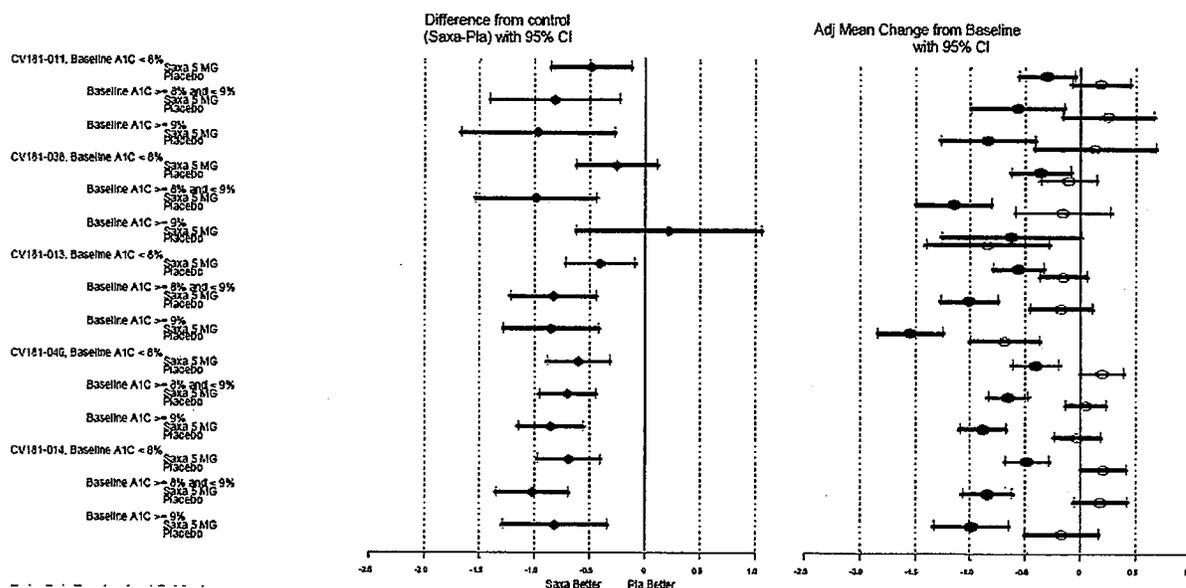


### Baseline A1c

Although shown to be effective across baseline A1c subgroups, saxagliptin 5 mg was shown in most studies to produce numerically greater reductions from baseline for those with higher baseline A1c. The treatment-by-subgroup interaction p-value was <0.1 for in 3 of the 6 studies. As seen in Figure 6.6 below, the trend of greater reduction in A1c in subjects with higher baseline A1c values was not seen in Study CV181038. The Sponsor did not present this analysis for Study CV181039, however noted that a statistically significant interaction was not generated because a similar pattern of greater reduction in A1c was seen in the active-control group.

**Figure 6.6. Plot of Adjusted Mean Change from Baseline in A1c and 95% Confidence Intervals at Week 24 for Saxagliptin 5 mg Groups in Each Protocol, by Baseline A1c Subgroups**



Source: Summary of Clinical Efficacy, Figure 3.3A

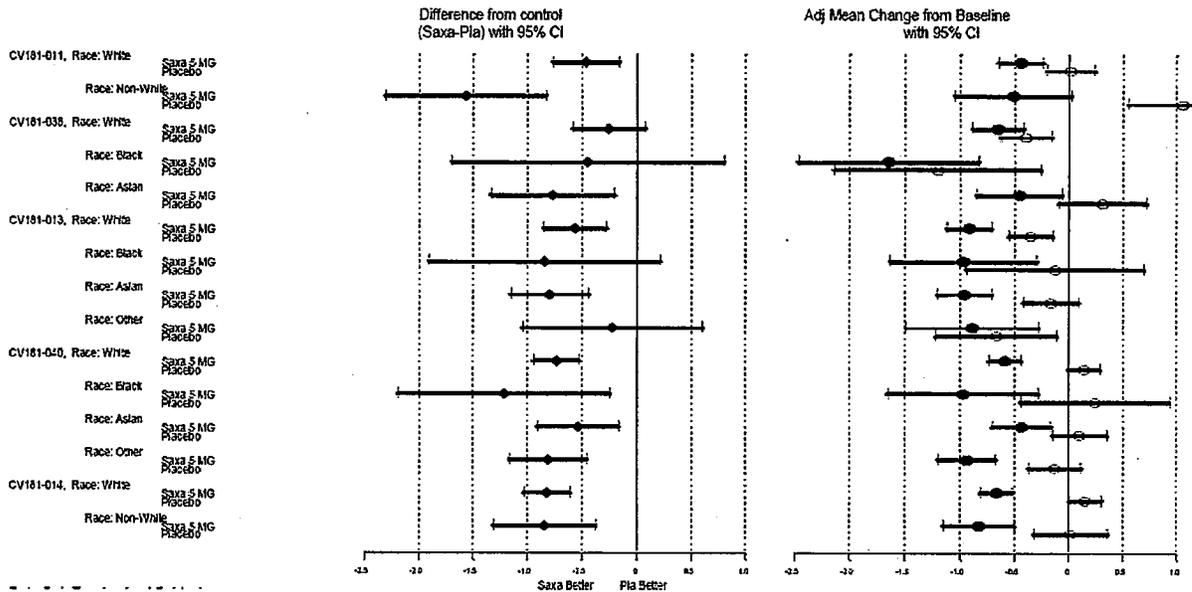
### Race

In the Core Phase 3 studies, the majority of subjects enrolled were white. P-values for treatment-by-race interactions were <0.1, however the Sponsor asserts that this is due to variability in A1c responses in the placebo or active-control treatment groups. The point estimate of the adjusted change from baseline in A1c for the saxagliptin 5 mg group was fairly consistent for race subgroups across studies, and the 95% CI crossed zero only for nonwhite subjects in CV181011 (n=13, right panel in Figure 6.7 below).

The treatment-by-race subgroup interaction p-value was <0.1 in the trials with treatment-naïve subjects (CV181011, CV181038, and CV181039). It is unclear why this was seen. Overall, however, it appears that no conclusions regarding the effect of race in saxagliptin treatment can be made.

**Reviewer comment: According to Ms. Mele’s analysis of HbA1c treatment effect by race, although Asians were a minority of enrolled subjects (highest enrollment was 15% in Study CV181039), two studies (CV181011 and CV181039) produced significant interactions. Given this, the clinical implications for the treatment of Asians, including PK exposure, and safety, should be considered.**

**Figure 6.7. Plot of Adjusted Mean Change from Baseline in A1c and 95% Confidence Intervals at Week 24 for Saxagliptin 5 mg Groups in Each Protocol, by Race Subgroups**

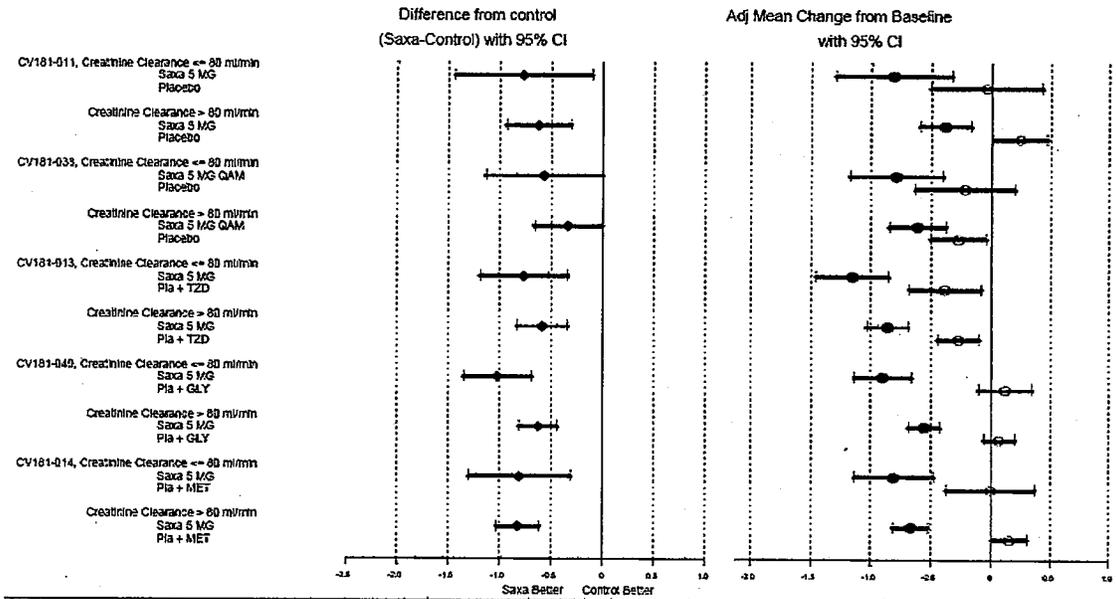


Source: Summary of Clinical Efficacy, Figure 3.3B

**Baseline Creatinine Clearance**

The interaction p-values were >0.1 in both monotherapy trials and <0.1 in 2 of the 3 add-on combination trials. This may be explained by a greater dose-response separation in subjects in the subgroups with baseline creatinine clearance ≤80 mL/min in the add-on combination studies. The saxagliptin 5 mg group had a greater adjusted mean reduction in A1c at Week 24 than the 2.5 mg groups in the add-on combination studies. However, the change from baseline A1c in the control group was similar between the subgroups. As seen in Figure 6.8 below, the control-corrected adjusted mean A1c reduction and the adjusted mean A1c reduction was consistently greater for saxagliptin 5 mg in the subgroup with creatinine clearance ≤80 mL/min. The Sponsor hypothesizes that reduced renal clearance of insulin (saxagliptin increases post-prandial insulin secretion) may contribute to these findings.

**Figure 6.8. A1c Changes from Baseline in Subgroups Based on Creatinine Clearance in Monotherapy and Add-on Therapy Studies**



Source: Summary of Clinical Efficacy, Figure 3.3D

**Other subgroups**

Several subgroups, including gender, had interaction p-values <0.1 in only one trial; each of these trials involved treatment-naïve subjects.

For age and baseline BMI, there were no analyses with an interaction p-value <0.1. Regarding age, it is important to note that the percentage of subjects >75 years old in the Core Phase 3 studies was low (1.4%). Interpretation of this specific subgroup analysis is therefore limited.

Overall, subgroup analyses did not reveal any unexpected conclusions. Greater reductions in A1c associated with higher baseline A1c is typically seen with other drugs used for the treatment of diabetes.

**6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

In Phase 1 and 2 studies, saxagliptin 5 mg was associated with greater inhibition of plasma DPP4 activity at the trough of the dosing interval compared to 2.5 mg. In the Phase 2b study, the 5 mg dose also resulted in maximal reductions in A1c and fasting serum glucose (Section 4.4). The Phase 3 studies confirmed the effects of saxagliptin 5 mg on A1c. A major strength of the

Sponsor's clinical development program was the incorporation of multiple doses in the Phase 3 studies, allowing for a more thorough evaluation of the dose chosen from Phase 2.

In the Phase 3 studies, saxagliptin 10 mg did not result in incremental benefit, and in fact, was associated with certain adverse effects not observed with the 5 mg dose (Section 7).

The benefit of 5 mg versus 2.5 mg was adequately demonstrated in the primary efficacy endpoint:

- With the exception of the monotherapy studies, subjects in the saxagliptin 5 mg groups demonstrated greater decreases from baseline in A1c at 24 weeks versus the 2.5 mg groups. In both monotherapy studies, subjects in the 2.5 mg and 5 mg groups demonstrated similar A1c reductions.

**Reviewer comment:** In Study CV181038, the decreases from baseline in A1c at 24 weeks for the 2.5 mg and 5 mg groups were -0.71% and -0.66%, respectively. As mentioned earlier in this Review, this study had the smallest number of subjects per dose group and therefore was more prone to confounding factors or chance findings. This one exception to the otherwise demonstrated benefit of 5 mg over 2.5 mg should be viewed with this study limitation.

When analyzing secondary endpoints, the benefit of 5 mg versus 2.5 mg was also generally demonstrated.

- In all studies, the saxagliptin 5 mg group had a greater reduction in postprandial glucose AUC versus the 2.5 mg group, although differences in the monotherapy trials were modest.
- The proportion of subjects who achieved a glycemic response of A1c<7% was higher in the saxagliptin 5 mg groups versus the 2.5 mg groups in one of the monotherapy studies and the add-on combination study to metformin. Minimal differences were observed in the other monotherapy study and the 2 add-on combination studies.
- In the add-on combination studies only, the saxagliptin 5 mg group had greater decreases from baseline in FPG than the saxagliptin 2.5 mg groups, although differences were modest for the add-on to sulfonylurea trial and the 2.5 mg and 5 mg groups reduced FPG to a similar extent in the monotherapy trials.

As discussed in Section 4.4, while the 5 mg per day dose appears to be the optimal dose in most subjects, those with moderate or severe renal insufficiency are recommended a dose adjustment to 2.5 mg.

Finally, the Sponsor examined subgroups to determine if there was a particular group of subjects in which the greater efficacy of the 5 mg dose versus the 2.5 mg dose was observed. This was seen in the subjects with creatinine clearance  $\leq 80$  ml/min in the add-on studies, with an approximately 2-fold difference in the reduction from baseline A1c at the 5 mg dose compared to 2.5 mg. This was previously discussed in Section 6.1.7.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Each Core Phase 3 study included an extension phase of at least 12 months to allow for additional safety and efficacy data. These periods were ongoing at the time of NDA submission, and therefore only interim results were submitted. Subjects remained in the treatment group to which they were assigned in the ST period, although some required rescue in addition to their randomized treatment.

Despite these long-term extensions, the Phase 3 studies were not designed to specifically look at persistence of drug effect beyond Week 24. LOCF methodology is used in the Sponsor's analyses, and this is problematic, particularly if subjects were rescued early in the study. There are limitations to the utility of such analyses. Sample sizes by the end of the evaluated periods are low. For example, in Study CV181038, approximately 10 subjects each remained in the treatment groups. Such low sample sizes limit a meaningful interpretation and extrapolation to a wider population.

### 6.1.10 Additional Efficacy Issues/Analyses

## 7 Review of Safety

### Safety Summary

In general, saxagliptin appears to have a favorable safety profile. The safety database from the Phase 2b/3 program is based on exposure of 3422 subjects. Of these, 2642 subjects were exposed to study drug for  $\geq 24$  weeks and 1080 subjects were exposed for  $\geq 52$  weeks.

Issues that will be discussed in this section of the Review include:

**Deaths and Major Adverse Cardiovascular Events (MACE):** There were no increased deaths in saxagliptin-treated subjects. As discussed in depth in this Section, although the saxagliptin clinical development program did not prospectively plan an evaluation of MACE, a retrospective and comprehensive analysis did not reveal an increased frequency of MACE events among saxagliptin-treated subjects. This was also the subject of an Advisory Committee meeting, discussed at length in Section 9.3.

**Serious Adverse Events:** There were no concerning signals of specific serious adverse events among saxagliptin-treated subjects.

**Common adverse events:** Overall, common adverse events were higher in saxagliptin-treated subjects versus placebo. The following common AEs were more frequent in saxagliptin groups compared to placebo:

- In monotherapy studies: urinary tract infection, sinusitis, influenza, vomiting, nausea, diarrhea, arthralgia, musculoskeletal pain, and rash. The 5 mg group had the highest frequency of vomiting and nausea.
- In the add-on combination study with metformin: URI, abdominal pain, arthralgia, pharyngolaryngeal pain, and blood CK increased.
- In the add-on combination study with sulfonylurea: gastroenteritis, abdominal pain, headache, and hypertension.
- In the add-on combination with TZD: URI, sinusitis, arthralgia, musculoskeletal pain, headache, anemia, peripheral edema, and blood CK increased.
- In the initial combination with metformin study: For the saxagliptin 5 mg + metformin group, these included nasopharyngitis, URI, bronchitis, dyspepsia, headache, back pain, arthralgia, and hypertension.

Of note, none of these adverse events (except arthralgia) occurred consistently more frequently with saxagliptin than comparator across the phase 3 studies.

Of the most common AEs occurring more frequently with saxagliptin than comparator, the following appeared to exhibit a possible dose-dependency:

- In the monotherapy studies: influenza and arthralgia.
- In the add-on combination study with SU: hypertension.
- In the add-on combination study with TZD: URI, musculoskeletal pain, and anemia appeared to be dose-related.
- Initial combination with metformin: dyspepsia and hypertension.

Although hypertension is an adverse event that appears to have a possible relationship to saxagliptin dose in the add-on to SU and initial combination with metformin studies, the objective blood pressure data do not support an adverse effect of saxagliptin on blood pressure.

**Hypoglycemia:** The frequency of reported hypoglycemia was higher in the monotherapy studies and particularly in the add-on combination study to glyburide (CV181040). The frequency of confirmed hypoglycemic episodes was higher in saxagliptin-treated subjects only in Study CV181040 (1.6% versus 0.7% in placebo subjects).

**Decreased lymphocyte counts:** Decreases in lymphocyte count were seen in all studies, particularly in the saxagliptin 10 mg groups. However, an increase in infections associated with T-cell dysfunction among saxagliptin-treated subjects was not found.

