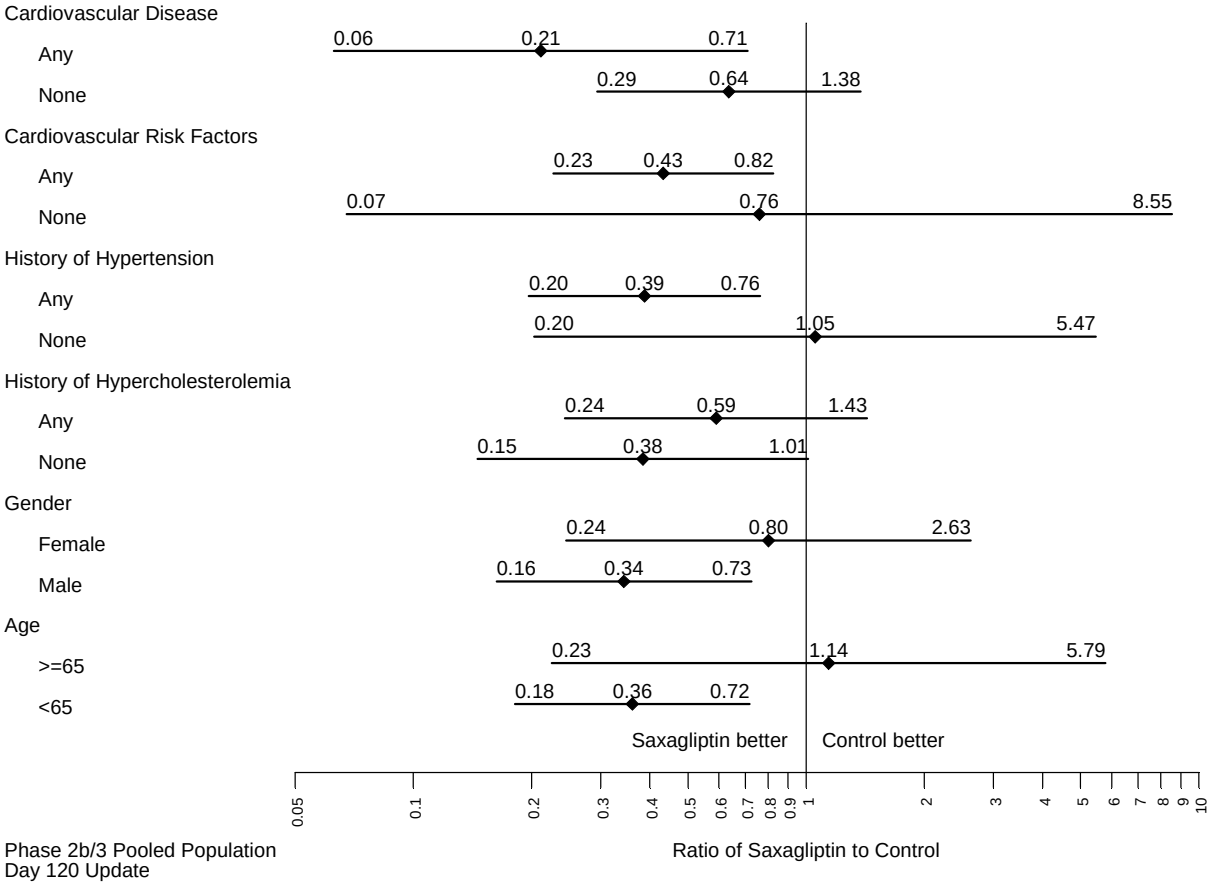
In the saxagliptin group, the incidence rates ranged between 6.2 and 28.4 events per 1000 patient years. In the ACCORD study, the incidence of the primary outcome (MACE) was 21.1 and 22.9 events per 1000 patient years in the intensive and standard therapy group, respectively.

Table 15: Incidence Rates per 1000 Patient Years for SMQ MACE, Custom MACE, Acute Cardiovascular Events, Primary MACE, and Secondary MACE (120 Day Database) Phase 2b/3 Pooled Population

Type of CV Event	Treatment Group	Incidence Rate ± SE (events/1000 pt-yrs)
SMQ MACE	Saxagliptin	28.4 ± 2.9
	Control	31.9 ± 5.0
Custom MACE	Saxagliptin	6.2 ± 1.3
	Control	13.1 ± 3.2
Acute CV Events	Saxagliptin	10.7 ± 1.8
	Control	17.6 ± 3.7
Primary MACE	Saxagliptin	6.2 ± 1.3
	Control	13.9 ± 3.3
Secondary MACE	Saxagliptin	7.0 ± 1.4
	Control	15.4 ± 3.5

To assess whether saxagliptin was associated with CV risk in subjects at higher risk of CV events, hazard ratios and corresponding 95% CI for saxagliptin/comparator using the Cox Proportional Hazards model for Primary MACE were assessed in subgroups defined by history of CV disease, presence of CV risk factors, gender, and age (see Figure 14). These data provide reassurance that even in subgroups of subjects at increased risk of CV events, saxagliptin was not associated with increased CV risk.

Figure 14: Hazard Ratios of Sponsor-Defined Primary MACE (120 Day Database) Subgroups of the Phase 2b/3 Pooled Population



7.5.6 Discussion of Processes for Identification and Analysis of Cardiovascular Events

Given the retrospective application of the FDA Guidance on evaluating CV risk to the saxagliptin clinical database, it is important to consider whether the methods used for identification and analysis of CV events were appropriate and robust. Identification of CV events in the saxagliptin clinical program relied upon the process for identifying, reporting, and encoding AEs. Several aspects of study design and conduct were intended to enhance complete reporting of AEs, including CV AEs.

7.5.6.1 Measures to Enhance Complete Reporting of Cardiovascular Events

Each investigative site received training in the collection and reporting of AEs. Many CV events (particularly MACE) were reported as serious adverse events (SAEs), and each study incorporated specialized instruction and processes for reporting SAEs. All protocols mandated a regular schedule of visits for each subject. Investigative site personnel were instructed to inquire about and record AEs at each visit. The Sponsor regularly monitored the collection of safety data during site monitoring visits; source document verification was performed by the Sponsor at each site monitoring visit to ensure complete reporting of AEs, especially SAEs.

Each protocol in the saxagliptin Phase 3 program had a long-term, controlled extension to permit the longitudinal collection of safety data. All Core Phase 3 studies incorporated rescue therapy for hyperglycemia to permit retention of patients who may have experienced deterioration of glycemic control; rescue therapy was used both in the short-term and the long-term period of each study. Rescue therapy increased exposure to study medication, thereby augmenting safety experience and enabling observation of a greater number of CV events in subjects who otherwise may have discontinued due to deteriorating glycemic control.

The components of MACE (CV death, non-fatal myocardial infarction, and non-fatal stroke) are events that are clinically evident. Ascertainment of the components of MACE was facilitated by the fact that many of these events resulted in hospitalization due to the significant signs and symptoms that accompany stroke and myocardial infarction. Assessment of MACE was facilitated further by the high level of scrutiny paid to reporting of SAEs. All events of Custom, Primary, and Secondary MACE were reported as SAEs, and all non-fatal events of Custom, Primary, and Secondary MACE resulted in hospitalization.

7.5.6.2 Measures to Prevent Bias in the Reporting and Analyses of Cardiovascular Events

All studies were blinded to the Sponsor, site, and subjects during the short-term period of each study (eg, initial 24 weeks for pivotal Phase 3 studies). After reporting of the short-term results, all studies remained blinded to all site personnel, subjects, and site monitors.

While the process for identifying MACE was defined retrospectively, the process for identifying Acute Cardiovascular Events was defined before database lock for most of the Phase 3 program. Analyses of Acute Cardiovascular Events were included in the original NDA, prior to requests from the FDA to analyze MACE.

While rescue therapy was utilized in the Core Phase 3 studies, it is still possible that differential retention of patients could have resulted in differential ascertainment of CV events by treatment group. To minimize the effects of differential duration of treatment, CV events were analyzed by the incidence rate ratio (normalizing for treatment duration) and the Cox proportional hazard method (a survival method that adjusts for treatment duration).

Studies included in the Phase 2 and Phase 3 program used differing randomization ratios and recruited differing patient populations with potentially different levels of CV risk. In order to minimize potential bias related to differing levels of CV risk, all pooled analyses were stratified by study.

7.5.6.3 Measures to Ensure Accurate Diagnosis of CV Events

As noted previously, all non-fatal events of Custom, Primary, and Secondary MACE resulted in hospitalization. As part of the source document verification process, the Sponsor made a concerted effort to collect hospital discharge summaries on patients hospitalized with MACE. These discharge summaries were reviewed to ensure that the discharge diagnoses were consistent with the diagnosis of MACE.

The Sponsor and the FDA generated lists of Preferred Terms to identify cases of Primary MACE and Custom MACE, respectively. The processes used for Primary MACE and Custom MACE identified nearly identical sets of patients (differing by a single patient).

The concordance of the cases of Primary MACE and Custom MACE provides reassurance that MACE was correctly identified by these processes.

For the analyses of SMQ MACE, Custom MACE, and Primary MACE, all deaths were reviewed to identify CV deaths that did not code to fatal myocardial infarction or fatal stroke. It is possible that incorrect assignment of cause of death affected the analyses. Accordingly, the Sponsor performed a sensitivity analysis in which all deaths, regardless of etiology, were included in the assessment of MACE (ie, Secondary MACE). The results for Secondary MACE were similar to the results for Primary MACE.

It should be noted that the set of subjects with Primary MACE is primarily a subset of subjects who had Acute Cardiovascular Events. Thus, significant CV events not captured by Primary MACE would likely have been captured by Acute Cardiovascular Events. The concordance of the results based on Acute Cardiovascular Events and Primary MACE provides reassurance that saxagliptin is not associated with an increase in CV risk.

There are limitations to the retrospective application to the FDA Guidance to the saxagliptin clinical database. However, study design, study conduct, and methods of analysis helped to maximize event ascertainment and minimize bias and errors in the assessment of CV risk. It is reassuring that multiple analyses of multiple CV events led to a similar conclusion; that there is no indication of a CV safety-related signal for saxagliptin.

7.5.7 QTc Evaluation

In a thorough QTc study, saxagliptin was not associated with clinically significant prolongation of QTc interval at daily doses up to 40 mg. Likewise, there was no apparent effect of saxagliptin 10 or 40 mg on heart rate. Saxagliptin and BMS-510849 plasma concentrations were not correlated with QTc interval following administration of 10 or 40 mg saxagliptin to healthy subjects. There were similar findings showing an absence of effect of saxagliptin and BMS-510849 on QTc and heart rate in exploratory analyses at doses up to 400 mg QD.

7.6 Additional Safety Considerations

The following safety topics are presented in greater detail to enable a thorough understanding and characterization of saxagliptin's safety profile with regards to:

- Adverse effects commonly observed in the treatment of T2DM, as they relate to:
  - Hypoglycemia
  - Lipids
  - Body weight and blood pressure
- Adverse events based on findings observed in the saxagliptin non-clinical program, in the Phase 1 and 2b program at higher doses, safety-related concerns reported for other DPP4 inhibitors, and theoretical considerations related to the mechanism of action of DPP4 inhibitors, including:
  - Dermatological safety
  - Localized edema
  - Lymphocytes
  - Infections
  - Platelets

In addition, comprehensive evaluations of hepatic, pancreatic and renal safety, as well as other laboratory parameters have been performed given their importance in the development of all therapeutic compounds.

7.6.1 Hypoglycemia

Saxagliptin treatment was associated with a low risk of hypoglycemia. In subjects who received saxagliptin 5 mg as monotherapy or in combination with metformin or TZD, the frequency of reported hypoglycemia was low, with rates similar to those reported in subjects who received placebo (Tables 16 and 17). Events of confirmed hypoglycemia (defined as symptoms of hypoglycemia and with fingerstick blood glucose measurement $\leq$ 50 mg/dL) were infrequent and occurred at similar rates for saxagliptin 5 mg and placebo. Medical assistance was not required for any of the confirmed events of hypoglycemia.

While the incidence of hypoglycemia was numerically higher for subjects who received saxagliptin 5 mg when added to an intermediate dose of SU compared with uptitration of

SU monotherapy in study CV181040, the difference (14.6% compared with 10.1%) was not statistically significant. The rate of confirmed hypoglycemia was 0.8% in the saxagliptin 5 mg treatment group and 0.7% in the control group in Study CV181040. The slightly higher rate of hypoglycemia in the saxagliptin 5 mg group compared with the placebo group in the Placebo-controlled Pooled Safety Population is in large part the result of events in the add-on to SU study (CV181040). In a pooled analysis of the two monotherapy studies and the add-on combination studies with metformin and TZD, the rate of all reported hypoglycemic AEs was 4.8% in the saxagliptin 5 mg group and 4.3% in the placebo group.

Table 16: All Reported Hypoglycemic AEs - Monotherapy and Combination Studies (NDA Database)

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
ST Period, Excluding Rescue					
Pooled Monotherapy (CV181011, CV181038)	4.0% (10/247)	5.6% (14/252)	8.2% (8/98)	5.4% (32/597)	4.1% (7/169)
Add-on Combination					
+ Met (CV181014)	7.8% (15/192)	5.2% (10/191)	3.9% (7/181)	5.7% (32/564)	5.0% (9/179)
+ SU (CV181040)	13.3% (33/248)	14.6% (37/253)	N/A	14.0% (70/501)	10.1% (27/267)
+ TZD (CV181013)	4.1% (8/195)	2.7% (5/186)	N/A	3.4% (13/381)	3.8% (7/184)
Up to Week 24, Regardless of Rescue Status					
Placebo-controlled Pooled Safety	7.6% (67/882)	7.8% (69/882)	5.4% (15/279)	7.4% (151/2043)	6.8% (54/799)

Note: The frequencies for the individual populations added together do not equal the frequencies for Pooled Safety since that analysis included AEs after the initiation of rescue therapy.

Abbreviations: AE = adverse event; Met = metformin; N/A = not applicable; Saxa = saxagliptin; ST = short-term; SU = sulfonylurea; TZD = thiazolidinedione.

Table 17: All Reported Hypoglycemic AEs - ST Period Excluding Rescue - Initial Combination Study with Metformin (NDA Database)

Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	All Saxa	Met
3.4% (11/320)	5.0% (16/323)	1.5% (5/335)	3.3% (32/978)	4.0% (13/328)

Abbreviations: AE = adverse event; Met = metformin; Saxa = saxagliptin; ST = short-term.

7.6.2 Lipids

Saxagliptin treatment did not lead to adverse effect in lipid parameters (Table 18).

Table 18: Mean Percent Change from Baseline in LDL-C, HDL-C, and TG to Week 24 (LOCF) - Core Phase 3 Studies

	LDL-C (%)		HDL-C (%)		TG (%)	
	Saxa 5 mg	**Placebo**	**Saxa 5 mg**	**Placebo**	**Saxa 5 mg**	**Placebo**
Monotherapy						
(-011)	0.4 (3.2)	5.3 (3.1)	2.6 (1.6)	5.3 (1.6)	3.9 (4.7)	2.8 (4.5)
(-038)	4.5 (5.2)	10.8 (4.3)	4.7 (3.4)	4.9 (2.5)	6.1 (5.3)	5.9 (6.0)
Add-on Combination						
+ MET (-014)	6.5 (2.9)	4.3 (2.1)	-0.3 (1.1)	2.0 (1.0)	5.0 (3.4)	7.8 (3.2)
+ SU (-040)	3.5 (1.8)	4.8 (2.0)	-4.5 (0.9)	-1.8 (1.1)	8.3 (4.1)	9.3 (2.6)
+ TZD (-013)	9.4 (2.7)	3.4 (2.7)	1.5 (1.4)	0.1 (1.3)	-3.2 (3.2)	0.7 (3.4)
	Saxa 5 mg + Met	**Met**	**Saxa 5 mg + Met**	**Met**	**Saxa 5 mg + Met**	**Met**
Initial Comb with MET (-039)	-4.6 (1.7)	-4.0 (1.4)	6.7 (1.3)	8.9 (1.4)	-5.8 (3.6)	-1.5 (2.7)

Data are presented as mean percent change from baseline (SE).
Abbreviations: Met = metformin; Saxa = saxagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

7.6.3 Body Weight and Vital Signs

Saxagliptin treatment was associated with no or minimal differences in body weight change compared with control. When given as monotherapy, saxagliptin 5 mg was weight neutral in the monotherapy study CV181011 (Table 19). Treatment with saxagliptin 5 mg led to small decreases in weight in the monotherapy study CV181038 compared with a small, but greater numerical reduction in weight observed in subjects in the placebo group. In the add-on to metformin study, similar decreases in weight were observed in subjects who received saxagliptin 5 mg and placebo. In the add-on to SU and TZD studies, small increases in weight were seen in subjects given saxagliptin, which generally were of comparable magnitude to those seen in the control group.

Table 19: Mean Body Weight Changes from Baseline to Week 24 (LOCF) - Core Phase 3 Studies

	Saxagliptin 5 mg	Placebo
Monotherapy		
(-011)	-0.05 (0.42) kg	-1.35 (0.30) kg
(-038)	-0.9 (0.31) kg	-1.3 (0.40) kg
Add-on Combination		
+ MET (-014)	-0.87 (0.23) kg	-0.92 (0.22) kg
+ SU (-040)	0.8 (0.13) kg	0.3 (0.14) kg
+ TZD (-013)	1.4 (0.23) kg	0.9 (0.20) kg
	Saxagliptin 5 mg + Metformin	**Metformin**
Initial Combination with MET (-039)	-1.8 (0.20) kg	-1.6 (0.18) kg

Data are presented as mean change from baseline (SE).
Abbreviations: Met = metformin; Saxa = saxagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

Saxagliptin treatment did not lead to adverse effects in blood pressure or heart rate. There were no trends in elevation of mean systolic or diastolic blood pressure in any of the studies (Table 20). Blood pressure generally declined minimally in all the Core Phase 3 studies to an extent comparable to comparator (placebo or metformin).

Table 20: Mean Change from Baseline in SBP and DBP to Week 24 – Core Phase 3 Studies

	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)	
	Saxa 5 mg	**Placebo**	**Saxa 5 mg**	**Placebo**
Monotherapy				
(-011)	-4.8 (1.3)	-6.9 (2.1)	-1.7 (0.8)	-2.8 (1.1)
(-038)	-1.8 (1.6)	-1.5 (2.1)	-0.5 (1.0)	-1.1 (1.2)
Add-on Combination				
+ MET (-014)	-3.8 (1.4)	-3.7 (1.3)	-1.8 (0.9)	-1.9 (0.8)
+ SU (-040)	-3.2 (1.0)	-2.0 (1.1)	-1.8 (0.6)	-2.4 (0.7)
+ TZD (-013)	-0.5 (1.0)	-0.6 (1.2)	-1.1 (0.6)	-1.9 (0.8)
	Saxa 5 mg + Met	**Met**	**Saxa 5 mg + Met**	**Met**
Initial Combination with MET (-039)	-5.1 (0.8)	-5.3 (0.9)	-3.0 (0.5)	-4.1 (0.6)

Data are presented as mean change from baseline (SE).
Abbreviations: Met = metformin; Saxa = saxagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

7.6.4 Dermatological Safety

The administration of some DPP4 inhibitors has been associated with skin lesions in monkeys. The administration of saxagliptin to cynomolgus monkeys was associated with reversible skin lesions (erosions and ulcers) at multiple distal sites (digits, nose, feet, scrotum, and tail), observed at an AUC multiple of ≥ 7 times the RUCD. As a consequence, extensive monitoring for similar skin-related lesions was instituted for the saxagliptin Phase 3 program. Overall, evaluation of the saxagliptin clinical data has not revealed any signals that correlate to the skin findings observed in monkeys.

Skin-related AEs were identified in an ongoing manner to gather additional information using supplemental CRFs. Investigators were informed of the need to monitor for skin-related AEs and to complete these supplemental forms, heightening awareness and likely increasing case ascertainment. In addition, a pre-defined MedDRA PT list was generated,

specific to the nonclinical skin-related events which included terms such as skin ulcer and skin necrosis to identify AEs in the Phase 3 clinical database for further evaluation.

The overall frequency of skin-related AEs was generally comparable in subjects who received saxagliptin 5 mg and control (Table 21 and Table 22). Compared with the saxagliptin 5 mg and placebo groups, numerically higher proportions of subjects reported skin and subcutaneous tissue AEs in the saxagliptin 2.5 and 10 mg groups (Table 21 and Table 22). The difference was in part due to a higher proportion of subjects with rash in the saxagliptin 2.5 and 10 mg groups compared with the saxagliptin 5 mg and control groups. There was no consistent evidence for a dose-response relationship for AEs in this SOC. The rate of discontinuations for AEs in the SOC Skin and Subcutaneous Tissue Disorders was similar in the saxagliptin and control groups.

Table 21: Skin and Subcutaneous Tissue Disorders (SOC) AEs - Monotherapy and Combination Studies (NDA Database)

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
ST Period, Excluding Rescue					
Pooled Monotherapy (CV181011, CV181038)	13.4% (33/247)	9.1% (23/252)	13.3% (13/98)	11.6% (69/597)	8.3% (14/169)
Add-On Combination					
+ Met (CV181014)	8.3% (16/192)	6.8% (13/191)	9.9% (18/181)	8.3% (47/564)	7.8% (14/179)
+ SU (CV181040)	8.9% (22/248)	4.7% (12/253)	N/A	6.8% (34/501)	4.9% (13/267)
+ TZD (CV181013)	5.1% (10/195)	7.5% (14/186)	N/A	6.3% (24/381)	6.0% (11/184)
Up to Week 24, Regardless of Rescue Status					
Placebo-controlled Pooled Safety	9.3% (82/882)	7.1% (63/882)	12.2% (34/279)	8.8% (179/2043)	7.3% (58/799)

Note: The frequencies for the individual populations added together do not equal the frequencies for Placebo-controlled Pooled Safety since that analysis included after the initiation of rescue therapy.
Abbreviations: Met = metformin; N/A = not applicable; Saxa = saxagliptin; ST = short-term; SU = sulfonylurea; TZD = thiazolidinedione.