**Thrombocytopenia:** Although small decreases were observed in all dose groups, subjects in the 10 mg dose group had the largest mean decrease in percent change from baseline in platelets.

Overall, these changes were of unclear clinical significance and were not associated with an increased rate of bleeding.

**Skin findings:** Higher frequencies of rash-related AEs were seen in saxagliptin-treated subjects versus comparator groups in all analyses, and the highest rates were seen in the 10 mg groups. However, pre-defined events intended to capture AEs related to non-clinical findings were rare.

**Peripheral edema:** With the exception of the add-on combination to TZD study (CV181013), there were generally low rates of reported localized edema. In Study CV181013, whose placebo group had a higher frequency of localized edema AEs compared to placebo groups in other studies, the frequency of localized edema AEs was highest in the 5 mg group (7.0% vs 2.5% in placebo group). None of the events resulted in study drug discontinuation.

Aside from the lymphocyte and platelet abnormalities mentioned above, there were no other significant saxagliptin-related laboratory findings. In addition, there were no clinically significant changes in vital signs or EKGs observed in the safety monitoring program.

Limitations of the safety evaluation include low enrollment of non-white subjects and elderly subjects. In addition, the Phase 3 program had very limited enrollment of subjects with renal impairment. No subjects had severe renal impairment at baseline. However, an ongoing dedicated renal study will provide data on the safety and efficacy of saxagliptin in subjects with type 2 diabetes mellitus with moderate, severe, or end-stage renal disease. Additional information in renally impaired patients will be obtained in the longer-term cardiovascular safety trial that will be required as a condition of approval.

## 7.1 Methods

### 7.1.1 Clinical Studies Used to Evaluate Safety

The Sponsor presented all safety data for Treated Subjects, defined as subjects who received at least one dose of study drug (saxagliptin, placebo, glyburide, metformin, or a TZD). Section 5.1 summarized all clinical studies in the development program. Table 7.1 summarizes the studies used in the saxagliptin safety database.

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**Table 7.1. Overview of Safety Database for Saxagliptin**

Source of data	Details
Controlled safety/efficacy trials	8 Studies: 2 monotherapy studies (CV181011, CV181038) 3 add-on combination studies (CV181013, CV181014, CV181040) 1 initial combination with metformin study (CV181039) 1 Phase 2b study (CV181008) 1 Phase 3 Mechanism of Action Study (CV181041)
Uncontrolled safety/efficacy trials	1 study: CV181011: 10 mg open-label cohort
Other sources of safety data	27 Clinical Pharmacology Studies (includes thorough QT study CV181032)
Ongoing studies (not included in NDA)	3 safety/efficacy studies: Saxagliptin + metformin vs. glipizide + metformin (CV181054) Saxagliptin + metformin vs. sitagliptin + metformin (CV181056) Renal impairment (CV181062)

### 7.1.2 Adequacy of Data

All AEs were coded and grouped into Preferred Terms (PTs) by System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA version 10.1 was used for the Core Phase 3 studies. Narratives for deaths, serious adverse events, and discontinuations were reviewed. Overall, terms appeared to be coded appropriately. Exceptions identified by this Reviewer were as follows:

- Subject CV181038-87-811 (placebo group) was coded as having “coronary artery disease” on Day 84. However, the narrative provided described this subject as having had an “extensive AW STEMI”. The Sponsor was questioned regarding this and clarified that they reported an SAE “extensive anterior wall ST elevation myocardial infarction” only after database lock. Indeed, the Sponsor did later identify this subject as having had a MACE event.

The Sponsor was asked to provide narratives for subjects with potential cardiac PTs that may have been classified under other SOCs. This process identified 2 subjects who had no AE in the cardiac SOC, but had cardiac procedures. The Sponsor recognized that these events should have been coded differently:

- Subject CV181040-149-862, a subject in the saxagliptin 2.5 mg group, was coded as having “chest pain” in the General Disorders SOC. However, the Sponsor confirmed that he had an acute stent placement.
- Subject CV181014-183-1096, a subject in the placebo group, was coded as having “pain in extremity”. However, the Sponsor confirmed that he had an angioplasty that appeared to have been done as a response to the workup for the index event.

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The focus of the Sponsor’s safety evaluation was the 24-week double-blind treatment period of the 6 core Phase 3 studies. Four populations (termed Population 1-Population 4), summarized in Table 7.2 below, were created to summarize the safety of saxagliptin. Although there is utility in using a pooled safety population, particularly when monitoring for rare events, in this Review I frequently present the safety of the individual studies rather than using pooled data. This is done to assess for potential differences in the safety profile of the varying study populations. Population 3 (Table 7.2) contains pooled safety data for the 2 monotherapy studies and the 3 add-on combination studies. A major limitation of this population is the pooling of dissimilar subjects with dissimilar background therapies. Population 4 is independently presented from the pooled safety population as this study had an active metformin comparator arm without a placebo arm. Therefore, it did not fit the pooling strategy for used for Population 3.

<b>Table 7.2. Summary of Populations for Safety Evaluation</b>				
<b>Population 1: Pooled Monotherapy Safety</b>				
At least one dose of double-blind treatment				
Includes studies: CV181011 and 038				
Treatment Groups				
saxagliptin 2.5 mg (includes 2.5/5 titration arm from 038)	saxagliptin 5 mg (includes PM dosing arm from 038)	saxagliptin 10 mg (OL arm in 011 not included)	All saxagliptin	Placebo
<b>Population 2: Pooled Monotherapy Long-term Safety</b>				
At least 24 weeks of double-blind treatment				
Includes studies: CV181011 and 038				
Treatment Groups				
saxagliptin 2.5 mg	saxagliptin 5 mg (includes PM dosing arm from 038)	saxagliptin 10 mg (OL arm in 011 not included)	All saxagliptin	Placebo
<b>Population 3: Pooled Safety</b>				
At least one dose of double-blind treatment				
Includes studies: CV181011, 038, 013, 040, and 014				
Treatment Groups				
saxagliptin 2.5 mg (includes 2.5 to 5 titration arm from 038)	saxagliptin 5 mg (includes PM dosing arm from 038)	saxagliptin 10 mg (OL arm in 011 not included)	All saxagliptin	Placebo
<b>Population 4: CV181039 Safety</b>				
At least one dose of double-blind treatment				
Includes studies: CV181039				
Treatment Groups				
saxagliptin 5 mg + metformin	saxagliptin 10 mg + metformin	saxagliptin 10 mg + placebo	All saxagliptin	Placebo + metformin

Source: *Integrated Summary of Safety, Table 1.1.1*

The following data were not pooled for safety analyses (except for exposure and deaths):

- Data from subjects in Study CV181008: this study was of shorter duration (12 weeks) and therefore exposure was not comparable to the Core Phase 3 studies.
- Data from subjects in Study CV181041 (12-week mechanism of action study): this study was of shorter duration, employed difference baseline A1c criteria, and was of small sample size.
- Data from subjects in Study CV181039: this was discussed above.

- Data from subjects receiving open-label 10 mg saxagliptin in Study CV181011: there was no control group and A1c criteria for inclusion at baseline were higher in this cohort (10-12%) than in the other placebo-controlled studies.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Guidelines and recommendations regarding study drug design and exposure can be found in both International Conference on Harmonization (ICH) guidelines and the FDA Draft Guidance on Diabetes.

The Draft Guidance from February 2008, which provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at FDA for the treatment and prevention of diabetes mellitus, refers to 6 month, placebo-controlled phase 3 studies as well as an extension phase of 6-12 months.<sup>1</sup> The Guidance also recommends that phase 3 trial data for drugs developed for type 2 diabetes 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 product for 1 year or more and at least 300-500 subjects exposed to the product for 18 months or more. The Table below summarizes these exposures, and confirms that the Sponsor met these recommendations.

	<b>NDA</b>	<b>Safety Update</b>
N ≥ 24 Weeks	2642	2655
N ≥ 52 Weeks	1080	1937

Limitations of the safety assessments, including limited enrollment of certain populations, was previously discussed above under Section 7, Safety Summary.

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<sup>1</sup> FDA Guidance for Industry (Draft Guidance), Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, February 2008.

## 7.2.2 Explorations for Dose Response

In the Phase 1-3 clinical development program, a total of 4042 subjects (3018.7 subject-years) were exposed to saxagliptin, including 620 in clinical pharmacology studies, 315 in the Phase 2b clinical study, 20 in a Phase 3 MOA study, and 3087 in the 6 Core Phase 3 studies. The extent of exposure for the ST + LT periods of the phase 2/3 studies (from 120-day safety update) have been presented by individual study in Table 2.2 in Section 2.5. Table 7.4 and 7.5 below present the exposures by dose for the ST + LT Periods for the phase 2/3 studies, both from the initial submission and the safety update.

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**Table 7.4. Exposure in ST + LT Periods from the NDA submission: Phase 2/3 Studies**

	Saxa 2.5mg	Saxa 5mg	Saxa 10mg	Saxa 20mg	Saxa 40mg	Saxa 100mg	All Saxa <sup>a</sup>	Placebo	Met
	N=937	N=1269	N=1066	N=54	N=52	N=44	N=3422	N=923	N=328
N (%) ≥24	773 (83%)	1038 (82%)	831 (78%)	0	0	0	2642 (77%)	679 (74%)	263 (80%)
N (%) ≥52	417 (45%)	399 (31%)	264 (25%)	0	0	0	1080 (32%)	352 (38%)	8 (2%)
Mean (SD)	52.1 (28)	46.6 (27)	44.6 (31)	11.2 (2.6)	11.6 (2.4)	6.1 (0.4)	45.9 (29)	46.3 (29)	31.3 (14)
Median	50.1	38.1	37	12.1	12.1	6.1	37.6	48.7	33.9
Range	0.1, 116.9	0.1, 119.0	0.1, 117.1	3.9, 16.0	1.3, 14.6	5.1, 8.1	0.1, 119.0	0.1, 116.1	0.1, 75.4
<i>Adapted from Applicant's "Response to 74 Day Letter"</i>									
<i><sup>a</sup>Included saxagliptin 20mg (N=54), saxagliptin 40mg (N=52), saxagliptin 100mg (N=44) in Study CY181008 and saxagliptin 10mg open-label group in Study CY181011</i>									

Weeks	Saxa 2.5mg N=937	Saxa 5mg N=1269	Saxa 10mg N=1066	All Saxa N=3422	Control N=1251
N (%) ≥24	773 (83%)	1046 (82%)	836 (78%)	2655 (78%)	945 (76%)
N (%) ≥52	622 (66%)	772 (61%)	543 (51%)	1937 (57%)	689 (55%)
Mean (SD)	64.0 (35)	60.1 (33)	58.5 (36)	58.5 (36)	53.9 (33)
Median	65.1	63	52.6	62.3	60
Range	0.1, 141.6	0.1, 144.3	0.1, 157.1	0.1, 157.1	0.1, 141.1

*Source: Applicant's 120-day Safety Update, Appendix 1.4.5*

Demographic data has already been presented in Section 6.1.2.

### 7.2.3 Special Animal and/or In Vitro Testing

Refer to Dr. Fred Alavi's review for details.

### 7.2.4 Routine Clinical Testing

Laboratory tests, vital signs, and EKGs were performed at acceptable time points during the studies. This Reviewer did not identify missing key measurements.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The Sponsor's testing of saxagliptin's metabolism, clearance, and potential for interaction has already been discussed in Section 4.4.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Sponsor adequately monitored for adverse events that have been associated with other DPP-4 inhibitors, including infections, skin-related AEs, hypersensitivity, and liver test abnormalities. The Phase 3 program incorporated pre-defined analyses related to these potential events.

The development program was not prospectively designed to monitor for Major Adverse Cardiovascular Events (MACE), although the Sponsor adequately responded to Division requests for analysis of such events. This is further discussed in this Section under Cardiovascular Safety as well as in Section 9.3

## 7.3 Major Safety Results

### 7.3.1 Deaths

In the Phase 2-3 studies, a total of 16 deaths were reported during the ST and LT periods as of the data cutoff for LT interim CSRs. These include 2 subjects (0.2%) in the 2.5 mg saxagliptin group, 2 subjects (0.2%) in the 5 mg group, 3 subjects (0.3%) in the 10 mg group, 5 subjects (0.5%) in the placebo group, and 4 subjects (1.2%) in the metformin monotherapy group. As expected for this patient population, most of the deaths were due to cardiovascular causes. Of the 7 deaths in saxagliptin-treated subjects, 2 occurred during ST and 5 during LT. There were no deaths among subjects who received a 20 mg or 40 mg dose, although exposure to these doses was of short duration. Short narratives for the deaths follow the table below.

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**Table 7.6. Deaths—Summary by Preferred Term for Saxagliptin Phase 2 and 3 Studies (ST and LT as of data cutoff for LT interim CSRs)**

Preferred Term	Saxa 2.5mg N=937	Saxa 5mg N=1269	Saxa 10mg N=1066	Saxa 20mg N=54	Saxa 40mg N=52	Saxa 100mg N=44	Placebo N=923	Placebo + Metformin N=328
Total Subjects with AE (%)	2 (0.2)	2 (0.2)	3 (0.3)	0	0	0	5 (0.5)	4 (1.2)
Acute MI	0	1 (<0.1)	0	0	0	0	0	1 (0.3)
Atrioventricular (AV) Block Complete	0	1 (<0.1)	0	0	0	0	0	0
Cardiogenic Shock	0	1 (<0.1)	0	0	0	0	1 (0.1)	0
Tetanus	0	1 (<0.1)	0	0	0	0	0	0
Arteriosclerosis Coronary Artery	0	0	1 (<0.1)	0	0	0	0	0
Cardiac Failure	0	0	0	0	0	0	0	1 (0.3)
Cardiac Failure Congestive	0	0	0	0	0	0	1 (0.1)	0
CVA	0	0	0	0	0	0	0	1 (0.3)
Hemorrhagic Stroke	0	0	0	0	0	0	1 (0.1)	0
Lung Neoplasm	0	0	1 (<0.1)	0	0	0	0	0
Myocardial Infarction (MI)	0	0	0	0	0	0	1 (0.1)	0
Pancreatic Neoplasm	0	0	0	0	0	0	0	1 (0.3)
Pneumococcal Sepsis	1 (0.1)	0	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0	1 (0.1)	0

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Pulmonary Embolism	0	0	0	0	0	0	0	0	0	0
Road Traffic Accident	1 (0.1)	0	0	0	0	0	0	0	0	0
Sepsis	0	0	0	0	0	0	0	0	1 (0.3)	0
Sudden Cardiac Death	0	0	0	0	0	0	0	1 (0.1)	0	0
Sudden Death	0	0	0	0	1 (<0.1)	0	0	0	0	0

## Brief Narratives of Deaths

### Deaths during ST

#### Saxagliptin-treated subjects

Subject CV181038-85-572, a 47 year old white male with a history of splenectomy secondary to trauma was in the saxagliptin 2.5 mg group, died on Day 54 with a recent history of upper respiratory symptoms 5 days prior. He had not received Pneumovax. On Day 54, the subject awoke with fever and chills and presented to the emergency room (ER) with abdominal pain, hypotension, and bradycardia. He was treated for **sepsis**, but his clinical condition deteriorated and he died despite cardiopulmonary resuscitation. Post-mortem results from blood cultures obtained in the ER demonstrated *Streptococcus pneumoniae*. The investigator characterized the death as unrelated to study medication.

Subject CV181013-74-386, a 66 year old white female in the saxagliptin 2.5 mg group, died in an **automobile accident** on Day 102. She encountered slippery road conditions, and the car lost control and spun onto oncoming traffic. She died from trauma. The investigator characterized the event leading to death as not likely related to study medication.

#### Placebo-treated subjects

Subject CV181014-171-1341, a 35 year old white male in the placebo group, died of **cardiogenic shock** on Day 157. He had a history of hypertension and hypertriglyceridemia. The investigator characterized the death as unrelated to study medication.

Subject CV1810040-68-1424, a 58 year old Asian male in the placebo group, died of **sudden cardiac death** on Day 112. He had a medical history of coronary artery disease and cerebrovascular disease. The investigator characterized the death as unlikely related to study medication.

#### Metformin-treated subjects

Subject CV181039-60-1617, a 65 year old white male in the metformin group, was found dead in his home on Day 144 (death due to **cardiac failure**). He had a medical history of hypertension and myocardial infarction. The investigator characterized the death as unrelated to study medication.

Subject CV181039-140-1597, a 60 year old white male in the metformin group, died of an **acute myocardial infarction** on Day 6. He had a history of hypertension and myocardial infarction. The investigator characterized the death as unrelated to study medication.

Subject CV181039-141-1059, a 62 year old white male in the metformin group, had a **cerebrovascular accident** on Day 130 and underwent drainage for an intracerebral hematoma. He died on Day 135. The investigator characterized the death as unrelated to study medication.