Table 22: Skin and Subcutaneous Tissue Disorders (SOC) AEs - ST Period Excluding Rescue- Initial Combination Study with Metformin (NDA Database)

Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	All Saxa	Met
3.4% (11/320)	4.3% (14/323)	4.2% (14/335)	4.0% (39/978)	2.7% (9/328)

Abbreviations: Met = metformin; Saxa = saxagliptin; ST = short-term.

Adverse events, as defined in the pre-defined list of PTs specific to the nonclinical skin-related events, were reported infrequently, without clear imbalance between the saxagliptin and control groups. There was no evidence for a dose-response relationship in any study. None of the events in the pre-defined list of PTs was reported as related to study drug and none resulted in study drug interruption or discontinuation. In general, the causes of the identified skin lesions from this pre-defined list were believed to be secondary to underlying disease (eg, diabetic ulcers) or related to trauma.

Overall, evaluation of clinical data has not revealed any signals that correlate to the skin findings in the cynomolgus monkey; indicating that the findings in the monkey are not applicable to humans.

There was no AE reported with the PT Stevens-Johnson syndrome in the Phase 2b/3 clinical program

7.6.5 Localized Edema

In March 2007, the US FDA notified all sponsors developing DPP4 inhibitors that symptomatic edema of the hands/feet and laboratory abnormalities had been observed in healthy human subjects receiving a DPP4-inhibitor. The Agency advised all sponsors who were developing drugs in this class that subjects should be closely monitored for similar findings that may be potentially drug related. Edema has not been observed in any nonclinical species at any dose of saxagliptin evaluated. However, based on the communication from the Agency, localized edema was considered an event of special interest for monitoring in the Phase 3 program.

Adverse events of localized edema in the saxagliptin Phase 3 program were identified using a pre-defined list of MedDRA lower-level terms. Across the saxagliptin Phase 3 program, the incidence of localized edema was generally comparable between saxagliptin- and placebo-treated subjects (Tables 23 and 24). The sole deviation from this generalization occurred in the saxagliptin 5 mg group of the add-on combination study with TZD (CV181013). In this study, there was a higher rate of events constituting localized edema in the 5 mg saxagliptin group compared with placebo, whereas the rate was lower in the saxagliptin 2.5 mg group compared with placebo. The majority of these events in the saxagliptin 5 mg plus TZD group were for pedal edema; there was no imbalance seen for events of hand edema. It is well established that peripheral edema is associated with TZD therapy, and that this finding is more common when a TZD is used concomitantly with other oral diabetes agents.[21] Across the clinical program, the majority of localized edema AEs were of mild to moderate intensity and did not result in discontinuation of study drug. In a clinical pharmacology study, saxagliptin was well tolerated at doses of up to 400 mg given for 14 days without any reports of localized edema of the hands or feet. Overall, there was no evidence that saxagliptin led to an increased risk of localized edema.

Table 23: Localized Edema AEs - Monotherapy and Combination Studies (NDA Database)

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
ST Period, Excluding Rescue					
Pooled Monotherapy (CV818011, CV181038)	1.2% (3/247)	1.2% (3/252)	1.0% (1/98)	1.2% (7/597)	1.2% (2/169)
Add-on Combination					
+ Met (CV181014)	0 (0/192)	1.6% (3/191)	0.6% (1/181)	0.7% (4/564)	1.1% (2/179)
+ SU (CV181040)	0.4% (1/248)	0.4% (1/253)	N/A	0.4% (2/501)	0 (0/267)
+ TZD (CV181013)	1.0% (2/195)	7.0% (13/186)	N/A	3.9% (15/381)	2.7% (5/184)
Up to Week 24, Regardless of Rescue Status					
Placebo-controlled Pooled Safety	0.9% (8/882)	2.3% (20/882)	0.7% (2/279)	1.5% (30/2043)	1.1% (9/799)

Note: The frequencies for the individual populations added together do not equal the frequencies for the placebo-controlled Pooled Safety since that analysis included AEs after initiation of rescue therapy.
Abbreviations: AE = adverse event; Met = metformin; N/A = not applicable; Saxa = saxagliptin; ST = short-term; SU = sulfonylurea; TZD = thiazolidinedione.

Table 24: Localized Edema AEs - ST Period Excluding Rescue- Initial Combination Study with Metformin (NDA Database)

Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	All Saxa	Met
0.6% (2/320)	0.3% (1/323)	0 (0/335)	0.3% (3/978)	0 (0/328)

Abbreviations: AE = adverse event; Met = metformin; Saxa = saxagliptin; ST = short-term.

7.6.6 Lymphocytes

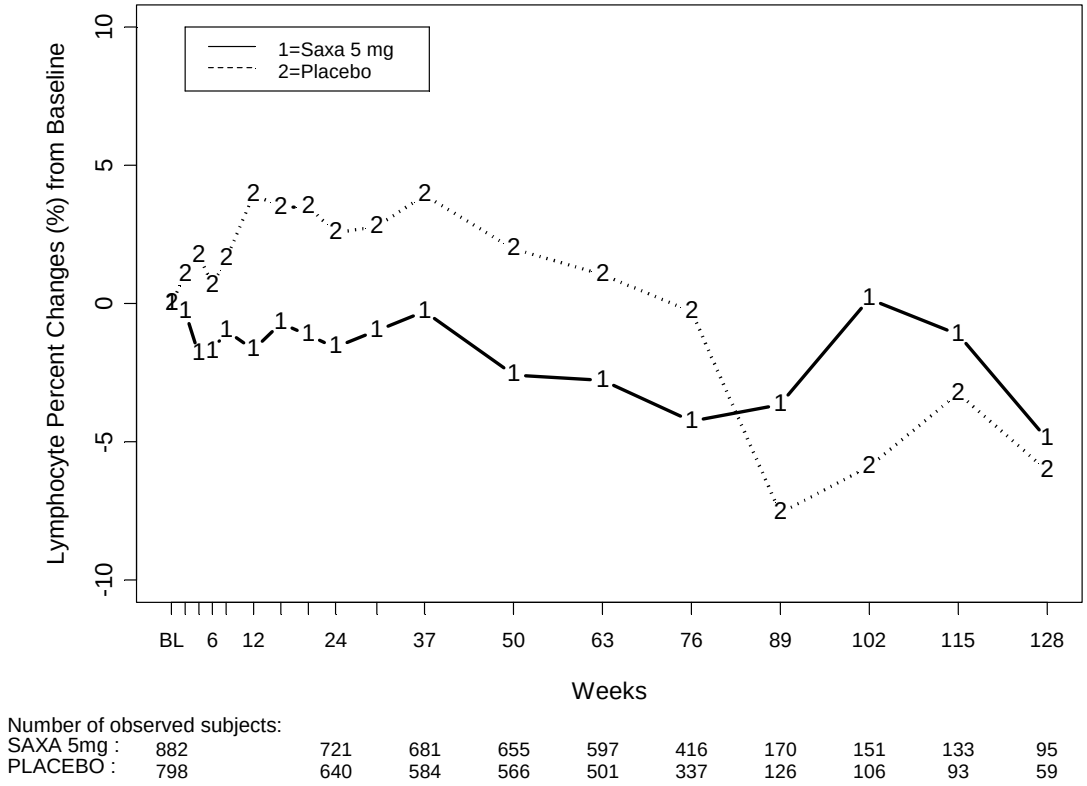
Lymphocyte counts were monitored frequently and AEs related to decreased lymphocyte counts were carefully evaluated in the saxagliptin development program because of low lymphocyte counts observed in two drug-drug interaction studies in healthy volunteers given doses of saxagliptin at 100 mg (20 times the RUCD) and a modest, reversible,

dose-related decrease in mean lymphocyte count that was most apparent at doses of saxagliptin ≥ 20 mg in the Phase 2b study.

In the Phase 3 program, a small dose-dependent decrease in mean absolute lymphocyte count was observed in the saxagliptin 5 and 10 mg groups when compared with placebo. The mean decrease at Week 24 was approximately 100 cells/μL in the saxagliptin 5 mg group compared with placebo (from a baseline absolute lymphocyte count of approximately 2200 cells/μL) based on an analysis of the Placebo-controlled Pooled Safety Population. An analysis of mean decrease in lymphocyte count by baseline tercile showed that subjects with baseline absolute lymphocyte counts in the highest tercile had the greatest mean decline in absolute lymphocyte count in all groups. There was a mean increase in lymphocyte count in the saxagliptin 2.5 and 5 mg groups with baseline lymphocyte counts in the lowest tercile.

Overall, the decreases in lymphocyte counts were non-progressive with daily dosing of saxagliptin up to 128 weeks. Figure 15 shows the percent change from baseline up to Week 128 in absolute lymphocyte count based on the Placebo-controlled Pooled Safety Population for subjects who received saxagliptin 5 mg and placebo. Experience beyond 18 months (76 weeks) was provided through two Phase 3 studies where saxagliptin was administered as monotherapy or as add-on combination treatment with metformin. In the first 24 weeks there was a small increase in the percent change from baseline in the placebo group and a small decrease in the saxagliptin group (Figure 15). The differences between saxagliptin 5 mg and placebo seen at Week 24 did not progress at later timepoints. With saxagliptin treatment at and beyond 89 weeks, the magnitude of difference in percent change from baseline in absolute lymphocyte count was either similar or smaller than the change from baseline seen with placebo.

Figure 15: Percent Changes from Baseline in Absolute Lymphocyte Counts (x10^3 c/μL) During ST+LT Treatment Period (120 Day Database). Placebo-controlled Pooled Safety Population.



Note: data from visits where blood samples were drawn in the fasted state are shown.

Decreases in absolute lymphocyte counts to ≤ 0.75 x 10^3 c/μL (defined as a marked abnormality [MA]) were relatively infrequent in all treatment groups (Table 25). Analyses to explore the relationship between the frequency of MAs and baseline absolute lymphocyte count among the subjects whose laboratory values met pre-defined MA criteria in the Phase 2b and 3 studies revealed that the majority of saxagliptin-treated subjects with MAs had baseline lymphocyte counts at the lower portion of the normal range or below the LLN. In the subjects with a MA for decreased lymphocyte count, most who were re-challenged with saxagliptin did not experience a recurrent MA.

Table 25: Marked Abnormalities for Absolute Lymphocyte Count ($\leq 0.75 \times 10^3$ c/μL) - ST+LT Periods (NDA Database) Phase 2b/3 Pooled Population

		n/N (%)				
		Saxa 2.5 mg[a]	**Saxa 5 mg[b]**	**Saxa 10 mg[c]**	**Placebo[d]**	**Metformin[e]**
	N	937	1269	1066	923	328
ST+LT	n/N (%)	8/924 (0.9)	19/1255 (1.5)	15/1046 (1.4)	5/911 (0.5)	0

[a] Included subjects who were uptitrated to saxagliptin 5 mg or 10 mg in Study CV181038.

[b] Included subjects who were uptitrated to saxagliptin 10 mg in Study CV181038.

[c] Included open-label study medication.

[d] Combined placebo groups from all above referenced studies except Study CV181039.

[e] Data represent the metformin monotherapy control group from Study CV181039.

Note: Table included all available ST+LT data [Studies: -008, -011 (including the saxagliptin 10 mg open-label cohort), -013, -014, -038, -039, -040, and -041].

Abbreviations: LT = long-term; Saxa = saxagliptin; ST = short-term.

In a clinical study designed to better characterize the mechanism underlying the change in lymphocyte count, investigations did not show evidence of impairment in lymphocyte proliferation, apoptosis / necrosis, and did not show that any one lymphocyte population was disproportionately affected when decreases were observed. Thus, while the mechanism for the decreases in lymphocyte count remains unknown, the mechanism does not appear to be related to a defect in proliferation or to increased destruction of lymphocytes and does not appear to result in the selective loss of a particular population of lymphocytes.

To assess whether the lymphocyte count decreases were associated with clinical adverse consequences, infection-related AEs were reviewed in subjects who had decreases in absolute lymphocyte count to $\leq 0.75 \times 10^3$ c/μL. The types of infection observed in these subjects were similar to those reported in the overall population. Specifically, in these subjects, unusual infectious-related events that would be considered opportunistic in nature were not seen (eg, no events of CMV, EBV or PCP).

In an analysis of infection-related AEs broadly defined as potentially associated with T-cell dysfunction (eg, herpes infections) across the entire Phase 2b/3 clinical program, the frequency of these selected infection-related AEs were comparable between subjects who received saxagliptin and comparator treatment regimens. Thus, while the clinical significance of the decrease in lymphocyte count relative to placebo is not known, the decreases were not associated with clinically relevant infection-related adverse events.

7.6.7 Infections

Infection-related AEs were identified as an event of special interest given the role of DPP4, also known as CD26, as a co-stimulatory signaling molecule expressed on the surface of T-cells.

An analysis of the Placebo-controlled Pooled Safety Population demonstrated comparable AE frequencies in the SOC Infections and Infestations in the saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo groups (Tables 26 and 27); a higher frequency of AEs was observed in the saxagliptin 10 mg group.

In contrast, while a slightly higher proportion of subjects had infection-related AEs in the saxagliptin 10 mg monotherapy group relative to the metformin monotherapy group, the proportion was lower in the saxagliptin 10 mg + metformin group than in the metformin monotherapy group. These numerical differences were likely due to random variation rather than meaningful clinical differences.

Table 26: Infections and Infestations (SOC) AEs - Monotherapy and Combination Studies (NDA Database)

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
ST Period, Excluding Rescue					
Pooled Monotherapy (CV181011, CV811038)	30.4% (75/247)	29.8% (75/252)	38.8% (38/98)	31.5% (188/597)	23.7% (40/169)
Add-on Combination					
+ Met[a] (CV181014)	42.7% (82/192)	34.0% (65/191)	38.1% (69/181)	38.3% (216/564)	35.8% (64/179)
+ SU (CV181040)	37.5% (93/248)	41.1% (104/253)	N/A	39.3% (197/501)	39.0% (104/267)
+ TZD (CV181013)	30.8% (60/195)	33.9% (63/186)	N/A	32.3% (123/381)	30.4% (56/184)
Up to Week 24, Regardless of Rescue Status					
Placebo-controlled Pooled Safety	36.4% (321/882)	35.9% (317/882)	40.1% (112/279)	36.7% (750/2043)	34.8% (278/799)

[a] MedDRA version 9.1

Note: The frequencies for the individual populations added together do not equal the frequencies for Placebo-controlled Pooled Safety since that analysis included AEs after initiation of rescue therapy.

Abbreviations: Met = metformin; N/A = not applicable; Saxa = saxagliptin; ST = short-term; SU = sulfonylurea; TZD = thiazolidinedione.

Table 27: Infections and Infestations (SOC) AEs - ST Period Excluding Rescue- Initial Combination Study with Metformin (NDA Database)

Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	All Saxa	Met
22.8% (73/320)	20.1% (65/323)	26.6% (89/335)	23.2% (227/978)	23.5% (77/328)

Abbreviations: Met = metformin; Saxa = saxagliptin; ST = short-term.

Although AEs in the SOC Infections and Infestations were the most commonly reported AEs across the Core Phase 3 studies, relatively few were considered serious, and few led to discontinuation. The frequency of infection-related SAEs or infection-related AEs leading to discontinuation of study drug was similar in subjects who received saxagliptin and placebo (approximately 0.5%). Infection-related events that would be considered as

opportunistic infections were infrequent, with no indication of an increased rate in subjects who received saxagliptin in the Core Phase 3 program.

7.6.8 Platelets

In the Phase 2b study, although the mean values were within the normal range, there was a trend toward decreased platelet counts in the dose range of 5 mg and higher, which appeared to resolve after discontinuation of study medication. As a consequence of this finding, platelet counts were monitored frequently in the Phase 3 program.

The results from the Phase 3 clinical studies demonstrated no clinically meaningful or consistent effect on platelet counts. In the Placebo-controlled Pooled Safety Population, comparable reductions from baseline in mean platelet count were observed in all treatment groups, including placebo. The magnitude of the decrease from baseline to Week 24 was approximately 2% from a baseline platelet count of 260,000 cells/μL.

Adverse events of thrombocytopenia were reported with low frequency across all treatment groups. In the Placebo-controlled Pooled Safety Population (up to Week 24, regardless of rescue), the frequency of AEs of thrombocytopenia was comparable for the saxagliptin-treated subjects and placebo groups (0.4% for all subjects treated with saxagliptin compared with 0.1% for placebo). In the initial combination study with metformin, the frequencies of AEs of thrombocytopenia were comparable between the saxagliptin treatment groups and metformin monotherapy group (0.2% for all subjects treated with saxagliptin versus 0.3% for metformin).

7.6.9 Hepatic Safety

There was no safety signal related to drug induced liver injury (DILI) in nonclinical toxicological studies with saxagliptin. In the Phase 2b/3 studies, clinical assessment of the safety of saxagliptin with respect to DILI included analyses of change from baseline, marked laboratory abnormalities (MAs), shift tables, and combinations of laboratory parameters that may be indicative of DILI (ALT or AST > 3 x ULN with concomitant total bilirubin > 2 x ULN). The overall frequencies of MAs in liver function tests (LFTs) were low and balanced across treatment groups in the Phase 2b/3 Pooled Population

(Table 28). Based on these assessments, there was no evidence for DILI associated with the use of saxagliptin.

Table 28: Marked Laboratory Abnormalities of LFTs - ST+LT Periods (NDA Database) - Phase 2b/3 Pooled Population

Parameter	n/N, (%)					
	Saxagliptin				Placebo[a]	Metformin[b]
	2.5 mg[c] N = 937	5 mg[d] N = 1269	10 mg[e] N = 1066	All Saxa[f] N=3422	N = 923	N = 328
AST						
> 3 x ULN	8/926 (0.9)	8/1255 (0.6)	8/1046 (0.8)	25/3376 (0.7)	5/912 (0.5)	5/319 (1.6)
> 5 x ULN	3/926 (0.3)	1/1255 (0.1)	2/1046 (0.1)	7/3376 (0.2)	1/912 (0.1)	0
> 10 x ULN	1/926 (0.1)	0	1/1046 (0.1)	2/3376 (0.1)	0	0
> 20 x ULN	0	0	0	0	0	0
ALT						
> 3 x ULN	14/926 (1.5)	15/1255 (1.2)	7/1046 (0.7)	37/3376 (1.1)	7/912 (0.8)	4/319 (1.3)
> 5 x ULN	3/926 (0.3)	2/1255 (0.2)	2/1046 (0.2)	8/3376 (0.2)	2/912 (0.2)	0
> 10 x ULN	2/926 (0.2)	0	1/1046 (0.1)	4/3376 (0.1)	0	0
> 20 x ULN	0	0	0	0	0	0
Total Bilirubin						
> 2 mg/dL	4/926 (0.4)	5/1254 (0.4)	4/1046 (0.4)	13/3375 (0.4)	2/912 (0.2)	3/319 (0.9)
> 1.5 x ULN	7/926 (0.8)	5/1254 (0.4)	8/1046 (0.8)	23/3375 (0.7)	3/912 (0.3)	3/319 (0.9)
> 2 x ULN	2/926 (0.2)	1/1254 (0.1)	2/1046 (0.2)	5/3375 (0.1)	0	1/319 (0.3)
Alkaline Phosphatase						
> 3 x pre-Rx and ULN	0	2/1254 (0.2)	1/1046 (0.1)	3/3375 (0.1)	0	2/319 (0.6)
1.5 x ULN	38/926 (4.1)	37/1254 (3.0)	40/1046 (3.8)	115/3375 (3.4)	40/912 (4.4)	17/319 (5.3)

[a] Combined placebo groups from all above referenced studies except CV181039.

[b] Data represent the metformin monotherapy control group from CV181039.

[c] Included subjects who were uptitrated to saxagliptin 5 mg or 10 mg in Study CV181038.

[d] Included subjects who were uptitrated to saxagliptin 10 mg in Study CV181038.

[e] Included open-label study medication.

[f] Included additional data from higher dose groups in CV181008; therefore, numbers across the rows are not additive.

[Studies: -008, -011 (includes the saxagliptin 10 mg open-label cohort), -013, -014, -038, -039, -040, -041].

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; LFT = liver function test; LT = long-term; RX = treatment; Saxa = saxagliptin; ST = short-term; ULN = upper limit of normal.

7.6.10 Pancreatic Safety

Because of postmarketing reports of acute pancreatitis described in patients treated with a GLP-1 agonist[22], the sponsor examined the nonclinical data and the saxagliptin Phase 2b/3 database for all cases of pancreatitis. There was no safety signal related to pancreatitis in nonclinical studies with saxagliptin.

There was no safety signal related to pancreatitis in the saxagliptin clinical program. The overall incidence of AEs of pancreatitis in the Phase 2b/3 Pooled Population (comprised of the MedDRA PTs Pancreatitis, Acute Pancreatitis, and Chronic Pancreatitis) was low and balanced between saxagliptin (6/3422 or 0.18%) and comparator groups (0/923 in the placebo groups and 2/328 or 0.61% in the metformin group) (ST + LT Periods, NDA Database). Of the six subjects with pancreatitis in the saxagliptin treatment groups, five had at least one known risk factor for pancreatitis (alcohol use, cholelithiasis, prior history of hypertriglyceridemia, or prior history of pancreatitis). Only one subject, in the saxagliptin 5 mg + metformin group, had no known risk factors for pancreatitis. This subject had duodenitis and gastritis in the same episode. The investigator assessed the event to be of moderate intensity and not related to study medication. No action was taken in relationship to study medication and the event resolved 47 days after onset while the subject was still receiving study medication.

7.6.11 Renal Safety

There was no safety signal related to renal function. Marked abnormalities for parameters of renal function were balanced among saxagliptin and comparator groups in the Phase 2b/3 clinical program. The proportion of subjects with increase in creatinine > 2.5 mg/dL (pre-defined definition of a marked abnormality) was low and balanced between saxagliptin (5/3375, or 0.1%), placebo groups (1/912, or 0.1%), and the metformin group (0/328) (ST + LT Periods, NDA Database).

There were no consistent or clinically meaningful changes from baseline over time in serum creatinine, creatinine clearance, urine microalbumin, or in urine microalbumin/ creatinine ratio in any study.

Renal excretion is a major elimination pathway for saxagliptin and its major metabolite, BMS-510849. Because of this, the proposed dose recommended for patients with moderate, severe, or end-stage renal disease requiring hemodialysis is 2.5 mg (which is half of the dose recommended for most patients with T2DM). Therefore, additional analyses were performed to assess the safety of saxagliptin in subjects with impaired renal function. For these analyses, renal impairment was defined as a Cockcroft-Gault estimated creatinine clearance of ≤ 80 mL/min at baseline.