### Deaths during LT

#### Saxagliptin-treated subjects

Subject CV181014-171-778, a 48 year old white male in the saxagliptin 10 mg group, had a history of smoking, was diagnosed with a Grade 3 **pulmonary neoplasm** on Day 431. He had presented with weight loss, dysphagia, right eyelid ptosis, and leukocytosis. He was hospitalized on Day 449 for a bronchoscopy. However, on the same day, he experienced a **pulmonary embolism** and died. This occurred prior to rescue and 14 days after study medication was discontinued. The investigator characterized the event leading to death as unrelated to study medication.

Subject CV181039-148-943, a 57 year old white male in the saxagliptin 10 mg group, had a medical history of hypertension, **coronary artery disease**, previous myocardial infarction, stable angina, obesity, hypercholesterolemia, hypertriglyceridemia, and mixed dyslipidemia. According to the subject's relative, on Day 294, the subject died suddenly. The investigator characterized the event leading to death as unrelated to study medication.

Subject CV181039-232-2798, a 55 year old Asian male in the saxagliptin 10 mg+metformin group, died of "**sudden death**" on Day 254. He had a medical history of poorly controlled hypertension and overweight. He was noted to have a right bundle branch block on Days 101 and 180. On the day of his death, the subject reported feeling unwell and fell to the ground. There was no medical observation of the death or medical intervention performed. The investigator characterized the event leading to death as possibly related to study medication.

Subject CV181040-100-1810, a 68 year old male in the saxagliptin 5 mg group, died on Day 214 of **cardiogenic shock**. He had a medical history of diabetic neuropathy, hypertriglyceridemia, and hypertension. On Day 213, he experienced an **acute MI, AV block III**, and cardiogenic shock. ECG showed ST elevation in lead II and III with third degree AV block. Cardiac catheterization showed complete obstruction of the right main coronary artery. The investigator characterized the events leading to death as unlikely related to study medication.

Subject CV181039-155-2139, a 49 year old Asian man in the saxagliptin 5 mg + metformin group, died on Day 230 of acute respiratory failure secondary to **tetanus**. With a medical history of hypertension, he sustained a puncture wound and was treated with amoxicillin/clavulanate and tetanus toxoid injection. According to the subject's wife, he was not compliant with the injectable medication. The subject was admitted to the hospital on Day 229 and died the following day. The investigator characterized the event leading to death as unrelated to study medication.

#### Placebo-treated subjects

Subject CV181014-13-254, a 48 year old white male in the placebo group, died of **congestive heart failure** on Day 405. He had a history of obesity, hyperlipidemia, and tobacco use. The investigator characterized the death as unrelated to study medication.

Subject CV181040-65-981, a 54 year old Asian male in the placebo group, died of severe **pneumonia** on Day 424. He had a history of tobacco use and pulmonary tuberculosis. The investigator characterized the death as unrelated to study medication.

Subject CV181040-127-89, a 62 year old female in the placebo group, died of an **acute hemorrhagic stroke** on Day 201. She had a medical history of hypertension and stroke. The investigator characterized the death as unrelated to study medication.

#### Metformin-treated subjects

Subject CV181039-193-688, a 55 year old female in the metformin group, died due to **pancreatic neoplasm and sepsis** on unspecified day. She had a medical history of obesity and hypercholesterolemia. The investigator characterized the pancreatic neoplasm as possibly related and sepsis as unrelated to study medication.

#### 120 day Safety Update

In addition to the 16 deaths reported in the NDA, 6 new deaths were reported in the Core Phase 3 studies during the reporting period of the 120-day Safety Update. These included 3 subjects in the saxagliptin groups, 3 subjects in the placebo group, and 1 in the metformin group. Narratives are provided below:

Subject CV181014-175-1104, a 63 year old male in the saxagliptin 2.5 mg group, died on Day 777 after being hospitalized with a **hemorrhagic stroke** on Day 756. Additional information received after database lock indicated that he received study drug within 30 days prior to the event.

Subject CV181013-229-433, a 63 year old female in the saxagliptin 5 mg group (also receiving pioglitazone 45mg daily) died on Day 509 of **sudden cardiac arrest**. He had an SAE of atrial fibrillation with rapid ventricular response and was hospitalized on Day 494. On Day 497, he developed a cerebellar hemorrhage.

Subject CV181039-237-1549, a 71 year old male in the saxagliptin 10mg group, died of **cardiac arrest** in a taxi while on his way to the hospital for chest pain on Day 377.

Subject CV181011-125-649, a 74 year old female in the placebo group, died of **cerebral hemorrhage** on Day 861. This followed an SAE of myocardial infarction on Day 852. A CT scan on Day 854 showed cerebral hemorrhage.

Subject 181040-127-1070, a 64 year old white male in the placebo group, died on Day 452 of an **acute myocardial infarction**. He had a history of ischemic cardiomyopathy, and he died at home during the night.

Subject CV181039-222-1033, a 58 year old male in the metformin monotherapy group, was reported to have **sudden death** on Day 383.

### 7.3.2 Nonfatal Serious Adverse Events

There were a total of 127 SAEs reported for the ST period of the combined Core Phase 3 studies. These events were reviewed, and SAEs that occurred in the LT period were reviewed as well. Narratives for SAEs of interest and unusual SAEs, particularly those that lead to discontinuation of study drug, are included below. In this Section of the Review, both ST and ST + LT data are presented; both sets of data were reviewed, and particular data are included here if notable imbalances were seen. Tables 7.7 and 7.8 summarize the incidence of SAEs by dose for all Core Phase 3 studies.

<b>Table 7.7. SAEs—Monotherapy and Combination Studies</b>					
	<b>Saxa 2.5 mg</b>	<b>Saxa 5 mg</b>	<b>Saxa 10 mg</b>	<b>All Saxa</b>	<b>Placebo</b>
<b>ST Period, Excluding Rescue</b>					
<b>Pooled Monotherapy</b> (CV181011, CV181038)	4.9% (12/247)	4.0% (10/252)	2.0% (2/98)	4.0% (24/597)	3.0% (5/169)
<b>Add-on Combination</b>					
+ Met (CV181014)	2.6% (5/192)	4.2% (8/191)	2.8% (5/181)	3.2% (18/564)	2.8% (5/179)
+ SU (CV181040)	1.6% (4/248)	2.4% (6/253)	N/A	2.0% (10/501)	2.2% (6/267)
+ TZD CV181013	4.1% (8/195)	3.8% (7/186)	N/A	3.9% (15/381)	5.4% (10/184)
<b>Up to Week 24, Regardless of Rescue Status</b>					
<b>Placebo-controlled</b>	3.5%	3.4%	2.5%	3.3%	3.4%
<b>Pooled Safety</b>	(31/882)	(30/882)	(7/279)	(68/2043)	(27/799)

Abbreviations: SAE=serious adverse event; Met=metformin; SU=sulfonylurea; TZD=thiazolidinedione; N/A=not applicable

Source: Summary of Clinical Safety, Table 2.1.3.1A

<b>Table 7.8. SAEs--ST Period Excluding Rescue--Initial Combination Study with Metformin</b>				
<b>Saxa 5 mg + Met</b>	<b>Saxa 10 mg + Met</b>	<b>Saxa 10 mg</b>	<b>All Saxa</b>	<b>Met</b>
2.5% (8/320)	3.7% (13/323)	1.8% (6/335)	2.7% (26/978)	2.4% (8/328)

Abbreviations: Met=Metformin; SAE=serious adverse event; ST=short-term

Source: Summary of Clinical Safety, Table 2.1.3.1B

#### Monotherapy Studies

SAEs for the pooled Monotherapy Studies are listed by MedDRA SOC below. This summary includes SAEs captured before rescue. The same summary, but including events after rescue, was reviewed and yielded similar results. Based on the summary below, SAEs in each SOC were infrequent and there did not appear to be any concerning signals, particularly when taking

into account the 3-fold larger “all saxagliptin” group (n=597) compared to the placebo group (n=169). There were no SAEs of hypoglycemia in saxagliptin-treated subjects in either monotherapy study.

**Table 7.9. SAEs--Summary by SOC During ST Period for Monotherapy Studies**

SOC (%)	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
Total Subjects with AE	12 (4.9)	10 (4.0)	2 (2.0)	24 (4.0)	5 (3.0)
Musculoskeletal and Connective Tissue Disorders	0	3 (1.2)	0	3 (0.5)	0
Cardiac Disorders	2 (0.8)	2 (0.8)	0	4 (0.7)	1 (0.6)
Injury, Poisoning and Procedural Complications	2 (0.8)	2 (0.8)	0	4 (0.7)	0
Eye Disorders	0	1 (0.4)	0	1 (0.2)	0
Gastrointestinal Disorders	0	1 (0.4)	0	1 (0.2)	1 (0.6)
General Disorders and Administration Site Conditions	1 (0.4)	1 (0.4)	1 (1.0)	3 (0.5)	0
Nervous System Disorders	0	1 (0.4)	0	1 (0.2)	2 (1.2)
Reproductive System and Breast Disorders	0	1 (0.4)	0	1 (0.2)	0
Vascular Disorders	0	1 (0.4)	0	1 (0.2)	1 (0.6)
Ear and Labyrinth Disorders	1 (0.4)	0	0	1 (0.2)	0
Endocrine Disorders	0	0	0	0	1 (0.6)
Infections and Infestations	4 (1.6)	0	0	4 (0.7)	0
Neoplasms Benign, Malignant and Unspecified	2 (0.8)	0	0	2 (0.3)	0
Renal and Urinary Disorders	0	0	0	0	1 (0.6)
Respiratory, Thoracic, and Mediastinal Disorders	0	0	1 (1.0)	1 (0.2)	0
Skin and Subcutaneous Tissue Disorders	1 (0.4)	0	0	1 (0.2)	0

Source: Integrated Summary of Safety, Appendix 5.1.1

For Study CV181011, there were a total of 38 subjects with SAEs reported in the ST + LT period. In this study, there was an imbalance of SAEs, with the highest frequency observed in the saxagliptin 5 mg group. This is shown in the table below; only cardiac disorders and nervous system disorders are listed as these appeared to contribute to the imbalance, although these differences were not driven by any particular adverse event. This imbalance was not observed in the saxagliptin 10 mg group. Under cardiac disorders, only the SAE of acute myocardial infarction resulted in discontinuation of study drug. Under nervous system disorders, both

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events of CVA resulted in study discontinuation. Similar imbalances were not observed in CV181038.

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SOC (%)	ST + LT Treatment Period			
	Saxa 2.5mg N=102	Saxa 5mg N=106	Saxa 10mg N=98	Placebo N=95
<b>Total Subjects with AE</b>	9 (8.8)	15 (14.2)	6 (6.1)	8 (8.4)
<b>Cardiac Disorders</b>	2 (2.0)	5 (4.7)	1 (1.0)	2 (2.1)
Atrial fibrillation	0	2 (1.9)	0	0
Coronary Artery Disease	1 (1.0)	1 (0.9)	0	0
Acute Myocardial Infarction	0	1 (0.9)	0	0
Aortic Valve Stenosis	0	0	1 (1.0)	0
Cardiac Failure Congestive	1 (1.0)	0	0	0
Supraventricular Tachycardia	0	1 (0.9)	0	0
Angina Unstable	0	0	0	1 (1.1)
Tachycardia	0	0	0	1 (1.1)
<b>Nervous System Disorders</b>	2 (2.0)	4 (3.8)	0	2 (2.1)
Cerebrovascular Accident (CVA)	0	2 (1.9)	0	0
Syncope	2 (2.0)	0	0	1 (1.1)
IV <sup>th</sup> Nerve Paralysis	0	1 (0.9)	0	0
Syncope Vasovagal	0	1 (0.9)	0	0
Vascular Headache	0	0	0	0
All Saxa	30 (9.8)	30 (9.8)	30 (9.8)	30 (9.8)

Source: Interim Clinical Study Report, CV11011, Table 8.3

Narratives for Subjects with SAEs of Special Interest, Unusual SAEs, or SAEs Leading to Discontinuation of Study Drug in Study CV181011 and Study CV181038

ST Period

Subject CV181011-66-84, a 47 year old white male in the saxagliptin 2.5 mg group, had an SAE of “**rash-torso worsening**” on Day 57. He had a history of psoriasis and right leg cellulitis. The rash was thought to be related to his psoriasis. On Day 58, he also experienced an SAE of “**worsening of wound right lower leg**”, for which he was hospitalized. The microscopic diagnosis was “**spongiotic dermatitis, probably spongiotic drug eruption.**” This AE resolved on Day 64, but study drug was not resumed.

**Reviewer comment: Although this subject had a history of dermatological problems, the second AE may be drug-related.**

Subject CV181011-142-670, a 56 year old male in the saxagliptin 2.5 mg group, was diagnosed with **hepatitis C** on Day 43 after elevations of liver tests were noted. He discontinued the study on Day 56.

Subject CV181011-10-231, a 69 year old female in the saxagliptin 10 mg group, was hospitalized and diagnosed with **exacerbation of COPD** on Day 63. She had a history of emphysema. Study drug was discontinued on the same day.

LT Period

Subject CV181011-9-147, a 68 year old female in the saxagliptin 2.5 mg group, had an episode of **pyelonephritis** on Day 394. She was hospitalized and study drug was discontinued on the same day. She responded to antibiotics. On Day 408, 14 days after discontinuation of study drug, she was hospitalized again with **syncope and hypotension**. This reportedly resolved on Day 433.

Subject CV181011-72-590, a 61 year old male in the saxagliptin 2.5 mg group, was found to have **congestive heart failure and pneumonia** on Day 343. He had a history of cigarette smoking. Intubation was required, and study drug was discontinued. The events resolved on Day 352.

Subject CV181011-140-619, a 59 year old male in the saxagliptin 2.5 mg group, noted blood stool on Day 546. Tests revealed a mild anemia, and a colonoscopy revealed a large **rectal mass**. Pathologic diagnosis was tubulovillous adenoma with focal high grade dysplasia; grade 2. Study drug was discontinued on 568.

Subject CV181011-37-532, a 56 year old male in the saxagliptin 5 mg group, was diagnosed with an **acute myocardial infarction** on Day 210. He had a history of CAD. Cardiac catheterization revealed an occluded right coronary artery. Study drug was interrupted and the event was considered resolved on the same day. However, the following day he became aphasic, and imaging showed a large left pontine infarction (**cerebrovascular accident**). He was discontinued from the study.

Subject CV181011-153-722, a 73 year old male in the saxagliptin 10mg group, was diagnosed with kidney stones on Day 363. He also complained of dyspnea, and a chest X-ray revealed a lung mass (**lung neoplasm malignant**). A 4 cm lung malignancy was diagnosed on Day 412. He had no history of lung problems or smoking. Study drug was discontinued on Day 370. He underwent surgery and was scheduled for chemotherapy.

Subject CV181011-159-793, a 68 year old male in the saxagliptin 5mg group, was hospitalized for **right fourth cranial nerve palsy** on Day 201. A CT scan showed no apparent disease. Although this event was not considered an SAE leading to study discontinuation, the subject subsequently chose not to continue study drug.

Subject CV181011-109-300, a 63 year old male was admitted to the hospital on Day 517 due to **syncope**. Cardiac markers, EKG, and glucose were normal. It was thought to possibly be due to a vasovagal etiology. The subject continued in the trial.

#### CV181038

There were a total of 22 subjects with SAEs reported during the ST + LT periods in this study.

#### ST Period

Subject CV181038-31-838, a 61 year old white female in the saxagliptin 2.5/5mg qam group, was diagnosed with **pancreatic cancer** on Day 13. She had an elevated alkaline phosphatase since screening and abdominal symptoms prior to randomization. She was discontinued from the study. She was also diagnosed with **metastatic hepatic cancer** on Day 18.

Subject CV181038-87-811, a 54 year old female in the placebo group, was diagnosed with **coronary artery disease** on Day 84. She presented to the ER with chest and cardiac catheterization confirmed the diagnosis.

Subject CV181038-073-669, a 39 year old female in the saxagliptin 2.5mg qam group, was reported to have an **overdose** on Day 34. The subject was reported to have had poor compliance, and she reportedly took 19 tablets of study drug in 14 days. No symptoms were noted, and no treatment was needed. The subject continued in the study.

Subject CV181038-070-443, a 63 year old female in the saxagliptin 5mg qpm group, was reported to have an **overdose** on Day 175. The subject started taking study drug twice daily instead of once daily. No symptoms were noted. The subject was reeducated, and she continued in the study.

Subject CV181038-67-164, a 56 year old male in the saxagliptin 2.5mg group, had an SAE of **cellulitis** of both legs on Day 94. He had multiple prior episodes of cellulitis. He continued in the study, but had another SAE of cellulitis with ulceration of the skin of right foot on Day 266 (occurred during LT period). Study drug was then discontinued on Day 274.

**Reviewer comment: The Investigator considered this AE to be possibly related to study drug.**

LT Period

Subject CV181038-67-341, a 71 year old male in the placebo group, had an SAE of hypoglycemia on Day 264. He had been rescued with metformin on Day 238 and had multiple prior episodes of hypoglycemia.

Add-on Combination Studies

SAEs for the add-on combination studies are summarized below by individual study. These summaries include SAEs captured before rescue. The same summary, but including events after rescue, was reviewed and yielded similar results. There were no SAEs of hypoglycemia.