The largest of the datasets examined was the Placebo-controlled Pooled Safety Population, which included two monotherapy studies and three add-on combination studies (with SU, TZD and metformin). Among subjects with renal impairment in the Placebo-controlled Pooled Safety Population, the overall frequency of AEs (up to Week 24, including rescue) was numerically lower for saxagliptin- than placebo-treated subjects (67.4% vs 73.1%). Among the common AEs (> 2%) among subjects with renal impairment where there was a difference of > 1% in either direction between the All Saxagliptin and Placebo groups, the only AE that was reported more frequently in saxagliptin- than placebo-treated subjects with renal impairment was gastroenteritis. These data suggest that the safety profile of saxagliptin among subjects with renal impairment was comparable to the overall study population.

7.6.12 Other Laboratory Safety

There was no safety signal related to skeletal myopathy. In the Phase 2b/3 studies, MAs of CK (with levels > 5 x ULN) were uncommon and balanced across the saxagliptin and placebo groups. Overall, 38/3376 (1.1%) of subjects in the saxagliptin group, 10/912 (1.1%) of subjects in the placebo groups, and 2/319 (0.6%) subjects in the metformin groups had MAs of elevated CK (ST + LT Periods, NDA Database).

There was no evidence for clinical meaningful effects on other hematology or chemistry parameters associated with saxagliptin treatment.

8 PLAN FOR CONTINUED ASSESSMENT OF BENEFIT/RISK POST-APPROVAL

The safety profile of saxagliptin observed in this program was consistent across diverse studies and diverse populations of patients with T2DM, suggesting a predictable safety profile that will be broadly applicable to the T2DM population anticipated in general practice. The Sponsor recognizes that Phase 2b/3 clinical studies are limited in terms of detecting rare AEs or AEs appearing after long latency periods, therefore, the Sponsor will continue to assess the long-term benefits and risks of treatment under the conditions of usual clinical care. The planned activities represent an integrated, complementary set of pharmacovigilance (PV) activities (spontaneous reports, prospective observational studies, and controlled clinical studies) which are designed to continually assess and maximize the benefit/risk profile of saxagliptin in the marketplace.

8.1 Risk Management Plan

The Sponsor has submitted a Risk Management Plan for review by the FDA, which includes the following safety specification briefly summarized below:

Summary of Safety Specification	
Potential Risks	1. Skin lesions, 2. Localized edema 3. Lymphopenia, 4. Thrombocytopenia, 5. Infections, 6. Hypoglycemia

These AEs have been classified as potential risks following review of nonclinical, clinical and class data, without any evidence of correlation or any clinical impact in the saxagliptin treated patient population in the Phase 2b/3 program. No identified risks have been found for saxagliptin at this time.

The Sponsor will work with the FDA on providing appropriate labeling to support the safe and appropriate use of saxagliptin. Therefore, additional risk minimization activities are not warranted and not currently recommended.

8.1.1 Enhanced Pharmacovigilance Plan

In addition to the routine pharmacovigilance activities of evaluating spontaneous reports of adverse events and reports from the scientific literature, the Sponsor will use targeted questionnaires to enhance the quality of the information captured for the potential risks. Furthermore, the Sponsor will enhance signal detection capabilities through periodic review of the FDA AERS safety database using additional analyses that may help to assess any potential signal identified from spontaneous reports.

8.1.2 Safety Monitoring in Randomized Controlled Trials

The routine evaluation of safety reports in clinical trials, individually and in aggregate, will be supplemented by the following two additional approaches to enhance risk assessment:

- Supplemental CRFs will be used to collect additional details for the previously described potential risks.
- Major CV events are being adjudicated by an independent committee in ongoing Phase 3b studies.

8.1.3 Pharmacoepidemiology Plan

The Sponsor proposes to conduct prospective observational studies of adult patients with T2DM, as part of the post-launch active surveillance activities, in order to assess the safety profile of saxagliptin in the general population under conditions of usual care and to assess the risk for major adverse cardiac events, acute renal and acute hepatic failure, hospitalization for infections, and risk factors for decrease in lymphocyte count.

These studies are planned to begin at the launch of saxagliptin in the US and/or the EU, and the study population will be followed for approximately 3 to 5 years. The number of saxagliptin users required per study will depend on the outcome of interest. The primary comparison of interest will be metformin users newly starting saxagliptin versus metformin users newly starting any other oral antidiabetic (OAD) agent.

These studies will provide insight into the benefit/risk profile of saxagliptin in the general population. Final study protocols and timelines will be discussed with the FDA and epidemiology experts prior to the implementation of the studies.

9 ONGOING PHASE 3B STUDIES AND FUTURE CLINICAL PLANS

The Phase 3 registrational studies described in Sections 5 through 7 of this briefing document provided necessary information for the US NDA and for global regulatory submissions. Bristol-Myers Squibb and Astra-Zeneca are jointly continuing active investigation of saxagliptin in several ongoing Phase 3b clinical studies, listed in Table 29.

Table 29: Summary of Ongoing Phase 3b Studies with Saxagliptin

Study No.	Study objective (Population)	No. (planned) Randomized and treated All/Saxa	Duration short-term (total)	Saxagliptin dose (mg)
CV181054 / D1680C00001 [a]	Safety and efficacy of saxagliptin in combination with metformin compared with SU in combination with metformin (A1C 6.5%-10%)	(838/419)[b]	52 Weeks (104 Weeks)	5 mg (+ metformin IR)
CV181056/ D1680C00002 [a]	Safety and efficacy of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin (A1C 6.5%-10%)	(710/355)[b]	18 Weeks	5 mg (+ metformin IR)
CV181057	Efficacy and safety of saxagliptin compared with placebo as add-on therapy to insulin (or to insulin combined with metformin). (A1C 7.5%-11.0%)	(435/290)[b]	24 Weeks (52 Weeks)	5 mg
CV181062/ D1680C00007 [a]	Effect of saxagliptin compared with placebo in adult subjects with T2DM and renal impairment (moderate, severe, and end-stage). (A1C 7%-10%)	(168/84)[b]	12 Weeks (52 Weeks)	2.5 mg (+ background medications)

Table 29: Summary of Ongoing Phase 3b Studies with Saxagliptin

Study No.	Study objective (Population)	No. (planned) Randomized and treated All/Saxa	Duration short-term (total)	Saxagliptin dose (mg)
CV181063/ D1680C00005	Efficacy and safety of saxagliptin compared with placebo. Study conducted in Asia. (A1C 7.0%-10.0%)	(530/265)[b]	24 Weeks	5 mg
CV181064/ D1680C00006	Efficacy and safety of saxagliptin in combination with metformin compared with placebo in combination with metformin. Study conducted in Asia. (A1C 7.0%-10.0%)	(530/265)[b]	24 Weeks	5mg
CV181066	Efficacy and safety of saxagliptin in comparison to placebo as add-on treatment to metformin XR in subjects on a stable dose of metformin XR ≥ 1500 mg/day (A1C 7.0%-10.0%)	(92/46)[b]	4 Weeks	5 mg

[a] Study is included in a blinded review of the safety data for the 120 Day Update of Clinical Safety.
[b] Planned number of subjects when study completes.
Abbreviations: LT = long-term; IR = immediate release; Saxa = saxagliptin; ST = short-term; SU = sulfonylurea; TZD = thiazolidinedione; XR = extended release.

These current Phase 3b studies focus on the optimal clinical dose, saxagliptin 5 mg, as concluded from the assessment of doses in the Phase 3 studies. Direct head-to-head comparisons of saxagliptin 5 mg to sitagliptin 100 mg and to a commonly used sulfonylurea (glipizide) titrated to effect, as well as studies assessing saxagliptin 5 mg in combination with insulin and in Asian T2DM populations are in progress. Finally, the saxagliptin 2.5 mg dose recommended for T2DM patients with moderate or severe renal impairment, or end-stage renal disease, is being studied more extensively in this population in order to complement the information already provided for patients with T2DM and renal disease. All ongoing Phase 3b studies of saxagliptin include prospective adjudication of major CV events by an independent adjudication committee at the Montreal Heart Institute. Thus, as CV AEs occur and are reported in ongoing Phase 3b saxagliptin trials, collection of clinical safety data and prospective adjudication of major

CV events by this independent adjudication committee is conducted according to established processes.

Overall, Bristol-Myers Squibb and Astra-Zeneca each have a strong heritage of conducting clinical outcomes trials following past regulatory approvals, including Bristol-Myers Squibb sponsorship of the DPP (Diabetes Prevention Program)[23] following the US approval of metformin, Bristol-Myers Squibb sponsorship of the WOSCOPS,[24] CARE,[25] and LIPID[26] trials following the initial approval of pravastatin, and AZ sponsorship of the GALAXY set of clinical Astra-Zeneca trials, most recently the JUPITER trial,[27] following the initial approval of rosuvastatin.

Bristol-Myers Squibb and AstraZeneca are committed to further understanding both the short-term and long-term benefit/risk profile of saxagliptin. Besides the ongoing Phase 3b studies described above, there are additional studies planned, including both randomized controlled trials and observational studies. In addition, Bristol-Myers Squibb and AstraZeneca are actively evaluating several options for a longer-term event-driven study with saxagliptin. This would be a large, randomized, and controlled clinical trial to assess the overall clinical effectiveness of saxagliptin in the management of T2DM. This study could provide further information on measures of glycemic control and end-organ effects, and enhance our understanding of the CV profile of saxagliptin.

10 BENEFIT/RISK ASSESSMENT

T2DM is a chronic progressive disease associated with devastating microvascular and macrovascular complications. The achievement of glycemic control reduces the risk of microvascular complications. Multiple therapeutic modalities are typically required to achieve optimal metabolic control. In spite of the availability of a number of different antihyperglycemic classes of agents, achievement of A1C targets remains suboptimal. Many available treatments are associated with undesirable side effects including increased risk of hypoglycemia, weight gain, gastrointestinal adverse events, or edema, which present barriers to their use and acceptance. Due to the progressive nature of the disease, more than one medication will be necessary for the majority of patients over time.[28] As a consequence, there remains the need to identify additional effective, safe,

and well-tolerated antihyperglycemic agents to help patients achieve and sustain target glycemic levels.

10.1 Summary of Benefits

The results from the eight clinical studies in the saxagliptin Phase 2b and 3 program in over 4600 subjects combined with the results from clinical pharmacology studies support the oral dose of saxagliptin 5 mg once daily in a wide range of subjects with T2DM, as either monotherapy, add-on combination therapy with metformin, a TZD, or a SU, or initial combination therapy with metformin.

In the Phase 2b dose-ranging study, administration of saxagliptin 5 mg was associated with significant inhibition of plasma DPP4 activity at the trough of the dosing interval as well as clinically meaningful decreases in A1C, fasting serum glucose and postprandial serum glucose. The results from the Phase 3 studies confirmed clinically meaningful benefits of saxagliptin 5 mg on A1C, as well as FPG, postprandial glucose, insulin, C-peptide, glucagon levels, and β-cell function. The results also demonstrated that treatment with saxagliptin resulted in a high percentage of subjects being able to achieve glycemic goals including A1C levels < 7%. Sustained glycemic effect relative to placebo was observed. Saxagliptin treatment consistently demonstrated a beneficial antihyperglycemic effect across subgroups of demographic and baseline diabetes characteristics. In elderly subjects (≥ 65 years of age), A1C reductions and AE profiles were comparable to those in younger subjects, supporting a positive benefit/risk ratio in the elderly.

There was no evidence that the 10 mg saxagliptin dose provided any incremental efficacy benefit over that observed with the 5 mg dose. Subjects in the saxagliptin 5 mg groups consistently demonstrated better glycemic control than subjects in the saxagliptin 2.5 mg group. Specifically:

- The saxagliptin 5 mg treatment group demonstrated greater reductions from baseline in A1C than the saxagliptin 2.5 mg group in four of five Phase 3 studies (note that Study CV181039 did not contain a saxagliptin 2.5 mg dose group). Similarly, maximal A1C benefit in the Phase 2b dose-ranging study was seen at a saxagliptin dose of 5 mg.

- The proportion of subjects who achieved A1C reductions ≥ 0.7% was greater in subjects who received saxagliptin 5 mg compared with 2.5 mg in four of five Phase 3 studies.
- There was a greater reduction from baseline in postprandial glucose AUC, which closely reflects the primary incretin-based mechanism for saxagliptin, for the saxagliptin 5 mg groups compared with the 2.5 mg groups in all Phase 3 studies.
- The proportion of subjects achieving a glycemic response of A1C < 7% was larger in the saxagliptin 5 mg groups compared with the 2.5 mg groups in four of five Phase 3 studies.

These observations demonstrate that saxagliptin 5 mg per day is the optimally efficacious dose.

10.2 Summary of Risks

Once-daily, orally-administered saxagliptin was well-tolerated at doses of up to 400 mg (80 times the RUCD) QD for 2 weeks, 100 mg (20 times the RUCD) QD for 6 weeks, 40 mg (8 times the RHCD) and 20 mg (4 times the RUCD) QD for 12 weeks, and at 2.5, 5, and 10 mg QD for up to 128 weeks. Overall, in the extensive Phase 2b/3 program in 3422 subjects treated with saxagliptin, the safety profiles of saxagliptin 2.5 mg and 5 mg were generally comparable. Although the rate of certain AEs was higher in subjects who received saxagliptin 10 mg compared with those who received 2.5 and 5 mg, saxagliptin 10 mg was also well tolerated, providing a reassuring safety margin of exposure for the chronic use of the saxagliptin 5 mg dose, the RUCD.

Long-term dosing of saxagliptin in the Phase 3 program, which included exposure up to 128 weeks in duration, did not reveal any unexpected events or emergent safety signals when compared with analyses of the ST (24-week) study periods. The overall profile of AEs associated with extended dosing of saxagliptin for up to 2.5 years was consistent with that seen at 24 weeks.

A number of measures were implemented to monitor and collect information on specific events of special interest to complement standard safety monitoring. The events of interest included: (1) hypoglycemia; (2) events related to skin lesions; (3) selected infections (eg, events related to herpes simplex virus or Mycobacterium tuberculosis); (4) decreased lymphocyte counts; (5) decreased platelet counts; and (6) events of localized

edema. Extensive analyses were also conducted to evaluate CV events, abnormalities in liver function tests, and hypersensitivity reactions. In general, the safety profile for saxagliptin given at doses of 2.5 and 5 mg were indistinguishable for these events of special interest, except for those related to lymphocyte counts.

Overall, based on a thorough analysis of over 3,400 subjects with T2DM treated for up to 128 weeks, including subjects with significant CV disease comorbidity, there is no evidence for a CV safety signal. In order to reach this conclusion, a variety of CV safety evaluations were conducted, including broad, inclusive assessments aimed at sensitive detection of any possible clinical CV risk signal as well as more targeted, specific assessments intended to discern possible differences in more severe CV events, including CV death. The results of all evaluations, as described in this document, support and demonstrate internal consistency with regard to the absence of any indication of a CV safety-related signal associated with saxagliptin. There is no evidence of a CV safety concern with the use of saxagliptin as a novel treatment for T2DM. It is reassuring that the absence of a CV signal is based on both more specific evaluations of severe CV events and death from the saxagliptin clinical program data as well as broader, more inclusive analyses.

Treatment with saxagliptin led to rates of hypoglycemia that were generally similar to placebo. This is consistent with the mechanism of action of DPP4 inhibitors, which exert their insulinotropic effects at the level of the β-cell in a glucose-dependent manner. However, the rate of hypoglycemia was numerically higher in subjects who received 2.5 or 5 mg of saxagliptin added on to an intermediate dose of glyburide compared with up-titration of glyburide monotherapy plus placebo. The difference in hypoglycemia rates between the saxagliptin treatment arms and placebo was not statistically significant. SUs, alone and in combination with other antihyperglycemic agents, are known to cause hypoglycemia, and decreases in SU dose may be warranted for certain subjects to reduce the risk of hypoglycemia.

At a saxagliptin dose of 5 mg, a small decrease in mean absolute lymphocyte count from baseline was observed. While the mechanism for the decrease in lymphocyte count is unknown, further investigation did not show any evidence of impairment in lymphocyte proliferation, did not show evidence for any increase in apoptosis / necrosis, and did not suggest that any one lymphocyte subtype was disproportionately affected during the time

of decrease. While the clinical significance of the decrease in lymphocyte count relative to the comparator is not known, the decreases were not associated with clinically relevant adverse events. There was no evidence for an association of saxagliptin treatment with an increased risk of elevation of liver function tests or of elevation of serum creatinine.

In summary:

- Once-daily, orally-administered saxagliptin was well-tolerated.
- The clinical safety profile of saxagliptin has been consistently confirmed across a large and diverse development program with few potential risks. The few potential risks were not associated with any clinical consequences.
- The overall clinical AE profile was comparable between the saxagliptin 2.5 and 5 mg doses.

10.3 Conclusion

Saxagliptin represents a new treatment option for T2DM, a disease with many currently available treatments, but one that is increasing in prevalence, where many patients do not achieve satisfactory glycemic control, and where current treatments are limited by tolerability and safety concerns. Compared with several of the available therapies for T2DM, saxagliptin provides an improved tolerability and safety profile with respect to hypoglycemia, weight gain, gastrointestinal AEs, heart failure, and edema. Saxagliptin provides clinically meaningful glycemic benefits, is well tolerated with no evidence of an increase in CV risk and provides a favorable benefit/risk profile when given as monotherapy, add-on therapy with metformin, TZDs, and SUs as well as in initial combination use with metformin, when treatment with dual saxagliptin and metformin therapy is appropriate.

11 LIST OF ABBREVIATIONS

Abbreviation	Definition
A1C	glycosylated hemoglobin
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under plasma concentration-time curve from zero to infinity [amount•time/volume]
BMI	body mass index
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
Cmax	maximum plasma (peak) drug concentration after single dose administration [amount/volume]
CMV	Cytomegalovirus
CrCl	creatinine clearance
CRF	case report form
CV	cardiovascular
CYP3A4/5	cytochrome P450 3A4/5
DCCT	Diabetes Control and Complications Trial
DILI	drug induced liver injury
DMC	Data Monitoring Committee
DPP4	dipeptidyl peptidase 4
EBV	Epstein-Barr virus
ECG	electrocardiogram
EDIC	Epidemiology of Diabetes Interventions and Complications
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FW	formula weight
GIP	glucose dependent insulinotropic peptide
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide-1
hERG	human Ether-a-go-go Related Gene

Abbreviation	Definition
IC50	half maximal inhibitory concentration
ICH	International Conference for Harmonisation
Ig	immunoglobulin
IKr	delayed inward rectifier potassium channel
Ki	dissociation constant
LFT	Liver function test
LOCF	last observation carried forward
LT	long-term
LVEF	left ventricular ejection fraction
MA	marked abnormality
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
Met	metformin
MI	myocardial infarction
NDA	New Drug Application
NOEL	no-observable-effect level
NYHA	New York Heart Association
OGTT	oral glucose tolerance test
OL	open label
PCP	Pneumocystis carinii pneumonia
PPG	post prandial glucose
PT	preferred term
PV	pharmacovigilance
QD	once daily
QTc	corrected QT interval
RUCD	recommended usual clinical dose
SAE	serious adverse event
SE	standard error
SMQ	standardized MedDRA queries
SOC	system organ class
ST	short-term
SU	sulfonylurea

Abbreviation	Definition
t1/2	half-life
T2DM	type 2 diabetes mellitus
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
ULN	upper limit of normal

REFERENCES

1 Guidance for Industry. Diabetes Mellitus - Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CEDER). December 2008.

2 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329:977-986.

3 United Kingdom Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998; 352:854-865.

4 Cleary PA, Orchard TJ, Genuth S, et al. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes. 2006; 55:3556-3565.

5 Holman RR, Paul SK, Bethel MA, et al. 10-Year follow-up of intensive glucose control in Type 2 Diabetes. N Engl J Med. 2008; 359:1577-1589.

6 Koro CE, Bowlin SJ, Bourgeois N, et al. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care. 2004; 27:17-20.

[7] Nathan DM, Buse JB, Davidson, MB. et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care. 2006; 29:1963-1972.

[8] Nauck MA, Kleine N, Orskov C, et al. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993; 36:741-744.

[9] Dunning BE, Foley JE, Ahrén B. Alpha cell function in health and disease: influence of glucagon-like peptide-1. Diabetologia. 2005; 48:1700-1713.

[10] Ito T, Chatani F, Sasaki S, Ando T, Miyajima H. Spontaneous Lesions in Cynomolgus Monkeys used in Toxicity Studies. Exp. Anim. 1992; 41:455-469.

[11] Gorrell MD, Gysbers V, McCaughan GW. CD26: A multifunctional integral membrane and secreted protein of activated lymphocytes. Scand J Immunol. 2001; 54:249-264.

[12] Boonacker E and Van Noorden CJF. The multifuctional or moonlighting protein CD26/DPPIV. European J Cell Biol. 2003; 82: 53-73.

[13] Lambeir A-M, Durinx C, Scharpé S, et al. Dipeptidyl peptidase IV from bench to bedside: An update on structural properties, functions and clinical aspects of the enzyme DPP IV. Critical Reviews in Clinical Laboratory Sciences. 2003; 40:209-294.

[14] Ohnuma K, Takabashi N, Yamochi T, Hosono O, Dang NH, Morimoto C. Role of CD26/dipeptidyl peptidase IV in Human T Cell Activation and Function. Frontiers in Bioscience, 2008; 13: 2299-2310.

[15] Dunning BE, Foley JE, Ahrén B. Alpha cell function in health and disease: influence of glucagon-like peptide-1. Diabetologia. 2005; 48:1700-1713.

[16] Rosenstock J, Foley JE, Rendell M, et al. Effects of the dipeptidyl peptidase-IV inhibitor vildagliptin on incretin hormones, islet function, and postprandial glycemia in subjects with impaired glucose tolerance. Diabetes Care. 2008; 31:30-35.

[17] Cervera A, Wajcberg E, Sriwijitkamol A, et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. Am J Physiol Endocrinol Metab. 2008; 294:E846-E852.

[18] ICH E1: The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. October 27, 1994.

[19] Guidance for Industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. FDA Draft Guidance, February 2008.