CV181014

There were a total of 23 subjects with SAEs reported during the ST period, and 56 subjects with SAEs reported during the ST + LT treatment periods. The data obtained from the ST period did not indicate a safety signal for any particular SOC.

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**Table 7.11. CV181014: SAEs--Summary by SOC During ST Period**

SOC (%)	Saxa 2.5 mg +		Saxa 5 mg +		Saxa 10 mg +		All	
	Met	N=192	Met	N=191	Met	N=181	Saxa	Placebo + Met
Total Subjects with AE	5 (2.6)		8 (4.2)		5 (2.8)		N=564	N=179
Cardiac Disorders	0		1 (0.5)		2 (1.1)		18 (3.2)	5 (2.8)
Gastrointestinal Disorders	1 (0.5)		1 (0.5)		1 (0.6)		3 (0.5)	3 (1.7)
Neoplasms Benign, Malignant and Unspecified	0		0		1 (0.6)		3 (0.5)	0
Psychiatric Disorders	1 (0.5)		0		1 (0.6)		1 (0.2)	0
Hepatobiliary Disorders	1 (0.5)		0		0		2 (0.4)	0
Infections and Infestations	2 (1.0)		1 (0.5)		0		1 (0.2)	0
Injury, Poisoning, and Procedural Complications	0		2 (1.0)		0		3 (0.5)	1 (0.6)
Metabolism and Connective Tissue Disorders	0		1 (0.5)		0		2 (0.4)	0
Musculoskeletal and Connective Tissue Disorders	0		1 (0.5)		0		1 (0.2)	0
Reproductive System and Breast Disorders	1 (0.5)		0		0		1 (0.2)	1 (0.6)
Respiratory, Thoracic and Mediastinal Disorders	0		1 (0.5)		0		1 (0.2)	0
Surgical and Medical Procedures	0		1 (0.5)		0		1 (0.2)	0

Source: Final Clinical Study Report, CV181014, Table 8.3

In the ST+LT Period, there were slight imbalances seen in several SOCs. These are summarized below. Within Infections and Infestations, events were spread across various PTs. Within this SOC, only diverticulitis and sinusitis occurred in more than one saxagliptin-treated subject. Two cases of appendicitis were recorded: one under Infections and Infestations, one under Gastrointestinal disorders. Other notable events under Infections and Infestations are included in the narratives below. Within Injury, Poisoning and Procedural Complications, several falls and accidents were seen. Narratives for these are included below. None appeared to be the result of a hypoglycemic event. Within Gastrointestinal Disorders, events were spread across a number of PTs (appendicitis mentioned above). Within Hepatobiliary Disorders, cholelithiasis and/or cholecystitis were not seen in the placebo group, but did account for all 5 events (4 cholecystitis, 1 cholelithiasis) seen in 4 saxagliptin-treated subjects. Interestingly, 3 of the 4 cases of cholecystitis occurred at Days 445-497 (Days 445, 493, and 497). The fourth case occurred at Day 18.

**Reviewer comment: The incidence of new-onset biliary pain among patients with previously asymptomatic gallstones is approximately 2% per year for the first 5 years and increases to 15% at 10 years.<sup>2</sup> In the US, over 10% of men and 20% of women have gallstones by age 65.<sup>3</sup>**

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<sup>2</sup> Emergency Medicine: A Comprehensive Study Guide, 6<sup>th</sup> Edition (2004)

<sup>3</sup> Current Consult Medicine 2007.

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**Table 7.12. CV181014: SAEs—Summary of SOCs with Imbalances in Frequency of SAEs for ST + LT Periods**

SOC (%)	Saxa 2.5mg +				Placebo + Met N=179
	Met N=192	Saxa 5mg + Met N=191	Saxa 10mg + Met N=181	All Saxa N=564	
<b>Total Subjects with</b>					
AE	17 (8.9)	19 (9.9)	20 (11.0)	56 (9.9)	10 (5.6)
Infections and Infestations	5 (2.6)	3 (1.6)	3 (1.7)	11 (2.0)	1 (0.6)
Injury, Poisoning and Procedural					
Complications	3 (1.6)	4 (2.1)	1 (0.6)	8 (1.4)	0
Gastrointestinal Disorders	4 (2.1)	1 (0.5)	1 (0.6)	6 (1.1)	0
Hepatobiliary Disorders	1 (0.5)	1 (0.5)	3 (1.7)	5 (0.9)	0

Source: Interim LT +ST Clinical Study Report, CV181014, Table 8.3A

### Narratives

#### ST Period

Subject CV181014-134-1022, a 62 year old white female in the saxagliptin 2.5 mg group, was diagnosed with **diverticulitis** on Day 48. Because of persistent diarrhea and tenderness, study drug was discontinued on Day 63.

Subject CV181014-176-883, a 74 year old female in the saxagliptin 2.5 mg group, was diagnosed with left breast mastitis (**breast abscess**) on Day 33. She had a prior episode of the same on Day -28 (during screening), at which time a nodule was removed. During this second episode, she received antibiotics and underwent drainage. She continued in the study.

Subject CV181014-112-1285, a 54 year old male in the saxagliptin 5 mg group, presented with polyuria and weakness and was diagnosed with **dehydration** on Day 119. This occurred several days after beginning therapy with hydrochlorothiazide for worsening nephrolithiasis. Laboratory values were significant for glucose 229 mg/dL, creatinine 1.6 mg/dL. He was treated with intravenous fluids and discharged the following day. He had another SAE of dehydration on Day 286. At that time glucose was 358 mg/dL, creatinine 2.3 mg/dL, and sodium 127 mEq/L. Study drug was interrupted on Day 287 and never resumed.

Subject CV181014-135-535, a 58 year old female in the saxagliptin 5 mg group, was hospitalized for **C. difficile colitis** on Day 161. She had taken a course of clindamycin several weeks earlier for a tooth extraction. The colitis eventually required subtotal colectomy and ileostomy on Day 164. On Day 184, she presented to the ER with an SAE of **pulmonary emboli**. She withdrew consent from the study on Day 205. The last dose of study drug was given on Day 151.

**Reviewer comment: This subject had multiple risk factors, including recent surgery and estrogen therapy, for developing pulmonary embolism.**

Subject CV181014-199-669, a 46 year old male in the saxagliptin 5 mg group, had a **motor vehicle accident** and sustained a **right ankle fracture** on Day 20. Information was not provided regarding his glucose level during the time of the accident.

Subject CV181014-129-359, a 59 year old male in the saxagliptin 10 mg group, was diagnosed with **gastrointestinal carcinoma** with large bowel obstruction on Day 52. Study drug was discontinued on Day 54. Surgical pathology revealed an invasive adenocarcinoma.

#### LT Period

Subject CV181014-56-458, a 62 year old male in the saxagliptin 2.5 mg group, was reported to have a **hip fracture** after slipping and falling in his home on Day 509. No symptoms of hypoglycemia were reported. This subject also had an SAE of **prostate cancer** of Day 284.

Subject CV181014-164-1417, a 54 year old male in the saxagliptin 2.5 mg group, was hospitalized on Day 85 for a **scrotal abscess**. There was no prior history of the same and no

predisposing factor, other than diabetes. He was treated with drainage and antibiotics, and study drug was temporarily interrupted. He discontinued on Day 183, due to lack of efficacy.

Subject CV181014-167-422, a 59 year old female in the saxagliptin 2.5 mg group, was diagnosed with **non-Hodgkins' lymphoma** on Day 641, after she was noted to have anemia. Study drug was discontinued. Treatment for the lymphoma ensued.

Subject CV181014-89-761, a 59 year old male in the saxagliptin 5 mg group, had a **fall** on Day 499. He was moving heavy furniture when the dolly slipped out from under him, causing the fall. No hypoglycemic symptoms were noted. Glucose in the ER was 77 (units not stated).

#### CV181040

There were a total of 16 subjects with SAEs reported in the ST period and 39 subjects with SAEs reported in the ST + LT periods. The data obtained from the ST period did not indicate a safety signal for any particular SOC. There was one SAE of hypoglycemia, reported in the LT period (narrative below).

**Table 7.13. CV181040: SAEs--Summary by SOC During ST Treatment Period**

<b>SOC (%)</b>	<b>Saxa 2.5mg + Gly</b>	<b>Saxa 5mg + Gly</b>	<b>All Saxa</b>	<b>Placebo + Gly</b>
	<b>N=248</b>	<b>N=253</b>	<b>N=501</b>	<b>N=267</b>
<b>Total Subjects with AE</b>	<b>4 (1.6)</b>	<b>6 (2.4)</b>	<b>10 (2.0)</b>	<b>6 (2.2)</b>
Hepatobiliary Disorders	0	2 (0.8)	2 (0.4)	1 (0.4)
Infections and Infestations	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.4)	1 (0.4)	2 (0.4)	0
Cardiac Disorders	1 (0.4)	1 (0.2)	1 (0.2)	2 (0.7)
Gastrointestinal Disorders	0	1 (0.4)	1 (0.2)	0
General Disorders and Administration Site Conditions	1 (0.4)	0	1 (0.2)	1 (0.4)
Injury, Poisoning, and Procedural Complications	0	1 (0.4)	1 (0.2)	0
Renal and Urinary Disorders	0	0	0	1 (0.4)

Source: Final Clinical Study Report. CV181040, Table 8.3

There were no major imbalances among SOCs observed during the LT period. Narratives of interest are included below.

#### Narratives

#### ST Period

Subject CV181040-37-232, a 52 year old female in the saxagliptin 5 mg group, was diagnosed with a **salivary gland mass** on Day 138. She underwent an uncomplicated right parotidectomy on Day 326. She continued in the study.

Subject CV1818040-57-1874, a 50 year old male in the saxagliptin 5 mg group, had a **road traffic accident** on Day 4. He was hospitalized with a diagnosis of cervical and lumbar sprain on Day 8. Information was not provided regarding the subject's glucose level at the time of the accident, but he had no reported AEs of hypoglycemia.

Subject CV181040-29-235, a 25 year old female in the saxagliptin 5 mg + glyburide group, had an AE of elevated LFTs on Day 64: ALT 122 U/L and AST 70 U/L. She was started on oral contraceptives on Day -63 and had elevated ALT at baseline (value 68 U/L). The ALT/AST values continued to increase (Day 106: ALT 147 U/L and AST 113 U/L) and study drug was discontinued on Day 125. As per the narrative provided by the Sponsor, the event continued but no further follow up was available. Total bilirubin and alkaline phosphatase remained normal throughout. The Investigator considered the event probably related to study drug.

#### LT Period

Subject CV181040-52-1781, a 61 year old male in the saxagliptin 2.5 mg group (with background glyburide 7.5mg), had an SAE of **hypoglycemia** on Day 203. He was admitted to the hospital with weakness and his glucose was found to be 36mg/dL. He had missed or delayed a meal. Study drug was resumed on Day 206.

Subject CV181040-68-280, a 59 year old female in the saxagliptin 5 mg group, was diagnosed with **myelodysplastic syndrome** on Day 365. She presented with thrombocytopenia. She discontinued the study on Day 366.

Subject CV181040-100-770, a 57 year old female in the saxagliptin 2.5mg group, was diagnosed with **adenocarcinoma of the stomach** on Day 397. She had presented with weight loss, abdominal pain, and hypoglycemia. She was also diagnosed with spontaneous bacterial peritonitis. Palliative care was administered. Study drug was last given on Day 407.

#### CV181013

There were a total of 25 subjects with SAEs reported in the ST period and 45 subjects with SAEs reported for the ST + LT treatment periods. There were no SAEs reported for hypoglycemia in either treatment period. The summary below of the ST period did not indicate a safety signal. The SAEs for the ST + LT period did not indicate any major imbalances among dose groups across SOCs.

<b>SOC (%)</b>	<b>Saxa 2.5mg + TZD</b>	<b>Saxa 5mg + TZD</b>	<b>All Saxa</b>	<b>Placebo + TZD</b>
	<b>N=195</b>	<b>N=186</b>	<b>N=381</b>	<b>N=184</b>
<b>Total Subjects with AE</b>	<b>8 (4.1)</b>	<b>7 (3.8)</b>	<b>15 (3.9)</b>	<b>10 (5.4)</b>

Injury, Poisoning and Procedural Complications.	1 (0.5)	2 (1.1)	3 (0.8)	1 (0.5)
General Disorders and Administration Site Conditions	1 (0.5)	1 (0.5)	2 (0.5)	0
Infections and Infestations	1 (0.5)	1 (0.5)	2 (0.5)	2 (1.1)
Musculoskeletal and Connective Tissue Disorders	1 (0.5)	1 (0.5)	2 (0.5)	0
Neoplasms Benign, Malignant and Unspecified	1 (0.5)	1 (0.5)	2 (0.5)	1 (0.5)
Gastrointestinal Disorders	1 (0.5)	0	1 (0.3)	1 (0.5)
Hepatobiliary Disorders	1 (0.5)	0	1 (0.3)	0
Nervous System Disorders	1 (0.5)	0	1 (0.3)	1 (0.5)
Psychiatric Disorders	0	1 (0.5)	1 (0.3)	0
Vascular Disorders	1 (0.5)	0	1 (0.3)	0
Cardiac Disorders	0	0	0	4 (2.2)
Renal and Urinary Disorders	0	0	0	1 (0.5)
Skin and Subcutaneous Tissue Disorders	0	0	0	1 (0.5)

Source: Full Clinical Study Report, CV181013, Table 8.3

#### Narratives

##### ST Period

Subject CV181013-74-386, a 66 year old female in the saxagliptin 2.5 mg group, was reported to have died as a result of a **road traffic accident** on Day 102. Per the report, the roads were slippery and she lost control of the car. This subject had an event of hypoglycemia on Day 20, with no treatment required at that time.

##### LT Period

Subject CV181013-271-385, a 62 year old male in the saxagliptin 5 mg group, was reported to have **acute pancreatitis** on Day 236. His medical history was significant for alcohol use (2 drinks daily) and biliary disease. A radiographic study on Day 263 indicated chronic pancreatitis. Study drug was discontinued on Day 236 and the subject was discontinued from the study due to this SAE.

Subject CV181013-300-975, a 63 year old female in the saxagliptin 2.5 mg group, was reported to have **postmenopausal hemorrhage** on Day 228. She was menopausal for 20 years and was not receiving hormone replacement therapy. She was taking a 75 mg daily dose of aspirin. No cause was found, and no treatment was required. The subjects discontinued from the study.

##### CV181039

There were a total of 34 SAEs reported in the ST period and 50 SAEs reported for the ST + LT treatment periods. The data obtained from the ST period did not indicate a safety signal for any

particular SOC. There were no major imbalances across SOCs seen in the ST + LT treatment period. There were no SAEs of hypoglycemia reported.

<b>Table 7.15. CV181039: SAEs--Summary By SOC During ST Treatment Period</b>					
<b>SOC (%)</b>	<b>Saxa 5 mg + Met</b>	<b>Saxa 10 mg + Met</b>	<b>Saxa 10 mg</b>	<b>All Saxa</b>	<b>Metformin</b>
	<b>N=320</b>	<b>N=323</b>	<b>N=335</b>	<b>N=978</b>	<b>N=328</b>
Total Subjects with AE	8 (2.5)	12 (3.7)	6 (1.8)	26 (2.7)	8 (2.4)
Gastrointestinal Disorders	1 (0.3)	3 (0.9)	1 (0.3)	5 (0.5)	2 (0.6)
Injury, Poisoning and Procedural Complications	2 (0.6)	2 (0.6)	1 (0.3)	5 (0.5)	0
Infections and Infestations	2 (0.6)	1 (0.3)	1 (0.3)	4 (0.4)	0
Metabolism and Nutrition Disorders	1 (0.3)	0	1 (0.3)	2 (0.2)	0
Nervous System Disorders	1 (0.3)	1 (0.3)	0	2 (0.2)	2 (0.6)
Reproductive System and Breast Disorders	0	2 (0.6)	0	2 (0.2)	0
Blood and Lymphatic System Disorders	0	1 (0.3)	0	1 (0.1)	0
Cardiac Disorders	0	1 (0.3)	0	1 (0.1)	2 (0.6)
Congenital, Familial and Genetic Disorders	0	0	1 (0.3)	1 (0.1)	0
General Disorders and Administration Site Conditions	0	1 (0.3)	0	1 (0.1)	0
Neoplasms Benign, Malignant and Unspecified	1 (0.3)	0	0	1 (0.1)	0
Skin and Subcutaneous Tissue Disorders	1 (0.3)	0	0	1 (0.1)	0
Vascular Disorders	0	0	1 (0.3)	1 (0.1)	0
Hepatobiliary Disorders	0	0	0	0	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	0	0	0	0	1 (0.3)
Renal and Urinary Disorders	0	0	0	0	1 (0.3)

Source: Final Clinical Study Report, CV181039, Table 8.3

Narratives

ST Period

Subject CV181039-11-339, a 61 year old male in the saxagliptin 10 mg + Met group, had an SAE of **lymphopenia** on Day 56. Prior to this, he had an upper respiratory tract infection starting on Day 40 (to Day 76). An absolute lymphocyte count obtained on Day 60 was  $0.99 \times 10^3$  (normal 1.02-3.36; subject's baseline 1.54). On the same day, the subject reportedly had fever and hypotension that responded to hydration. He improved, but discontinued the study on Day 60. An absolute lymphocyte count obtained on Day 63 was  $1.29 \times 10^3$ .

Subject CV181039-144-902, a 62 year old female in the saxagliptin 10 mg + Met group, had **acute pancreatitis** on Day 9. She had a history of chronic pancreatitis with prior episodes of acute exacerbation of pancreatitis precipitated by dietary indiscretion. She discontinued from the study on Day 9. The event resolved on Day 24.

Subject CV181039-119-370, a 60 year old female in the metformin group, had pancreatitis on Day 25. He had a medical history of **pancreatitis** and fatty hepatitis. The event resolved 3 days later.

Subject CV181039-148-1830, a 54 year old male in the saxagliptin 5 mg + Met group, had an SAE of allergic dermatitis on Day 15. He was started on simvastatin therapy on Day 9. He was hospitalized on Day 18, simvastatin was discontinued, and he received intravenous dexamethasone. Study drug was interrupted on Day 22. The event resolved on Day 24, and study drug was resumed on Day 38. He continued in the study without further rash.  
**Reviewer comment: Given that this subject had no rash when rechallenged with saxagliptin, it seems unlikely that this event was related to the study drug.**

Subject CV181039-266-2802, a 41 year old male in the saxagliptin 5 mg + Met group, had an SAE of **lymphoproliferative disorder** on Day 46. Counts of WBC, neutrophils, monocytes, eosinophils, and basophils were low. Study drug was discontinued, and the event reportedly continued after database lock.

Subject CV181039-180-505, a 34 year old male in the saxagliptin 5 mg + Met group, was involved in an automobile accident and sustained an **upper limb fracture** on Day 24. Study drug was discontinued on Day 26. Information was not provided regarding the subject's glycemic status at the time of the accident. The subject withdrew consent to participate in the study on Day 31.

Subject CV181039-181-449, a 55 year old female in the saxagliptin 5mg + Metformin group, was reported to have a **wrist fracture** on Day 157 following a fall at home. No additional details regarding the subject's glycemic status were provided. She continued in the study.

#### LT Period

Subject CV181039-155-2139, a 49 year old male in the saxagliptin 5 mg + Metformin group, died on Day 230 due to respiratory failure secondary to severe **tetanus**. He had sustained a puncture wound 11 days prior, and he received antibiotics and tetanus toxoid injection, but was reportedly not compliant with the injectable medication.

Subject CV181039-75-1316, a 54 year old female in the saxagliptin 10 mg group, was reported to have a left leg fracture (**lower limb fracture**) on Day 259. No additional details regarding the subject's glycemic status were provided, but she remained in the study.

Subject CV181039-144-1127, a 53 year old male in the saxagliptin 10 mg group, had reported deafness in both ears on Day 277. A diagnosis of bilateral chronic sensorineural deafness was made. He reportedly improved with medication, physical therapy, and acupuncture. He continued in the study.

### 7.3.3 Dropouts and/or Discontinuations

There was a significant percentage of dropouts in all the saxagliptin Core Phase 3 studies. A major contributor was the high percentage of subjects dropping out for "lack of efficacy". In this program, subjects who met pre-defined rescue criteria (discussed in Section 5.3) were discontinued from the ST periods of each study and entered into the LT periods. These subjects were characterized as having "lack of efficacy", but additional safety and efficacy parameters continued to be measured in the LT periods as they remained on double-blind study drug with the addition of rescue medication.

Dropout rates due to adverse events were relatively low in all studies. The highest dropout rate due to AEs was seen in Study CV181013 in the saxagliptin 5 mg + TZD group (5.9%). This group had 14 discontinuations due to AEs, spread across a number of SOCs. One of these discontinuations was an SAE of colon neoplasm. In addition, there were 3 AEs of special interest that led to discontinuation of study drug: 2 subjects with rash, 1 subject with lymphopenia, and 1 subject with "lymphocyte count decreased". None of these AEs of special interest were seen in the lower dose group.

The second-highest discontinuation rate due to AEs was seen in CV181011, in the saxagliptin 10 mg group (5.1%). These AEs were also spread across a number of SOCs; there was one subject with an AE of rash.

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		Reasons for Discontinuation from ST Period						
		Completed ST	Continued LT	Lack of efficacy	Withdrawn consent	Adverse event	Deaths	Other
<b>Monotherapy Studies</b>								
<b>CV181011 (ST Period)</b>								
	102	72.0%	85.0%	14.0%	8.8%	3.9%	0.0%	1.9%
Saxa 2.5mg								
Saxa 5mg	106	64.0%	82.0%	19.0%	10.4%	2.8%	0.0%	2.8%
Saxa 10mg	98	70.0%	84.0%	14.0%	5.1%	5.1%	0.0%	6.1%
Placebo	95	58.0%	83.0%	26.0%	10.5%	0.0%	0.0%	5.2%
<b>CV181038 (ST Period)</b>								
Saxa 2.5mg qam	74	74.3%	83.8%	10.8%	5.4%	0	0	9.5%
Saxa 5mg qam	74	77%	89.2%	12.2%	5.4%	0	0	5.4%
Saxa 2.5mg/5mg qam	71	73.2%	84.5%	12.7%	1.4%	2.8%	1.4%	8.4%
Saxa 5mg qpm	72	76.4%	83.3%	9.7%	6.9%	1.4%	0	5.5%
Placebo	74	71.6%	85.1%	16.2%	5.4%	1.4%	0	5.4%
<b>Add-on Combination Studies</b>								
<b>CV181014 (ST Period)</b>								
Saxa 2.5mg + Met	192	77.1%	87.0%	13.0%	4.2%	2.6%	0.0%	3.1%
Saxa 5mg + Met	191	74.9%	84.8%	11.5%	6.8%	3.1%	0.0%	3.6%
Saxa 10mg + Met	181	77.3%	89.5%	14.9%	2.2%	2.8%	0.0%	3.3%
Placebo + Met	179	62.6%	83.2%	24.6%	6.1%	1.7%	0.6%	4.4%
<b>CV181040 (ST Period)</b>								
Saxa 2.5mg + Gly	248	77.4%	90.3%	16.5%	2.8%	0.4%	0.0%	2.8%
Saxa 5mg + Gly	253	77.1%	89.7%	15.0%	2.0%	2.4%	0.0%	3.5%
Placebo + Gly	267	65.9%	88.0%	24.7%	5.2%	1.5%	0.4%	2.2%
<b>CV181013 (ST Period)</b>								
Saxa 2.5mg + TZD	195	81.5%	88.7%	9.2%	3.6%	1.0%	0.5%	4.1%
Saxa 5mg TZD	186	75.3%	80.6%	6.5%	4.8%	5.9%	0.0%	7.5%
Placebo + TZD	184	75.0%	78.8%	10.3%	7.6%	2.7%	0.0%	4.3%
<b>Combination Therapy (Initial or First Line Therapy)</b>								
<b>CV181039 (ST Period)</b>								

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Table 7.16. Participation and Withdrawal in Core Phase 3 Studies (ST Period)									
Saxa 5mg + Met	320	81.9%	86.3%	6.3%	3.1%	2.2%	0.0%	6.5%	
Saxa 10mg + Met	323	80.8%	85.1%	5.9%	5.3%	2.2%	0.0%	5.8%	
Saxa 10mg	335	67.2%	85.4%	19.1%	3.6%	2.4%	0.0%	7.8%	
Metformin	328	74.1%	81.1%	9.1%	4.0%	3.4%	0.6%	8.8%	

Source: Individual Study Reports, Table 5.1

Tables 7.17-7.21 summarize the specific AEs that led to discontinuation in the ST periods of the pooled monotherapy studies, individual add-on combination studies, and the initial combination with metformin study (all prior to rescue). Narratives for those SAEs listed in these tables that led to discontinuation were discussed in Section 7.3.2. Subjects who discontinued due to AEs of rash and thrombocytopenia are discussed under those specific safety sections (Section 7.3.5). Narratives for subjects who discontinued because of lymphopenia are included in this Section.

#### Pooled Monotherapy

In the pooled monotherapy studies, adverse events were spread across a variety of SOCs and PTs. The following subjects each had an AE of lymphopenia:

- Subject CV181011-172-818, a 59 year old female in the saxagliptin 5 mg group, began radiation therapy for prostate cancer on Day 78. His lymphocyte counts were normal until Day 114 ( $0.55 \times 10^3$  c/ $\mu$ L). Lymphocyte counts remained abnormal, and he was discontinued on Day 183. Other components of the subject's hematology profile were unremarkable.

**Reviewer comment: Although this subject seemingly had an underlying risk factor for lymphopenia, one would have expected concomitant hematological abnormalities.**

- Subject CV181038-55-496, a 61 year old female in the saxagliptin 2.5 mg group, was found to have uterine cancer on Day 121. She received daily radiation from Days 139 to 163. A lymphocyte count on Day 155 was  $0.74 \times 10^3$  c/ $\mu$ L. The subject's hematocrit was slightly decreased, but no other hematologic abnormalities were observed.

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**Table 7.17. Adverse Events Leading to Discontinuation from Study--Summary by SOC and PT During ST Period for Pooled Monotherapy Studies**

SOC (%)	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
PT (%)					
Total Subjects with AE	7 (2.8)	4 (1.6)	5 (5.1)	16 (2.7)	1 (0.6)
Blood and Lymphatic System Disorders	1 (0.4)	1 (0.4)	0	2 (0.3)	0
Lymphopenia	1 (0.4)	1 (0.4)	0	2 (0.3)	0
Eye Disorders	0	1 (0.4)	0	1 (0.2)	0
Eye Pain	0	1 (0.4)	0	1 (0.2)	0
Gastrointestinal Disorders	0	1 (0.4)	1 (1.0)	2 (0.3)	0
Dry Mouth	0	1 (0.4)	0	1 (0.2)	0
Pancreatitis	0	0	1 (1.0)	1 (0.2)	0
Nervous System Disorders	0	1 (0.4)	1 (1.0)	2 (0.3)	0
Headache	0	1 (0.4)	0	1 (0.2)	0
Burning Sensation	0	0	1 (1.0)	1 (0.2)	0
Renal and Urinary Disorders	0	1 (0.4)	0	1 (0.2)	0
Hematuria	0	1 (0.4)	0	1 (0.2)	0
Skin and Subcutaneous Tissue Disorders	2 (0.8)	1 (0.4)	1 (1.0)	4 (0.7)	0
Purpura	0	1 (0.4)	0	1 (0.2)	0
Rash	2 (0.8)	0	1 (1.0)	3 (0.5)	0
Cardiac Disorders	1 (0.4)	0	0	1 (0.2)	1 (0.6)
Coronary Artery Disease	0	0	0	0	1 (0.6)
Tachycardia	1 (0.4)	0	0	1 (0.2)	0
Infections and Infestations	2 (0.8)	0	0	2 (0.3)	0
Hepatitis C	1 (0.4)	0	0	1 (0.2)	0
Tinea Pedis	1 (0.4)	0	0	1 (0.2)	0
Injury, Poisoning, and Procedural Complications	1 (0.4)	0	0	1 (0.2)	0

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Wound	1 (0.4)	0	0	1 (0.2)	0
Investigations	1 (0.4)	0	1 (1.0)	2 (0.3)	0
Blood CPK increased	0	0	1 (1.0)	1 (0.2)	0
Blood CK Increased	1 (0.4)	0	0	1 (0.2)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.4)	0	0	1 (0.2)	0
Pain in Extremity	1 (0.4)	0	0	1 (0.2)	0
Neoplasms Benign, Malignant and Unspecified	1 (0.4)	0	0	1 (0.2)	0
Pancreatic Carcinoma	1 (0.4)	0	0	1 (0.2)	0
Respiratory, Thoracic, and Mediastinal Disorders	0	0	1 (1.0)	1 (0.2)	0
COPD	0	0	1 (1.0)	1 (0.2)	0

Source: Integrated Summary of Safety, Appendix 6.1.1

#### Add-on Combination Studies

In Study CV181014, AEs were also spread across a variety of SOCs and PTs. AEs of special interest that led to study discontinuation in saxagliptin-treated subjects included lymphopenia, thrombocytopenia, and rash. The following are narratives for subjects who discontinued due to lymphopenia in Study CV181014:

- Subject CV181014-97-261, a 67 year old male in the saxagliptin 5 mg + metformin group with a normal baseline lymphocyte count, had an AE of lymphopenia ( $0.62 \times 10^3$  c/ $\mu$ L) on Day 31. He also had an AE of prostate infection, fever blisters and UTI between Days 28 and 111 and was treated with antibiotics between Days 28 and 35 and again between Days 37 and 77. A repeat lymphocyte count on Day 36 was normal. Saxagliptin was restarted on Day 40. On Day 43, the lymphocyte decreased to  $0.58 \times 10^3$  c/ $\mu$ L. Saxagliptin was held again on Day 43 and the lymphocyte count was normal on Day 45. Study drug was not restarted. On Day 51, the lymphocyte count was  $0.82 \times 10^3$  c/ $\mu$ L and on Day 111 was  $1.03 \times 10^3$  c/ $\mu$ L.

**Reviewer comment: It is unclear whether these events were study drug-related. The subject had underlying illness and was treated with concomitant antibiotics.**

**Lymphocyte counts remained at the lower end of normal range even months after study drug was discontinued.**

- Subject CV181014-131-1479, a 67 year old female in the saxagliptin 10 mg + metformin group, had an AE of lymphopenia ( $0.70 \times 10^3$  c/ $\mu$ L, baseline  $1.0 \times 10^3$  c/ $\mu$ L) on Day 21. Study drug was stopped on Day 28, and lymphocyte counts returned to normal ( $1.51 \times 10^3$  c/ $\mu$ L) on Day 36. Study drug was resumed on Day 40. On Day 49, lymphocyte counts again decreased on  $0.77 \times 10^3$  c/ $\mu$ L. Study drug was permanently discontinued. Lymphocyte counts returned to, and remained, normal on Day 56.

**Reviewer comment: Given a lack of predisposing factors to this event and the clear recovery with study drug discontinuation, it is possible that this event was study-drug related.**

**Table 7.18. Adverse Events Leading to Discontinuation from Study--Summary by SOC and PT During ST Period for CV181014**

SOC (%) PT (%)	Saxa 2.5 mg + Met		Saxa 5 mg + Met		Saxa 10 mg + Met		All	
	N=192	N=191	N=181	N=564	N=179	Placebo + Met		
Total Subjects with AE	5 (2.6)	6 (3.1)	5 (2.8)	16 (2.8)	2 (1.1)			
Blood and Lymphatic System Disorders	0	2 (1.0)	1 (0.6)	3 (0.5)	0			
Lymphopenia	0	1 (0.5)	1 (0.6)	2 (0.4)	0			
Thrombocytopenia	0	1 (0.5)	0	1 (0.2)				
Gastrointestinal Disorders	1 (0.5)	2 (1.0)	0	3 (0.5)	0			
Diarrhea	1 (0.5)	1 (0.5)	0	2 (0.4)	0			
Nausea	0	1 (0.5)	0	1 (0.2)	0			
Investigations	1 (0.5)	0	2 (1.1)	3 (0.5)	1 (0.6)			
Blood creatinine Increased	1 (0.5)	0	1 (0.6)	2 (0.4)	0			
Blood CPK Increased	0	0	1 (0.6)	1 (0.2)	0			
Lymphocyte Count Decreased	0	0	0	0	1 (0.6)			
Psychiatric Disorders	1 (0.5)	1 (0.5)	1 (0.6)	3 (0.5)	0			
Major Depression	1 (0.5)	0	0	1 (0.2)	0			
Psychiatric Symptom	0	0	1 (0.6)	1 (0.2)	0			
Schizophrenia	0	1 (0.5)	0	1 (0.2)	0			
Infections and Infestations	2 (1.0)	0	0	2 (0.4)	0			
Diverticulitis	1 (0.5)	0	0	1 (0.2)	0			
Viral Infection	1 (0.5)	0	0	1 (0.2)	0			
Neoplasms Benign, Malignant and Unspecified	0	0	1 (0.6)	1 (0.2)	0			
Gastrointestinal Carcinoma	0	0	1 (0.6)	1 (0.2)	0			

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Skin and Subcutaneous Tissue Disorders	0	1 (0.5)	0	1 (0.2)	0
Rash	0	1 (0.5)	0	1 (0.2)	0
Nervous System Disorders	0	0	0	0	1 (0.6)
Headache	0	0	0	0	1 (0.6)
Respiratory, Thoracic, and Mediastinal Disorders	0	0	0	0	1 (0.6)
Cough	0	0	0	0	1 (0.6)

Source: Clinical Study Report, CV181014, Table 8.4

In Study CV181040, the saxagliptin 5 mg + glyburide group had the highest frequency of discontinuation due to AEs. AEs in the Skin SOC were the most common reason for discontinuation in saxagliptin-treated subjects. One subject discontinued due to an AE of lymphopenia:

- Subject CV181040-127-195, a 66 year old female in the saxagliptin 5 mg + glyburide group, had an AE of lymphopenia on Day 98 ( $0.92 \times 10^3$  c/ $\mu$ L). Study drug was discontinued on Day 112. There were no predisposing factors. Lymphocyte count on Day 126 was  $1.09 \times 10^3$  c/ $\mu$ L.