[20] The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545-2559.

[21] Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation. 2003; 108:2941-2948.

[22] Byetta (exenatide) injection tablets. USPI, revised October 2007.

[23] Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346:393-403.

[24] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med. 1995; 333:1301-1307.

[25] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med. 1996; 335:1001-1009.

[26] The Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998; 339:1349–1357.

[27] Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008; 359: 2195–2207.

[28] Nathan DM, Buse JB, Davidson, MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care. 2006; 29:1963-1972.

Appendix 1: List of Preferred Terms for SMQ MACE

5 page(s) excluding cover page

APPENDIX 1 LIST OF PREFERRED TERMS FOR SMQ MACE

Acute coronary syndrome

Acute myocardial infarction

Agnosia

Amaurosis fugax

Angiogram cerebral abnormal

Aphasia

Balint's syndrome

Basal ganglia haemorrhage

Basilar artery occlusion

Basilar artery stenosis

Basilar artery thrombosis

Blood creatine phosphokinase abnormal

Blood creatine phosphokinase increased

Blood creatine phosphokinase MB abnormal

Blood creatine phosphokinase MB increased

Brain stem haemorrhage

Brain stem infarction

Brain stem ischaemia

Brain stem thrombosis

Capsular warning syndrome

Cardiac enzymes increased

Carotid aneurysm rupture

Carotid arterial embolus

Carotid arteriosclerosis

Carotid artery aneurysm

Carotid artery bypass

Carotid artery disease

Carotid artery dissection

Carotid artery insufficiency

Carotid artery occlusion

Carotid artery stenosis

APPENDIX 1 LIST OF PREFERRED TERMS FOR SMQ MACE

Carotid artery stent insertion

Carotid artery thrombosis

Carotid endarterectomy

Central pain syndrome

Cerebellar artery occlusion

Cerebellar artery thrombosis

Cerebellar embolism

Cerebellar haematoma

Cerebellar haemorrhage

Cerebellar infarction

Cerebral aneurysm ruptured syphilitic

Cerebral arteriosclerosis

Cerebral arteriovenous malformation haemorrhagic

Cerebral artery embolism

Cerebral artery occlusion

Cerebral artery stenosis

Cerebral artery thrombosis

Cerebral haematoma

Cerebral haemorrhage

Cerebral haemorrhage foetal

Cerebral haemorrhage neonatal

Cerebral infarction

Cerebral infarction foetal

Cerebral ischaemia

Cerebral thrombosis

Cerebral vasoconstriction

Cerebral venous thrombosis

Cerebrovascular accident

Cerebrovascular accident prophylaxis

Cerebrovascular disorder

Cerebrovascular insufficiency

APPENDIX 1 LIST OF PREFERRED TERMS FOR SMQ MACE

Cerebrovascular spasm

Cerebrovascular stenosis

Charcot-Bouchard microaneurysms

Coronary artery embolism

Coronary artery occlusion

Coronary artery reocclusion

Coronary artery thrombosis

Coronary bypass thrombosis

Diplegia

Dysarthria

Electrocardiogram Q wave abnormal

Electrocardiogram ST segment abnormal

Electrocardiogram ST segment elevation

Electrocardiogram ST-T segment elevation

Embolic cerebral infarction

Embolic stroke

Haematomyelia

Haemorrhage intracranial

Haemorrhagic cerebral infarction

Haemorrhagic stroke

Haemorrhagic transformation stroke

Hemiparesis

Hemiplegia

Infarction

Intra-cerebral aneurysm operation

Intracerebral haematoma evacuation

Intracranial aneurysm

Intracranial haematoma

Intraventricular haemorrhage

Intraventricular haemorrhage neonatal

Ischaemic cerebral infarction

APPENDIX 1 LIST OF PREFERRED TERMS FOR SMQ MACE

Ischaemic stroke

Lacunar infarction

Lateral medullary syndrome

Meningorrhagia

Millard-Gubler syndrome

Monoparesis

Monoplegia

Moyamoya disease

Myocardial infarction

Myocardial reperfusion injury

Papillary muscle infarction

Paralysis

Paralysis flaccid

Paraparesis

Paraplegia

Paresis

Post procedural myocardial infarction

Post procedural stroke

Postinfarction angina

Precerebral artery occlusion

Putamen haemorrhage

Quadriparesis

Quadriplegia

Red blood cells CSF positive

Reversible ischaemic neurological deficit

Ruptured cerebral aneurysm

Scan myocardial perfusion abnormal

Silent myocardial infarction

Spastic paralysis

Spastic paraplegia

Spinal artery embolism

APPENDIX 1 LIST OF PREFERRED TERMS FOR SMQ MACE

Spinal cord haemorrhage
Spinal epidural haemorrhage
Spinal haematoma
Stroke in evolution
Subarachnoid haemorrhage
Subarachnoid haemorrhage neonatal
Subdural haemorrhage
Subdural haemorrhage neonatal
Thalamic infarction
Thalamus haemorrhage
Thrombotic cerebral infarction
Thrombotic stroke
Transient ischaemic attack
Troponin I increased
Troponin increased
Troponin T increased
Vascular encephalopathy
Vascular graft occlusion
Vertebral artery occlusion
Vertebral artery stenosis
Vertebral artery thrombosis
Vertebrobasilar insufficiency
Visual midline shift syndrome
Wallenberg syndrome

MedDRA version 11.0

Appendix 2: List of Preferred Terms for Custom MACE

2 page(s) excluding cover page

APPENDIX 2 LIST OF PREFERRED TERMS FOR CUSTOM MACE

Acute myocardial infarction

Basilar artery thrombosis

Brain stem infarction

Brain stem thrombosis

Carotid arterial embolus

Carotid artery thrombosis

Cerebellar infarction

Cerebral artery embolism

Cerebral artery thrombosis

Cerebral infarction

Cerebral thrombosis

Cerebrovascular accident

Coronary artery thrombosis

Embolic cerebral infarction

Embolic stroke

Haemorrhagic cerebral infarction

Haemorrhagic stroke

Haemorrhagic transformation stroke

Ischaemic cerebral infarction

Ischaemic stroke

Lacunar infarction

Lateral medullary syndrome

Moyamoya disease

Myocardial infarction

Papillary muscle infarction

Post procedural myocardial infarction

Post procedural stroke

Silent myocardial infarction

Stroke in evolution

Thalamic infarction

APPENDIX 2 LIST OF PREFERRED TERMS FOR CUSTOM MACE

Thrombotic cerebral infarction
Thrombotic stroke
Wallenberg syndrome

MedDRA version 11.0.
Note that the PT "Brain Stem Stroke," indicated in the Response Letter from the Agency 11 January 2009 is not a PT in MedDRA version 11.0. This PT only appears in MedDRA version 11.1.

Appendix 3: List of Preferred Terms for Acute Cardiovascular Events

4 page(s) excluding cover page

APPENDIX 3 LIST OF PREFERRED TERMS FOR ACUTE CARDIOVASCULAR EVENTS

Acute coronary syndrome

Acute myocardial infarction

Agonal rhythm

Amaurosis fugax

Angina unstable

Arteriospasm coronary

Balint's syndrome

Basal ganglia haemorrhage

Basilar artery occlusion

Basilar artery stenosis

Basilar artery thrombosis

Brain stem haemorrhage

Brain stem infarction

Brain stem ischaemia

Brain stem thrombosis

Cardiac arrest

Cardiac death

Cardiogenic shock

Cardio-respiratory arrest

Carotid arterial embolus

Carotid artery bypass

Carotid artery dissection

Carotid artery insufficiency

Carotid artery occlusion

Carotid artery stenosis

Carotid artery stent insertion

Carotid artery thrombosis

Carotid endarterectomy

Cerebellar artery occlusion

Cerebellar artery thrombosis

APPENDIX 3 LIST OF PREFERRED TERMS FOR ACUTE CARDIOVASCULAR EVENTS

Cerebellar embolism
Cerebellar haemorrhage
Cerebellar infarction
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery stenosis
Cerebral artery thrombosis
Cerebral circulatory failure
Cerebral haemorrhage
Cerebral hypoperfusion
Cerebral infarction
Cerebral ischaemia
Cerebral thrombosis
Cerebrovascular accident
Cerebrovascular insufficiency
Cerebrovascular stenosis
Circulatory collapse
Coronary angioplasty
Coronary arterial stent insertion
Coronary artery bypass
Coronary artery dissection
Coronary artery embolism
Coronary artery insufficiency
Coronary artery occlusion
Coronary artery reocclusion
Coronary artery restenosis
Coronary artery stenosis
Coronary artery thrombosis
Coronary bypass thrombosis
Coronary endarterectomy

APPENDIX 3 LIST OF PREFERRED TERMS FOR ACUTE CARDIOVASCULAR EVENTS

Coronary ostial stenosis

Coronary revascularisation

Dissecting coronary artery aneurysm

Electromechanical dissociation

Embolic cerebral infarction

Embolic stroke

Haemorrhage coronary artery

Haemorrhage intracranial

Haemorrhagic cerebral infarction

Haemorrhagic stroke

Haemorrhagic transformation stroke

Infarction

In-stent coronary artery restenosis

Intraventricular haemorrhage

Ischaemic cerebral infarction

Ischaemic stroke

Lacunar infarction

Lateral medullary syndrome

Myocardial infarction

Myocardial ischaemia

Myocardial reperfusion injury

Papillary muscle infarction

Percutaneous coronary intervention

Post procedural myocardial infarction

Post procedural stroke

Postinfarction angina

Precerebral artery occlusion

Prinzmetal angina

Putamen haemorrhage

Reversible ischaemic neurological deficit

APPENDIX 3 LIST OF PREFERRED TERMS FOR ACUTE CARDIOVASCULAR EVENTS

Shock
Silent myocardial infarction
Sneddon's syndrome
Spinal artery embolism
Spinal cord haemorrhage
Spinal epidural haemorrhage
Stroke in evolution
Subarachnoid haemorrhage
Subendocardial ischaemia
Sudden cardiac death
Sudden death
Thalamic infarction
Thalamus haemorrhage
Thrombotic cerebral infarction
Thrombotic stroke
Transient ischaemic attack
Vascular graft occlusion
Ventricular asystole
Ventricular fibrillation
Ventricular flutter
Ventricular tachyarrhythmia
Ventricular tachycardia
Vertebral artery occlusion
Vertebral artery stenosis
Vertebral artery thrombosis
Vertebrobasilar insufficiency
Wallenberg syndrome