The following is the narrative for the subject with the AE of interest "weight increased":

- Subject CV181040-13-52, a 54 year old obese female in the saxagliptin 2.5 mg + glyburide group, had an AE of weight gain (6.4 lbs) on Day 169. On Day 189, she withdrew consent due to a total weight gain of 11 lbs. No other information was provided.

One subject, CV181040-29-235, was discontinued for elevated LFTs. This narrative was provided in Section 7.3.2.

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Table 7.19. Adverse Events Leading to Discontinuation of Study--Summary by SOC and PT During ST Treatment Period for Study CV181040				
SOC (%)	Saxa 2.5 mg + Gly N=248	Saxa 5 mg + Gly N=253	All Saxa N=501	Placebo + Gly N=267
PT (%)				
Total Subjects with AE	3 (1.2)	8 (3.2)	11 (2.2)	4 (1.5)
Skin and Subcutaneous Tissue Disorders				
Heat Rash	2 (0.8)	2 (0.8)	4 (0.8)	0
Pruritus	1 (0.4)	0	1 (0.2)	0
Rash Macular	1 (0.4)	0	1 (0.2)	0
Urticaria	0	1 (0.4)	1 (0.2)	0
Investigations	0	1 (0.4)	1 (0.2)	0
Blood CPK Increased	1 (0.4)	2 (0.8)	3 (0.6)	1 (0.4)
Liver Function Test Abnormal	0	1 (0.4)	1 (0.2)	0
Weight Increased	0	1 (0.4)	1 (0.2)	0
ALT Increased	1 (0.4)	0	1 (0.2)	0
AST Increased	0	0	0	1 (0.4)
Blood and Lymphatic System Disorders	0	0	0	1 (0.4)
Lymphopenia	0	1 (0.4)	1 (0.2)	0
Hepatobiliary Disorders	0	1 (0.4)	1 (0.2)	0
Acute Cholecystitis	0	1 (0.4)	1 (0.2)	0
Metabolism and Nutrition Disorders	0	1 (0.4)	1 (0.2)	0
Hypoglycemia	0	1 (0.4)	1 (0.2)	0
Renal and Urinary Disorders	0	1 (0.4)	1 (0.2)	0
Renal Failure	0	1 (0.4)	1 (0.2)	0
Cardiac Disorders	0	0	0	1 (0.4)

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Angina Pectoris	0	0	0	0	1 (0.4)
Psychiatric Disorders	0	0	0	0	2 (0.7)
Depression	0	0	0	0	2 (0.7)

Source: *Clinical Study Report, CV181040, Table 8.4*

In Study CV181013, the saxagliptin 5 mg + TZD group had the highest frequency of discontinuation due to AEs. AEs were spread across SOCs and PTs. One subject discontinued because of lymphopenia:

- Subject CV181013-108-742, a 72 year old female in the saxagliptin 5 mg + TZD group, had an AE of lymphopenia ( $0.66 \times 10^3$  c/ $\mu$ L, baseline  $0.83 \times 10^3$  c/ $\mu$ L) on Day 14. Study drug was interrupted. Counts remained low on Day 29 but then normalized on Day 38. Study drug was resumed on Day 40. On Day 43, lymphopenia was again reported ( $0.70 \times 10^3$  c/ $\mu$ L). Study drug was permanently discontinued on Day 48. Lymphocyte count on Day 66 returned to the lower end of normal ( $1.00 \times 10^3$  c/ $\mu$ L).

**Reviewer comment: In this subject with baseline low lymphocyte counts, it is unclear if study drug was an inciting factor in the further decreases observed.**

One subject in CV181013 had an AE of "weight increased":

- Subject CV181013-255-201, a 36 year old obese female in the saxagliptin 5 mg group +TZD, had a 7 kg weight gain from baseline to Day 170, at which time she discontinued from the study. No treatment was required.

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Table 7.20. Adverse Events Leading to Discontinuation of Study--Summary by SOC and PT During ST Treatment Period for Study CV181013					
SOC (%)	Saxa 2.5 mg + TZD N=195	Saxa 5mg + TZD N=186	All Saxa N=381	Placebo + TZD N=184	
PT (%)					
Total Subjects with AE	3 (1.5)	11 (5.9)	14 (3.7)	6 (3.3)	
Investigations	2 (1.0)	4 (2.2)	6 (1.6)	1 (0.5)	
Blood CPK Increased	1 (0.5)	2 (1.1)	3 (0.8)	0	
Hemoglobin Decreased	1 (0.5)	0	1 (0.3)	0	
Lymphocyte Count Decreased	0	1 (0.5)	1 (0.3)	0	
Weight Increased	0	1 (0.5)	1 (0.3)	1 (0.5)	
Blood and Lymphatic System Disorders	1 (0.5)	3 (1.6)	4 (1.0)	0	
Anemia	0	1 (0.5)	1 (0.3)	0	
Leukopenia	1 (0.5)	0	1 (0.3)	0	
Lymphopenia	0	1 (0.5)	1 (0.3)	0	
Neutropenia	0	1 (0.5)	1 (0.3)	0	
Musculoskeletal and Connective Tissue Disorders	1 (0.5)	1 (0.5)	2 (0.5)	0	
Musculoskeletal Pain	0	1 (0.5)	1 (0.3)	0	
Myalgia	1 (0.5)	0	1 (0.3)	0	
Skin and Subcutaneous Tissue Disorders	0	2 (1.1)	2 (0.5)	2 (1.1)	
Rash	0	2 (1.1)	2 (0.5)	1 (0.5)	
Erythema	0	0	0	1 (0.5)	
Neoplasms Benign, Malignant, and Unspecified	0	1 (0.5)	1 (0.3)	0	
Colon Neoplasm	0	1 (0.5)	1 (0.3)	0	
Cardiac Disorders	0	0	0	2 (1.1)	

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Angina Pectoris	0	0	0	0	1 (0.5)
Cardiac Failure Congestive	0	0	0	0	1 (0.5)
Gastrointestinal Disorders	0	0	0	0	1 (0.5)
Diarrhea	0	0	0	0	1 (0.5)
Vomiting	0	0	0	0	1 (0.5)

Source: *Clinical Study Report, CV181013, Table 8.4*

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In Study CV181039, the frequency of AEs leading to discontinuation was highest in the metformin alone group. The AEs in the metformin group were spread across a number of PTs and SOCs. There was one subject with an AE of lymphopenia:

- Subject CV181039-1139, a 61 year old male in the saxagliptin 10 mg/metformin 500 mg group, had an AE of lymphopenia on Day 56. He had concomitant AEs of upper respiratory infection and asthma exacerbation. On Day 60, the subject had fever and hypotension and was managed with antibiotics. The subject improved, but study drug was discontinued on Day 60.

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Table 7.21. Adverse Events Leading to Discontinuation from Study--Summary by SOC and PT During ST Treatment Period for Study CV181039					
SOC (%)	Saxa 5 mg + Met N=320	Saxa 10 mg + Met N=323	Saxa 10 mg N=335	All Saxa N=978	Met N=328
PT (%)					
Total Subjects with AE	8 (2.5)	7 (2.2)	8 (2.4)	23 (2.4)	11 (3.4)
Investigations	4 (1.3)	1 (0.3)	6 (1.8)	11 (1.1)	4 (1.2)
Blood Creatinine Increased	1 (0.3)	1 (0.3)	3 (0.9)	5 (0.5)	0
ALT Increased	3 (0.9)	0	1 (0.3)	4 (0.4)	1 (0.3)
AST Increased	2 (0.6)	0	1 (0.3)	3 (0.3)	0
Hepatic Enzyme Increased	0	0	1 (0.3)	1 (0.1)	0
Platelet Count Decreased	0	0	1 (0.3)	1 (0.1)	0
Blood CPK Increased	0	0	0	0	2 (0.6)
Transaminases Increased	0	0	0	0	1 (0.3)
Gastrointestinal Disorders	3 (0.9)	3 (0.9)	0	6 (0.6)	4 (1.2)
Dyspepsia	0	2 (0.6)	0	2 (0.2)	0
Diarrhea	1 (0.3)	0	0	1 (0.1)	2 (0.6)
Gastritis	1 (0.3)	0	0	1 (0.1)	0
Nausea	1 (0.3)	0	0	1 (0.1)	0
Pancreatitis Acute	0	1 (0.3)	0	1 (0.1)	0
Vomiting	1 (0.3)	0	0	1 (0.1)	0
Dry Mouth	0	0	0	0	1 (0.3)
Gastritis Erosive	0	0	0	0	1 (0.3)
Blood and Lymphatic System Disorders	0	2 (0.6)	0	2 (0.2)	0
Lymphopenia	0	1 (0.3)	0	1 (0.1)	0
Pancytopenia	0	1 (0.3)	0	1 (0.1)	0
Cardiac Disorders	0	1 (0.3)	0	1 (0.1)	0

**Table 7.21. Adverse Events Leading to Discontinuation from Study--Summary by SOC and PT During ST Treatment Period for Study CV181039**

Myocardial Infarction	0	1 (0.3)	0	1 (0.1)	0
Hepatobiliary Disorders	0	0	1 (0.3)	1 (0.1)	0
Hepatitis Alcoholic	0	0	1 (0.3)	1 (0.1)	0
Neoplasms Benign, Malignant, and Unspecified	1 (0.3)	0	0	1 (0.1)	0
Lymphoproliferative Disorders	1 (0.3)	0	0	1 (0.1)	0
Psychiatric Disorders	0	0	1 (0.3)	1 (0.1)	0
Psychotic Disorders	0	0	1 (0.3)	1 (0.1)	0
Congenital, Familial, and Genetic Disorders	0	0	0	0	1 (0.3)
Thalassemia	0	0	0	0	1 (0.3)
General Disorders and Administration Site Conditions	0	0	0	0	1 (0.3)
Chest Pain	0	0	0	0	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	0	0	0	0	1 (0.3)
Musculoskeletal Pain	0	0	0	0	1 (0.3)
Pain in Extremity	0	0	0	0	1 (0.3)
Nervous System Disorders	0	0	0	0	1 (0.3)
Cerebrovascular Accident	0	0	0	0	1 (0.3)
Reproductive System and Breast Disorders	0	0	0	0	1 (0.3)
Breast Pain	0	0	0	0	1 (0.3)
Respiratory, Thoracic, and Mediastinal Disorders	0	0	0	0	1 (0.3)
Dyspnea	0	0	0	0	1 (0.3)

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**Table 7.21. Adverse Events Leading to Discontinuation from Study--Summary by SOC and PT During ST Treatment Period for Study CV181039**

Skin and Subcutaneous Tissue Disorders	0	0	0	0	0	1 (0.3)
Dermatitis Allergic	0	0	0	0	0	1 (0.3)

Source: Clinical Study Report, CV181039

### 7.3.4 Significant Adverse Events

Adverse events leading to study discontinuation have already been discussed in Section 7.3.3., and SAEs leading to discontinuation were described in Section 7.3.2.

### 7.3.5 Submission Specific Primary Safety Concerns

This section contains a detailed discussion of special safety concerns. The Sponsor identified pre-defined subsets of AEs for skin disorders, lymphopenia, infections, hypoglycemia, thrombocytopenia, localized edema, and cardiovascular AEs. Criteria used by the Sponsor to identify these included:

- 1) they were of potential importance to antihyperglycemic agents in general (hypoglycemia, falls/trauma potentially related to hypoglycemia, cardiovascular AEs, abnormal liver tests);
- 2) they were considered relevant given the mechanism of action (lymphopenia, infections, localized edema, skin disorder);
- 3) due to nonclinical safety data (skin disorders);
- 4) they were noted as part of the safety profile of other DPP-4 inhibitors (liver abnormalities).

In addition, hypersensitivity reactions were added after completion of the Phase 3 program because of post-marketing reports of hypersensitivity reactions with Januvia. Finally, careful consideration was placed on monitoring absolute lymphocyte counts and platelet counts in the Phase 3 program after reductions in these parameters were noted in the Phase 2b study. For those topics below that contained multiple and lengthy analyses, overall conclusions can be found at the end of each topic.

#### Skin Disorders

Because some DPP-4 inhibitors, including saxagliptin, have been associated with necrotizing cutaneous lesions in monkeys, saxagliptin-treated subjects were monitored for similar findings in the clinical development program. Supplemental CRFs were used to gather additional information on skin-related AEs. A pre-defined MedDRA term list was generated, specific to the preclinical skin-related events. This list included 238 skin-related PTs, including skin ulceration and skin necrosis, with PTs drawn from a number of SOCs and appeared to be comprehensive. When AEs that were on this pre-defined list of PTs were reported, the supplemental CRF pages were distributed to Investigators to collect further information on the events, including location and appearance. The table below summarizes the frequencies of AEs in the SOC of Skin and Subcutaneous Disorders (not the pre-defined list) for the ST periods, prior to rescue therapy.

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
<b>Pooled Monotherapy</b> (CV181011, CV181038)	13.4% (33/247)	9.1% (23/252)	13.3% (13/98)	11.6% (69/597)	8.3% (14/169)
<b>Add-on Combination</b>					
+ 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)
<b>Up to Week 24, Regardless of Rescue Status</b>					
Placebo-controlled	9.3%	7.1%	12.2%	8.8%	7.3%
Pooled Safety	(82/882)	(63/882)	(34/279)	(179/2043)	(58/799)

*Source: Summary of Clinical Safety, Table 2.3.2.1A*

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

*Source: Summary of Clinical Safety, Table 2.3.2.1B*

Monotherapy studies

Although the frequency of AEs of Skin and Subcutaneous Disorders was higher in the all saxagliptin group compared to placebo, dose-dependent increases were not observed. Certain PTs appeared to drive the differences in skin-related events: rash (2.5% in all saxagliptin versus 0.6% in placebo) and contact dermatitis (1.2% in all saxagliptin versus 0% in placebo). Four subjects in the monotherapy studies had a skin-related AE or SAE (rash in 3 subjects, purpura in 1 subject) that led to discontinuation. All were in saxagliptin-treated subjects (2 in the 2.5 mg group, 1 in the 5 mg group, and 1 in the 10 mg group).

Add-on Combination Studies

Across the add-on combination studies, the frequency of AEs in the Skin and Subcutaneous Tissue Disorders SOC was somewhat higher in the all saxagliptin groups than the placebo groups. However, dose-dependent increases in AEs were not clearly observed, and the 5 mg dose generally did not appear to confer a greater risk of these AEs versus placebo when added to metformin (6.8% vs 7.8%), SU (4.7% vs 4.9%), or TZD (7.5% vs 6.0%), respectively.

Nine subjects had skin-related AEs that led to discontinuation (rash in 6 subjects, erythema, pruritus, and urticaria in 1 subject, each). Seven of the nine were treated with saxagliptin (2 with

2.5 mg and 5 with 5 mg) and 2 were treated with placebo, which is consistent with the approximately 3.5:1 ratio of saxagliptin-treated patients to placebo-treated patients.

Placebo-controlled Pooled Safety Analysis

This analysis again demonstrated a higher frequency of skin AEs in the saxagliptin 10mg group (12.2% vs. 7.3 % for placebo), but a comparable frequency in the saxagliptin 5mg group versus placebo (7.1% vs. 7.3%). There were no imbalances of PTs in the SOC of Skin and Subcutaneous Tissue Disorders in this analysis.

Initial Combination Study with Metformin

In the initial combination study with metformin, there was a higher frequency of AEs of Skin and Subcutaneous Tissue Disorders in the saxagliptin 10 mg group (4.2%) and saxagliptin 10 mg + metformin group (4.3%) relative to metformin monotherapy (2.7%). There were no imbalances of PTs in this SOC for these 3 treatment groups. There was one discontinuation in the metformin group due to allergic dermatitis.

Non-Core Phase 3 Studies

As in the Core Phase 3 studies, in Study CV181008 (Phase 2b), a dose relationship was not seen across the treatment groups, shown below. In the 0, 100 mg cohort (not included in table), 4/44 (9.1%) of subjects in the 100 mg group had AEs in the Skin and Subcutaneous Tissue Disorders SOC (which is consistent with the frequency of such events in the 2.5-40 mg groups), whereas none was observed in the placebo group.

Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	Saxa 20 mg	Saxa 40 mg	Placebo
14.5%	14.9%	7.9%	9.3%	13.5%	6.0%
(8/55)	(7/47)	(5/63)	(5/54)	(7/52)	(4/67)

*Source: Summary of Clinical Safety, Table 2.3.2.1C*

Finally, in CV181041 (MOA), there was one subject with an AE in the Skin and Subcutaneous Tissue Disorders SOC (rash). Study drug was not interrupted.