MedDRA version 11.0

Appendix 4: List of Preferred Terms for Primary and Secondary MACE

2 page(s) excluding cover page

APPENDIX 4 LIST OF PREFERRED TERMS FOR PRIMARY AND SECONDARY MACE

Acute coronary syndrome

Acute myocardial infarction

Agonal rhythm

Basal ganglia haemorrhage

Basilar artery thrombosis

Brain stem haemorrhage

Brain stem infarction

Brain stem thrombosis

Cardiac arrest

Cardiac death

Cardio-respiratory arrest

Carotid arterial embolus

Carotid artery thrombosis

Cerebellar artery thrombosis

Cerebellar embolism

Cerebellar haemorrhage

Cerebellar infarction

Cerebral artery embolism

Cerebral artery thrombosis

Cerebral haemorrhage

Cerebral infarction

Cerebral thrombosis

Cerebrovascular accident

Coronary artery embolism

Coronary artery thrombosis

Coronary bypass thrombosis

Electromechanical dissociation

Embolic cerebral infarction

Embolic stroke

Haemorrhagic cerebral infarction

APPENDIX 4 LIST OF PREFERRED TERMS FOR PRIMARY AND SECONDARY MACE

Haemorrhagic stroke

Haemorrhagic transformation stroke

Intraventricular haemorrhage

Ischaemic cerebral infarction

Ischaemic stroke

Lacunar infarction

Lateral medullary syndrome

Myocardial infarction

Myocardial reperfusion injury

Papillary muscle infarction

Post procedural myocardial infarction

Post procedural stroke

Precerebral artery occlusion

Putamen haemorrhage

Stroke in evolution

Sudden cardiac death

Sudden death

Thalamic infarction

Thalamus haemorrhage

Thrombotic cerebral infarction

Thrombotic stroke

Ventricular asystole

Vertebral artery thrombosis

Wallenberg syndrome

MedDRA version 11.0

Appendix 5: List of Deaths in the Saxagliptin Phase 2b/3 Program (120 Day Database)

1 page(s) excluding cover page

APPENDIX 5 LIST OF DEATHS IN THE SAXAGLIPTIN PHASE 2B/3 PROGRAM (120 DAY DATABASE)

Study	Treatment Group	Preferred Terms	Considered CV Death (Yes/No)
CV181011	PLA	Myocardial Infarction	Yes
CV181013	SAXA 2.5 + TZD	Road Traffic Accident	No
CV181013	SAXA 5 + TZD	Sudden Death	Yes
CV181014	SAXA 2.5 + MET	Cerebrovascular Accident	Yes
CV181014	SAXA 10 + MET	Lung Neoplasm / Pulmonary Embolism	Yes
CV181014	PLA + MET	Cardiac Failure Congestive	Yes
CV181014	PLA + MET	Cardiogenic Shock / Myocardial Infarction	Yes
CV181038	SAXA 2.5/5	Pneumococcal Sepsis	No
CV181039	SAXA 5 + MET	Tetanus	No
CV181039	SAXA 10 + MET	Sudden Death	Yes
CV181039	SAXA 10	Arteriosclerosis Coronary Artery	Yes
CV181039	SAXA 10	Cardiac Arrest	Yes
CV181039	MET	Cardiac Failure	Yes
CV181039	MET	Acute Myocardial Infarction	Yes
CV181039	MET	Cerebrovascular Accident	Yes
CV181039	MET	Pancreatic Neoplasm / Sepsis	No
CV181039	MET	Sudden Death	Yes
CV181040	SAXA 5 + GLY	Acute Myocardial Infarction / Atrioventricular Block Complete Cardiogenic Shock	Yes
CV181040	PLA + GLY	Pneumonia	No
CV181040	PLA + GLY	Sudden Cardiac Death	Yes
CV181040	PLA + GLY	Haemorrhagic Stroke	Yes
CV181040	PLA + GLY	Acute Myocardial Infarction	Yes

Abbreviations: CV = cardiovascular; Gly = glyburide; Met = metformin; Saxa = saxagliptin; TZD = thiazolidinedione.

Appendix 6: Details of Sponsor's Methods for Identification of Cardiovascular Events

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APPENDIX 6 DETAILS OF SPONSOR'S METHODS FOR IDENTIFICATION OF CARDIOVASCULAR EVENTS

Overall Cardiac Adverse Events

Overall Cardiac Adverse Events were defined using all PTs in the MedDRA SOC Cardiac Disorders, which includes cardiac-related AEs as defined in the MedDRA safety classification.

Acute Cardiovascular Events List of Preferred Terms

Acute Cardiovascular Events were identified in the AE database using a list of PTs. The list of PTs was specified by the Sponsor before database lock and data unblinding for studies CV181013, CV181038, CV181039, CV181040, and CV181041, and was formulated as a subset of select standardized MedDRA queries (SMQs) (ie, MI, Cerebrovascular Disorders, Cardiac Arrhythmias, Ischaemic Heart Disease, Shock Associated Circulatory or Cardiac Conditions, and Torsade de Pointes). The strategy for PT selection was to identify PTs with specificity for CV events which were acute, ischemic, and clinically relevant. PTs included, but were not limited to, cerebrovascular accident and MI, other high-intensity ischemic events, and cardiac and cerebral revascularizations. In addition, selected arrhythmia-related PTs were included which might suggest the occurrence of events that carried the potential to result in death without intervention.

Major Adverse Cardiovascular Events (MACE)

The pre-specified list of PTs for Acute Cardiovascular Events described above served as the basis for selecting a subset of PTs for a retrospective identification of MACE. MACE was defined in two ways. Primary MACE includes stroke (cerebrovascular accidents), MI, and CV death. Secondary MACE was defined in the same way as Primary MACE, except that all deaths were included. The analysis of Secondary MACE avoided the need for retrospective clinical judgment regarding cause of death.

General principles for term selection are described below. In order to be chosen for the MACE PT list, PTs were required, in general, to represent events that were: 1) acute; 2) symptomatic; and 3) thromboembolic in nature (including hemorrhagic stroke).

Stroke-Related Preferred Term Selection

1) Cerebral circulation-related PTs of hemorrhage, infarction, thrombosis, or embolus satisfied the three criteria above (thereby conforming to the medical concept "stroke") and were included in the MACE PT list.
2) Cerebral circulation-related PTs of stenosis, ischemia, insufficiency, hypoperfusion, and dissection, as well as cerebral procedures did not satisfy all three criteria above and were not included in the MACE PT list. Spinal infarction-related terms were not included.

Myocardial Infarction-Related Preferred Term Selection

3) Coronary-related PTs of infarction, thrombosis, or embolus satisfied the three criteria above (thereby conforming to the medical concept "myocardial infarction") and were included in the MACE PT list.
4) Coronary-related PTs of hemorrhage, stenosis, ischemia, insufficiency, hypoperfusion, and dissection, as well as coronary procedures did not satisfy all three criteria above and were not included in the MACE PT list.
5) The PT of acute coronary syndrome was considered to be a MI equivalent and was included in the MACE PT list. However, unstable angina and Prinzmetal angina were not included due to their potential lack of specificity.

Additional terms and concepts were identified that could not be confidently documented as MACE without clinical review. AEs that fell under the categories 1 - 4 below were reviewed on a case-by-case basis to determine whether the specific AE qualified as a MACE.

6) Infarction, unqualified;
7) Silent MI;
8) Cerebral or coronary events which included the term occlusion. Occlusion frequently reflects a procedural diagnosis which might not be indicative of an acute stroke or MI.
9) Serious cardiac rhythm disturbances (eg, ventricular fibrillation or ventricular tachyarrhythmia), given that these events may or may not have been secondary to an ischemic cardiac event (eg, MI).

Based on the clinical review, an additional seven subjects in the 120 Day database were identified as Primary MACE. Six were added based on review of all deaths which identified them as being CV events and as occurring within the study windows pre-specified in the statistical analytic plans for inclusion. One event was added due to a clarification of the event diagnosis after the database was locked (SAE of extensive anterior wall ST elevation MI).

Among the seven subjects that were added to primary MACE, three were added based on additional information identified post database lock:

- One subject in the placebo group in Study CV181011 was added based on review of CV deaths (this subject died of complications of a myocardial infarction - a cerebral hemorrhage). After database lock, additional information was received regarding dosing that indicated that study drug had been received within 30 days prior to the event. This subject is included in both FDA-defined (MACE, Custom MACE) and Sponsor-defined (acute CV, MACE) analyses.
- One subject in the saxagliptin 2.5 mg group in Study CV181014 was added based on review of CV deaths (subject died of a hemorrhage stroke). After database lock, additional information was received regarding dosing that indicated that study drug had been received within 30 days prior to the event. This subject is included in both FDA-defined (MACE, custom MACE) and Sponsor-defined (acute CV, MACE) analyses.
- In one subject in the placebo group in Study CV181038, a nonfatal SAE was changed from PT Coronary Artery Disease to Acute MI after database lock. This subject is included in Sponsor-defined (acute CV, MACE) analyses.

Appendix 7: Details of Sponsor's Methods for Analysis of Cardiovascular Events

2 page(s) excluding cover page

APPENDIX 7 DETAILS OF SPONSOR'S METHODS FOR ANALYSIS OF CARDIOVASCULAR EVENTS

Time to first MACE was calculated using weighted Kaplan-Meier estimates, with weights proportional to the number of subjects in each study.[1] Event-free times were compared between treatment groups using a Cox Proportional Hazards regression (Cox) model stratified for study with treatment as a model term. The risk ratio and corresponding 95% CI were reported for subjects who received saxagliptin versus control (primary comparison), and for each treatment dose versus control.

To obtain exposure-adjusted incidence rates, the number of subjects with events in each treatment group was divided by the number of subject-years of exposure (excluding exposure after a subject experiences a first event). The rates were presented per 1000 subject years. These rates adjusted for exposure imbalances between groups. The 95% CIs for the incidence rate ratio from each study were obtained using an exact procedure.[2] Estimates and 95% confidence intervals for the incidence rate ratios overall (stratified), and by study, were obtained using exact procedures for Poisson processes.[2]

As a further analysis, event and subject-years exposure data were combined across trials using the Mantel-Haenszel approach to provide an alternative estimate of the overall MACE common incidence rate ratio.[2] A confidence interval for the incidence rate ratio was provided.[3] For individual studies, a 95% Bayesian credibility interval for the incidence rate ratio was provided[4] assuming an uninformative prior for the incidence rate ratio; the median of the posterior distribution was used to provide a point estimate for the incidence rate ratio. These interval estimates are provided to account for individual studies in which no events were observed, as this interval is calculable even when the number of events within each treatment group is equal to 0. Further, the credibility interval quickly converges with the conventional asymptotic CI for the incidence rate ratio as the number of events increases. While two methods were used to calculate the incidence rate ratio for the pooled Phase 2b/3 data, the results of only one of the methods (the latter method) is presented in this document for the sake of clarity.

In addition, incidence ratios for MACE were calculated based on the ratio of the proportions of subjects reporting an event in the saxagliptin and comparator groups. The

95% CIs for the incidence ratio from each study were obtained using an exact procedure that inverted the 2-sided test statistics.[5] The estimate of the overall incidence ratio, stratified by study, and 95% confidence intervals were obtained from the Mantel-Haenszel procedure (normal approximation).

Additional analyses were provided to the FDA for comparing differences in incidence rate and incidence between treatment groups, using point estimates and 95% confidence intervals from the Mantel-Haenszel procedure (normal approximation). These analyses are not shown.

References

1 Amato DA. A generalized Kaplan-Meier estimator for heterogeneous populations. Communications in statistics - theory and methods. 1988; 17:263-286.

2 Breslow NE, Day NE. The design and analysis of cohort studies. IARC Scientific Publications. 1987; No. 82. Lyon, France.

3 Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. Biometrics. 1986; 42:311-323.

4 Barker L and Cadwell BL. An analysis of eight 95 per cent confidence intervals for a ratio of Poisson parameters when events are rare. Stat Med. 2008; 27:4030-4037.

5 Agresti A and Min Y. On small-sample confidence intervals for parameters in discrete distributions. Biometrics. 2001; 57:963-971.