Analyses Based on Pre-defined Terms

Based on the pre-defined list of PTs developed to identify skin disorders that could potentially correlate to monkey toxicology findings (described above), the following tables were generated. Data for CV181039 (initial metformin therapy) are presented as a separate table. Overall, there were 6 pre-defined skin events in the Core Phase 3 Studies: 4 saxagliptin-treated subjects and 2 receiving comparator (1 placebo and 1 metformin). None of the events resulted in discontinuation of study drug. In addition, one subject in the Phase 2b study (CV181008-22-87) in the saxagliptin 20mg group had a skin ulcer. The pre-defined list did not include tongue ulceration, of which one case was identified in Study CV181039 (subject in the Saxagliptin 5mg + Metformin group).

**Table 7.25. Summary of Skin Disorders by PT During Double-blind Period up to Week 24, Regardless of Rescue Status (Pooled Safety Population)**

	Saxa 2.5mg N=882	Saxa 5mg N=882	Saxa 10mg N=279	All Saxa N=2043	Placebo N=799
Total Subjects with an Event	2 (0.2)	2 (0.2)	0	4 (0.2)	1 (0.1)
Skin Ulcer	1 (0.1)	2 (0.2)	0	3 (0.1)	1 (0.1)
Lip Ulceration	1 (0.1)	0	0	1 (<0.1)	0

**Table 7.26. Summary of Skin Disorders by PT During Double-blind Period up to Week 24, Regardless of Rescue Status for CV181039**

	Saxa 5mg + Met N=320	Saxa 10mg + Met N=323	Saxa 10mg N=335	All Saxa N=978	Metformin N=328
Total Subjects with an Event	0	0	0	0	1 (0.3)
Lip Ulceration	0	0	0	0	1 (0.3)

The following are narratives for the subjects represented in the tables above:

- Subject CV181038-67-854 was a 44 year old male in the **saxagliptin 2.5/5mg qAM** group who struck his foot on the edge of a cot with a resulting AE of “skin ulcer” in addition to fever and eosinophilia reported on Day 61. The ulcer was described as exudative, yellow, and with a soft consistency and rough texture. He was treated with antibiotics, and the event resolved on Day 110 while continuing on study medication.
- Subject CV181014-2-250 was a 54 year old female in the **saxagliptin 2.5 mg** group with a lip ulcer reported on Day 101. This was preceded by aphthous stomatitis of the tongue on Day 71. The lesion was described as an isolated raised, scaly, red, firm, rough ulcer in the middle of her bottom lip. The event resolved on Day 105 while continuing on study medication.
- Subject CV181013-90-177 was a 71 year old female in the saxagliptin 5 mg group with “worsening diabetic foot ulcer” on Day 110.
- Subject CV181013-29-237 was a 74 year old female in the **saxagliptin 5mg** group who had small skin ulcers on the right arm and abdomen reported on Day 150. Each measured 10mm x 10mm x 10mm and 5mm x 5mm x 5mm. They were described as flat, red, soft, and smooth. Treatment was not administered and biopsy was not performed. The event resolved on Day 159 while continuing on study medication.
- Subject CV181008-22-87 was a 50 year old white male in the **saxagliptin 20mg** group with a left foot skin ulcer reported on Day 80. This was treated with antibiotics and the event lasted for 33 days. The event resolved while continuing on study medication.
- Subject CV181008-3-2071 was a 54 year old white male in the **metformin monotherapy** group who had a lip ulcer on Day 42 that lasted for 31 days.

- Subject CV181014-164-703 was a 66 year old female in the **placebo group** who had a skin ulcer of the right calf on Day 91 and on Day 463. The lesion was described as isolated, scaly, violaceous, firm, and smooth. She was treated with a dermatological agent from Day 463 through Day 616, and the event was considered resolved on Day 616.

Skin-Related SAEs and AEs Leading to Discontinuation of Study Drug

The following table summarizes those subjects with skin-related SAEs or events that led to discontinuation. The day of onset of the event is listed as well. Discontinuation rates for these events were low. Overall, 4 subjects (0.5%), 6 subjects (0.5%), 1 subject (0.1%), and 3 subjects (0.3%) had an AE that led to discontinuation of study drug in the 2.5, 5, 10 mg, or comparator treatment groups, respectively. Two of these discontinuations were SAEs (CV181011-66-84, CV181013-129-63). The narrative for Subject CV181011-54-52, listed below with an AE of purpura, is included following the table.

<b>Table 7.27. Skin-Related SAEs and AEs Leading to Discontinuation of Study Drug—ST Period—Core Phase 3 Studies</b>			
<b>Subject Age/Gender/Drug (Dose)</b>	<b>AE/SAE/PT/Intensity</b>	<b>Onset Day/Duration</b>	<b>Action</b>
<b>Pooled Monotherapy, Excluding Rescue</b>			
CV181011-46-176 34/M/Saxa 2.5mg	AE Rash/Mild	Day 159/ 3 days	DC
CV181011-66-84 47/M/Saxa 2.5mg	SAE Rash/Severe	Day 57/ 8 days	DC
CV181011-54-52 65/M/Saxa 5mg	AE Purpura/Moderate	Day 125/ 13 days	DC
CV181011-100-915 52/F/Saxa 10mg	AE Rash/Mild	Day 86/ 91 days	DC
<b>Add-on Combination Studies, prior to any rescue therapy</b>			
<b>+ Met (CV181014)</b>			
CV181014-92-219 50/F/Saxa 5mg	AE/ Rash/Moderate	Day 7/ 375 days	DC
<b>+SU (CV181040)</b>			
CV181040-36-290 33/F/Saxa 2.5mg	AE/ Heat rash/Moderate	Day 160/ 11 days	DC
CV181040-37-228 68/F/Saxa 2.5mg	AE/ Pruritus/Moderate	Day 87/ Unknown	DC
CV181040-49-1894 55/F/Saxa 5mg	AE Urticaria/Moderate	Day 7/ 13 days	DC
CV181040-130-1905 73/F/Saxa 5mg	AE/ Rash macular/Moderate	Day 136/47 days	DC
<b>+TZD (CV181013)</b>			
CV181013-258-391	AE/	Day 36/	DC

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40/F/Saxa 5mg + TZD	Rash/Moderate	17 days	
CV181013-82-93	AE	Day 26/320 days	DC
30/F/Saxa 5mg + TZD	Rash/Mild		
CV181013-129-63	SAE/ Rash/Moderate	Day 36/15 days	DC
50/F/Placebo + TZD			
CV181013-150-1075	AE	Day 55/ 12 days	DC
48/F/Placebo + TZD	Erythema/Moderate		
<b>Initial Combination Study, Prior to any Rescue Therapy</b>			
CV181039-148-1830	SAE/ Dermatitis allergic/Severe	Day 15/10 Days	Interrupted
54/M/Saxa 5mg + Met			
CV181039-119-1499	AE/ Dermatitis allergic/Moderate	Day 33/34 13 days	DC
73/M/Met			

Abbreviations: DC=discontinued study drug

Subject CV181011-54-52, a 65 year old male in the saxagliptin 5 mg group, was reported to have an AE of follicular rash on Day 125. Study drug was interrupted on Day 129, and subsequent information reported this event to be pigmented purpura. Dermatopathology confirmed this diagnosis. The purpura reportedly resolved on Day 137; however this purpura recurred on Day 143. The subject was discontinued from the study. The Investigator reported the first event as possibly related to study drug, but the second as not likely related to study drug.

The following are narratives for subjects with SAEs:

- Subject CV181011-66-84 was a 47 year old male in the saxagliptin 2.5 mg group who experienced an SAE of “rash-torso worsening” on Day 57. He had a history of right leg cellulitis and psoriasis. The rash was described as flat, red macules on the trunk and arms. The Investigator reported that the rash was similar to the subject’s history of psoriasis. On Day 58, the subject also had an SAE of “worsening of wound right lower leg”. He was hospitalized and study drug was discontinued. While hospitalized, a punch biopsy of the left arm was performed, with a microscopic diagnosis of “spongiotic dermatitis, probably spongiotic drug eruption.” The events resolved on Day 64 after treatment with antibiotics and steroid cream. The discharge diagnoses were cellulitis and drug rash. The Investigator considered the events as not likely related to study drug.

**Reviewer comment: Although the history of psoriasis in this subject confuses the picture, the microscopic diagnosis appears to support the hypothesis that the macular rash was drug-related.**

- Subject CV181013-129-63 was a 50 year old female in the placebo group (background pioglitazone 20mg) who experienced a rash on Day 36. At that time, she complained of itchiness on her face and noted a forearm rash, described as raised, vesicular, and linear. The lesions were extremely pruritic and photosensitive. The subject reported working in her yard a few days earlier. The Investigator thought this was consistent with contact dermatitis, but believed to be worsening on study drug, which was discontinued on Day 36. After one week off study drug and treatment with diphenhydramine, the lesions worsened and changed from vesicular to bullous. Treatment with prednisone and

antibiotics was initiated. The event resolved on Day 60. The Investigator considered the event probably related to study drug.

**Reviewer comment: The etiology of the rash in this subject is unclear, although the localized findings and recent history of yard work raise the possibility of a contact dermatitis.**

- Subject CV181039-148-1830 was a 54 year old male in the saxagliptin 5 mg/Metformin 500mg group who was reported to have an allergic skin reaction on Day 15, 6 days after having been started on simvastatin therapy. The rash was described as punctuate on the body and face. He was hospitalized on Day 18 at which time simvastatin was discontinued. Study drug was interrupted on Day 22. Inpatient treatment included intravenous steroids. The event resolved on Day 24. He was restarted on study drug on Day 28 and had no further rash. The Investigator considered the event unrelated to study drug but “certainly” related to simvastatin.

**Reviewer comment: Given the rechallenge of study drug without further rash, it seems unlikely that this event was related to saxagliptin.**

#### Additional Analyses Requested by FDA

Recognizing that the term “rash” appears under multiple SOCs and appears within multiple PTs (i.e. rash papular, rash macular, rash generalized), the Division requested that the Sponsor submit an additional analysis of all rash terms in the Phase 3 program. For All Phase 3 studies during the ST period, the frequency of rash was 2.1% in the all saxagliptin group versus 1.2% in the placebo group. This was driven mainly by the singular PT “rash”. The following table presents the frequency of AEs of all rash terms for the placebo-controlled studies for the ST + LT periods. Since the frequency of rash terms under SOCs other than “Skin and Subcutaneous Tissue Disorders” was very small, only events in this SOC are shown. Using this analysis, the highest frequency of AEs was seen in the 10 mg group vs. placebo (6.8% vs. 2.2%). Once again, this was mainly driven by the single PT “rash”. Sample size in the 10mg group was significantly lower than in all other groups.

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
SOC (%)					
PT (%)	N=882	N=902	N=279	N=2063	N=815
Total Subjects with any rash AE	29 (3.3)	34 (3.8)	19 (6.8)	82 (4.0)	18 (2.2)
Skin and Subcutaneous Tissue Disorders	25 (2.8)	32 (3.5)	19 (6.8)	76 (3.7)	15 (1.8)
Rash	17 (1.9)	23 (2.5)	14 (5.0)	54 (2.6)	11 (1.3)
Rash Papular	0	7 (0.8)	4 (1.4)	11 (0.5)	1 (0.1)
Rash Macular	1 (0.1)	2 (0.2)	1 (0.4)	4 (0.2)	2 (0.2)
Rash Maculo-Papular	2 (0.2)	2 (0.2)	0	4 (0.2)	1 (0.1)
Rash Erythematous	2 (0.2)	1 (0.1)	0	3 (0.1)	1 (0.1)
Heat Rash	1 (0.1)	0	0	1 (<0.1)	0
Rash Generalised	0	0	1 (0.4)	1 (<0.1)	1 (0.1)

Rash Pruritic	2 (0.2)	0	2 (0.7)	4 (0.2)	0
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Source: Response to FDA Questions Received on 19-Dec-2008, Table Q1.21

Conclusions regarding Skin Disorders:

- Higher frequencies of rash-related AEs were seen in saxagliptin-treated subjects versus comparator groups in all analyses.
- The highest rates of skin-related AEs were seen in the saxagliptin 10 mg groups.
- The single PT term “rash” primarily drove the increase seen in the saxagliptin 10 mg group.
- Although the highest number of AEs was generally seen in the 10 mg groups, a dose-dependent increase in events was not clearly seen among the 2.5 mg and 5 mg groups.
- Frequencies of pre-defined events intended to capture AEs related to non-clinical findings were very low.

Lymphocytes:

Given that DPP-4 and CD-26 are identical, theoretical risks of lymphocyte effects and infection exist. Because of this, as well as changes in absolute lymphocyte counts that were initially noted in Phase 1 and 2 clinical studies of saxagliptin, the Sponsor performed a variety of analyses related to changes in lymphocyte counts. A number of these analyses are presented in this section.

Percent and Mean Change from Baseline Analyses:

As shown in the table below, the percent change from baseline in absolute lymphocyte count was comparable for the saxagliptin 2.5, 5 mg, and placebo groups at 6, 12, 18, and 24 months of follow-up in the Pooled Monotherapy Analysis. However, saxagliptin 10 mg had a statistically significant decrease in absolute lymphocytes of approximately 10% at 12 months compared with baseline. At 18 months, a decrease in mean absolute lymphocyte count was seen in both the saxagliptin 10 mg group and placebo groups, although, at this timepoint, the median decreases were similar across all saxagliptin groups and the placebo group. At 24 months, only the saxagliptin 10 mg group had a statistically significant decrease in mean counts. The decrease in saxagliptin 10 mg group was comparable at 12 and 24 months.

	Treatment Group	N =	Percent Change from Baseline			
			Mean	SE	Median	95% CI
6 months (Week 24)	Saxa 2.5mg	194	3.17	2.353	0.22	-1.47, 7.81
	Saxa 5mg	195	-2.17	1.762	-3.78	-5.64, 1.31
	Saxa 10mg	78	-3.99	2.447	-5.49	-8.86, 0.88
	All Saxa	467	-0.25	1.295	-2.33	-2.8, 2.29
	Placebo	133	4.48	2.73	-1.66	-0.92, 9.88
12 months (Week 50)	Saxa 2.5mg	96	1.29	3.941	-3.5	-6.54, 9.11

	Saxa 5mg	99	-1.77	2.305	-2.74	-6.35, 2.8
	Saxa 10mg	71	-9.34	2.37	-11.29	-13.87, -4.82
	All Saxa	266	-2.69	1.781	-5.53	-6.19, 0.82
	Placebo	80	1.04	2.346	0	-3.63, 5.71
18 months (Week 76)	Saxa 2.5mg	51	2.39	5.946	-4.21	-9.55, 14.33
	Saxa 5mg	60	-0.67	3.284	-3.9	-7.25, 5.9
	Saxa 10mg	63	-6.34	2.749	-7.57	-11.84, -0.85
	All Saxa	174	-1.83	2.306	-5.53	-6.38, 2.72
	Placebo	49	-7.54	2.676	-6.79	-12.92, -2.16
24 months (Week 102)	Saxa 2.5mg	22	-4.34	4.868	-5.89	-14.46, 5.79
	Saxa 5mg	35	2.01	5.669	-4.03	-9.52, 13.53
	Saxa 10mg	40	-8.21	2.847	-10.68	-13.97, -2.45
	All Saxa	97	-3.64	2.618	-8.28	-8.84, 1.55
	Placebo	26	-5.38	3.686	-1.43	-12.97, 2.21

Source: Summary of Clinical Safety, Table 3.1A1

**Reviewer comment:** In the table above, it is important to note that the sample size for all groups, particularly the saxagliptin 2.5 mg group, became significantly smaller by 24 months. This limits the analysis at further time points.

An analysis of the absolute lymphocyte count for the placebo-controlled Pooled Safety analysis through Week 24 is presented below. In the 2.5 mg and placebo groups, the percentage change from baseline in lymphocyte count was an approximately 3% increase (upper panel). The CI for the saxagliptin 2.5 mg, 10 mg, and placebo groups did not cross zero. Mean decreases of approximately 2 % and 4.5% were seen for the 5 mg and 10 mg groups, respectively. For the mean change in absolute lymphocyte count (bottom panel), the CI included zero for the saxagliptin 2.5 mg and placebo groups. The saxagliptin 5 mg and 10 mg groups had mean decreases of 110c/ $\mu$ L and 130c/ $\mu$ L, respectively. Baseline absolute lymphocyte values ranged from 2190 to 2260. As reference, the baseline in the 5 mg was 2200c/ $\mu$ L.

<b>Table 7.30. Mean and Percent Change from Baseline in Absolute Lymphocyte Counts (<math>\times 10^3</math> c/<math>\mu</math>L)--Placebo-controlled Pooled Safety Analysis at Week 24 Regardless of Rescue - Completers</b>						
<b>Mean and Percent Change</b>						
<b>Percent Change from Baseline</b>						
	Treatment Group	N =	Percent Change from Baseline			
			Mean	SE	Median	95% CI
6 months (Week 24)	Saxa 2.5mg	434	3.06	1.450	-1.64	0.21, 5.91
	Saxa 5mg	445	-2.23	1.160	-7.34	-4.51, 0.05
	Saxa 10mg	137	-4.43	1.643	-7.34	-7.67, -1.18
	All Saxa	1016	-0.27	0.835	-4.12	-1.90, 1.37
	Placebo	394	2.90	1.375	-0.88	0.19, 5.60
<b>Mean Change from Baseline</b>						
	Treatment Group	N =	Mean Change from Baseline			
			Mean	SE	Median	95% CI
6 months (Week 24)	Saxa 2.5mg	434	-0.00	0.026	-0.04	-0.05, 0.05
	Saxa 5mg	445	-0.11	0.025	-0.11	-0.16, -0.06
	Saxa 10mg	137	-0.13	0.036	-0.15	-0.20, -0.06
	All Saxa	1016	-0.07	0.017	-0.09	-0.10, -0.03
	Placebo	394	-0.01	0.028	-0.02	-0.06, 0.05

Summary of Clinical Safety, Table 3.1A2

The Sponsor explored the effects of longer-term use of saxagliptin on absolute lymphocyte counts by studying the population in the add-on combination study with metformin (ST + LT), shown in the table below. This population was selected as it had the greatest number of subjects with treatment through 2 years. As was observed in the Pooled Monotherapy analysis, saxagliptin 10 mg was associated with a decrease in mean absolute lymphocyte count of approximately 10% at 12 months compared with baseline. This was also seen at 18 and 24 months, though less marked compared to placebo, which also demonstrated decreases in counts. For the 10 mg group at Months 12 and 24, these results were not inconsistent with those seen in the Pooled Monotherapy Analysis.

<b>Table 7.31. Absolute Lymphocyte Count (<math>\times 10^3</math>) in the Add-on Combination Study with Metformin (ST + LT)--Percent Change from Baseline - Completers</b>						
	Treatment Group	N	Percent Change from Baseline			
			Mean	SE	Median	95% CI
6 months (Week 24)	Saxa 2.5mg	162	6.58	2.306	1.28	2.03, 11.13
	Saxa 5mg	160	1.93	1.862	0.02	-1.75, 5.61
	Saxa 10mg	157	-2.64	1.603	-6.77	-5.81, 0.52
	Placebo	135	3.56	2.390	0.38	-1.17, 8.29
12 months (Week 50)	Saxa 2.5mg	150	-2.91	1.716	-5.19	-6.30, 0.49
	Saxa 5mg	142	-4.6	1.810	-6.85	-8.18, -1.02

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	Saxa 10mg	145	-9.62	1.989	-14.29	-13.55, -5.69
	Placebo	124	-2.41	1.841	-3.11	-6.05, 1.24
<b>18 months (Week 76)</b>	Saxa 2.5mg	134	-2.17	2.122	-5.82	-6.36, 2.03
	Saxa 5mg	127	-7.5	1.785	-7.86	-11.03, -3.97
	Saxa 10mg	129	-11.52	1.776	-14.17	-15.03, -8.01
	Placebo	93	-5.06	2.249	-6.25	-9.53, -0.59
<b>24 months (Week 102)</b>	Saxa 2.5mg	76	-3.53	2.764	-5.29	-9.04, 1.97
	Saxa 5mg	72	-1.79	3.262	-8.53	-8.30, 4.71
	Saxa 10mg	82	-11.29	2.021	-13.74	-15.31, -7.27
	Placebo	50	-7.25	3.155	-7.99	-13.60, -0.91

Source: Summary of Clinical Safety, Table 3.1B

#### Marked Abnormalities (MAs):

The table below presents the MAs for absolute lymphocyte counts ( $\leq 0.75 \times 10^3$ ) in ST + LT periods of the Phase 2/3 studies, independent of baseline values. As has been the Sponsor's convention, the saxagliptin 2.5 mg group included subjects who were uptitrated to 5 mg or 10 mg and the saxagliptin 5 mg group included subjects who were uptitrated to 10 mg in CV181038. There were a total of 45 saxagliptin-treated subjects whose laboratory values met pre-defined MA criteria. This includes 3 subjects, not represented by individual group below but represented in the "all saxa" column, who were in the saxagliptin 20 mg (2 subjects) and 40 mg (1 subject) groups of CV181008. Overall, there appears to be a higher frequency of MAs for absolute lymphocyte count for saxagliptin-treated subjects versus placebo. There also appears to be comparable frequencies of MAs between the 5 mg and 10 mg groups.

	n/N (%)					
	Saxa 2.5mg	Saxa 5mg	Saxa 10mg	All Saxa	Placebo	Metformin
N=	937	1269	1066	3422	923	328
n/N (%)	8/924 (0.9)	19/1255 (1.5)	15/1046 (1.4)	45/3374 (1.3)	5/911 (0.5)	0

Source: Integrated Summary of Safety, Appendix 8.5.1

The following table below focuses on the 50 subjects with MAs (45 saxagliptin-treated and 5 placebo) presented in the table above. Here, MAs of absolute lymphocyte count are organized according to subjects' baseline counts. Furthermore, the Sponsor arbitrarily divided the normal range of absolute lymphocyte count into low, medium, and high categories. These data indicate that most saxagliptin-treated subjects with MAs for absolute lymphocyte counts had normal, but within the lower end of normal, baseline counts. Notably, of the 7 saxagliptin-treated subjects with baseline counts  $\geq 2.0 \times 10^3$  c/ $\mu$ L, 6 had an isolated decrease in counts, defined by a one time decrease that met MA criteria, but then recovered to  $>LLN$  and did not decline below the  $LLN$  for the remainder of the study.

Range Values (x 10 <sup>3</sup> c/ $\mu$ L)	Subjects n (%)

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		All Saxa N=3374	Comparator N=1228
<b>Total Subjects Meeting MA Criteria for Absolute Lymphocyte Count</b>		<b>45 (1.3)</b>	<b>5 (0.4)</b>
Values in the Normal Range at Baseline	3.0-4.0	0	1
	2.0-2.99	7	1
	1.0-1.99	29	2
Value Below the Normal Range at Baseline	<LLN   <1.0	9	1

Source: Summary of Clinical Safety, Table 3.1K

Furthermore, among the 50 subjects with MAs for absolute lymphocyte counts, 20 (40%, 16 saxagliptin-treated and 4 comparator-treated subjects) had an isolated decrease in counts. Beginning with the Phase 3 program, an algorithm for absolute lymphocyte count was implemented in each core Phase 3 study that required further monitoring, interruption or discontinuation of study drug. Within this group of subjects with an isolated MA, the Sponsor reports that this algorithm resulted in interruption of study drug in 10 subjects and only one discontinuation overall, a subject in the placebo group.

In the Phase 2/3 program, thirty subjects overall (60%, 29 saxagliptin-treated and 1 placebo; 5 subjects in Phase 2b study, 25 in Phase 3 studies) had a non-isolated decline in absolute lymphocyte count. The majority of these subjects (96.7%) had baseline absolute lymphocyte counts of at the lower end of the normal range (1.0-1.99 x 10<sup>3</sup>) or below the LLN at baseline. Of the 30 subjects with non-isolated declines, 14 subjects interrupted study drug and 9 discontinued. Study drug was resumed in 12 of the 14 interruptions; 2 of the subjects who interrupted discontinued the study for other reasons. There were no discontinuations in the Phase 2b study due to lymphocyte MAs. The following lists the discontinuations by treatment group in the Phase 3 studies. At the time of NDA submission, there were an additional 2 discontinuations in the LT period (one each in the 5mg and 10mg groups). Discontinuations due to lymphopenia have been discussed in Section 7.3.3.

**Table 7.33. Lymphopenia AEs that Led to Discontinuation of Study Drug during the Double-Blind Period up to Week 24, Regardless of Rescue-- Placebo-controlled Pooled Safety Analysis**

Saxa 2.5mg N=882	Saxa 5mg N=882	Saxa 10mg N=279	All Saxa N=2043	Placebo N=799
1 (0.1)	4 (0.5)	1 (0.4)	6 (0.3)	0 (0.0)

Source: Summary of Clinical Safety, Table 2.1.4.1C

Regarding the above-mentioned 12 subjects who interrupted and resumed study drug, 3 had a MA recurrence.

Assessment of Possible Clinical Correlations of Reduced Lymphocyte Count and Infection-related AEs

The Sponsor addressed the potential clinical correlation between a reduction in absolute lymphocyte count and infection with several analyses focusing on those subjects with non-isolated declines. In saxagliptin's clinical development program, AEs in the Infection SOC were the most commonly reported AE, exceeding 50% in some studies' ST + LT periods.

Importantly, another DPP4 inhibitor, Januvia®, has been associated with an increased frequency of certain infection-related AEs, unrelated to lymphopenia.

Among the 30 subjects with non-isolated declines in absolute lymphocyte count, approximately 50% (16) had an infection-related AE at any time during the ST + LT period and approximately 50% (14) did not. Of the 16 with an infection-related AE, 11 had a temporal relationship (within 30 days of the MA value or other values <LLN). Importantly, all 11 had a baseline absolute lymphocyte count below LLN or in the low-normal range.

Infection-related AEs traditionally associated with T-cell dysfunction

The Sponsor reviewed the frequency of viral, bacterial, or serious fungal infections across all Phase 2/3 studies. Infections selected as potentially associated with T-cell dysfunction included: herpes virus, varicella, EBV, CMV, tuberculosis, and serious fungal infections. Frequencies of these infections, if applicable, are shown in the table below for subjects across Phase 2/3 studies.

Preferred Term	Subjects n (%)	
	All Saxa N=3422	Comparator N=1251
Herpes zoster	15 (0.44)	3 (0.24)
Oral herpes	14 (0.41)	5 (0.40)
Genital herpes	1 (0.03)	0 (0)
Herpes simplex	0 (0)	0 (0)
Pulmonary tuberculosis	1 (0.03)	0 (0)
Herpes ophthalmic	0 (0)	1 (0.08)
Herpes virus infection	1 (0.03)	0 (0)
<b>Total</b>	<b>32 (0.94)</b>	<b>9 (0.72)</b>

Source: Summary of Clinical Safety, Table 3.1.1

As a reference, the incidence of tuberculosis in the United States is 4.6 per 100,000 population (.004%), compared with the frequency of 0.03 seen in the Phase 2/3 studies, although the low event rate (a single case) limits meaningful conclusions. None of the events listed above were SAEs. However, the subject with pulmonary tuberculosis (TB) discontinued because of this AE that occurred on Day 284. She was a 51 year old woman from the Philippines with no previous history of TB. Importantly, she did not have any reported lymphopenia.

Among the infections listed in the table above, there were only 2 subjects with an AE or MA of lymphopenia. One of these subjects, in the saxagliptin 5mg group, had an AE or oral herpes between Days 31 and 45 and a concomitant AE of lymphopenia during that time period, with a nadir count on Day 43 of 0.58 (baseline 1.15 x 10<sup>3</sup> μL). This same subject also had a concomitant AE of prostate infection between Days 28 and 111, for which he received antibiotics between Days 28 and 77. The second subject, in the saxagliptin 5mg group, had an AE of herpes zoster between Days 275 and 330 and an MA for absolute lymphocyte count (0.67 x 10<sup>3</sup> c/ μL) on Day 1, prior to the first dose of study drug. This subject also had decreased

absolute lymphocyte counts (no AE reported) on Days 169 and 260 ( $0.85 \times 10^3$  c/  $\mu$ L and  $0.8 \times 10^3$  c/  $\mu$ L, respectively). The absolute lymphocyte count was normal on Day 274.

There was no increase in overall fungal infections (non-serious AEs) seen in the Placebo-Controlled Pooled Safety Population or in the Initial Combination Study with metformin.

#### Flu-like Syndrome Observed with Saxagliptin 100mg Dose in Clinical Pharmacology Studies

A flu-like syndrome was observed in a significant number of subjects in 2 drug-drug interaction studies (CV181005 and CV181017) following a second dose of saxagliptin 100 mg 1 to 2 weeks after the first dose. This was seen in 5 of 15 subjects in 1 study and 4 of 16 subjects in the other. All subjects who experienced this syndrome also had absolute lymphocyte counts below the lower limit of normal; lymphocyte counts did return to baseline values within 72 hours of the second 100 mg dose. Subjects who did not experience the syndrome also had decreased counts, although less in severity than their counterparts with signs and symptoms.

To study this phenomenon, the Sponsor conducted 2 studies (CV181022 and CV181031) which used daily and/or interrupted 5 to 40 mg doses of saxagliptin or 20 mg saxagliptin plus ketoconazole (used in CV181005). In these studies, the flu-like syndrome seen with interrupted saxagliptin 100 mg doses was not seen. Transient decreases in lymphocyte count were seen at the highest doses studied (saxagliptin 40 mg in CV181031).

The flu-like syndrome has not been observed with doses studied in the Phase 3 program, including 2.5, 5, and 10 mg daily for 2 years.

#### Conclusions regarding changes in lymphocyte count:

- For the Pooled Monotherapy Analysis, saxagliptin 10 mg had a statistically significant decrease in absolute lymphocytes of approximately 10% at 12 months and of approximately 8% at 24 months compared to baseline. A significant decrease was seen in both the saxagliptin 10 mg and placebo groups at 18 months.
- For the Placebo-controlled Pooled Safety Analysis, saxagliptin 10 mg had a significant decrease in absolute lymphocytes of approximately 4.5% at 6 months compared to baseline with a mean decrease of 130 c/ $\mu$ L.
- In the add-on combination study with metformin, saxagliptin was associated with a decrease in absolute lymphocytes of approximately 10% at 12 months as well as smaller decreases at 18 and 24 months.
- For the Pooled Analysis of Phase 2/3 studies, there were 45 subjects (1.3%) with MAs for absolute lymphocyte count, defined as  $\leq 0.75 \times 10^3$ , compared to 5 (0.5%) in the placebo population. The saxagliptin 5 mg and 10 mg groups had similar frequencies of these MAs.
- For the Pooled Analysis of Phase 2/3 studies, most subjects with MAs for absolute lymphocyte counts had baseline counts which were at the lower end of normal or below the LLN.
- Twenty subjects (40%, saxagliptin and placebo-treated) with MAs for absolute lymphocyte counts had an isolated decrease in counts.

- Of the 30 subjects (60%) with a non-isolated decrease in counts, 7 subjects discontinued the study because of this MA. Most of these discontinuations were in the saxagliptin 5 mg group.
- Of the subjects with a non-isolated decrease in counts, approximately 50% were associated with an infection-related AE during the ST or LT periods. The majority of these exhibited a temporal relationship with the MA. However, AEs in the Infection SOC were the most commonly reported AE in the saxagliptin clinical development program, and the incidence of infection-related AEs in patients with reduced lymphocyte count was consistent with the incidence of infection-related AEs in the overall Phase 2/3 program.
- The Sponsor assessed for infections traditionally associated with T-cell dysfunction. A significant trend in saxagliptin-treated subjects was not found.
- Although a flu-like syndrome associated with decreased lymphocyte counts was observed in subjects exposed to doses of saxagliptin 100 mg, this has not been observed with doses studies in the phase 3 program, including the proposed dose of 5 mg.

### Infections

As discussed in Section (lymphocyte abnormalities), because DPP-4 and CD-26 are identical, infections were considered an event of special interest because of the theoretical risks associated with this. Supplemental CRFs were used to gather additional information about infection-related AEs. Overall, in the Core Phase 3 studies, there were more AEs in the SOC of Infections and Infestations than any other individual MedDRA SOC.

Table 7.35 presents the frequencies of AEs in the SOC of Infections and Infestations during the ST periods of the monotherapy and add-on combination studies.

In the Pooled Monotherapy population, the frequency of AEs in this SOC was higher in saxagliptin-treated subjects versus placebo. The highest frequency was seen in the saxagliptin 10 mg group (38.8%). PTs that were more frequent (>1%) for the all saxagliptin group versus placebo included: UTI (4.7% vs. 3.6%), sinusitis (4.2% vs. 1.8%), gastroenteritis (1.3% vs 0%), influenza (2.3% vs. 0.6%), and bronchitis (1.7% vs. 0%). In the pooled monotherapy analysis, 2 saxagliptin-treated subjects discontinued the study because of an infection-related AE (hepatitis C and tinea pedis). Four saxagliptin-treated subjects in this analysis had a total of 5 infection-related SAEs: cellulitis, gastroenteritis, hepatitis C, pyelonephritis, and pneumococcal sepsis. Narratives for these subjects can be found in Section 7.3.2. No subjects in the placebo group had an infection that was serious or led to discontinuation.

In the add-on combination studies, higher frequencies of infection-related AEs were seen in the all saxagliptin groups relative to placebo, except in the add-on to sulfonylurea study, where comparable frequencies were observed. In Study CV181014, PTs that were more frequent (>1%) for the all saxagliptin group versus placebo included: URI (6.6% vs. 5.0%), furuncle (1.2% vs. 0%), and viral gastroenteritis (1.1% vs. 0%). Infection-related AEs led to study discontinuation in 2 saxagliptin-treated subjects. There were 3 subjects (0.5%) with infection-related SAEs versus 1 placebo subject (0.6%). In Study CV181040, only gastroenteritis was

more frequent (>1%) versus placebo (2.8% vs. 0%). No infection-related AEs led to discontinuation. There were 2 infection-related SAEs in saxagliptin-treated subjects (0.4% each) versus one in a placebo subject (0.4%). In CV181013, the following PTs were more frequent (>1%) in saxagliptin-treated subjects: URI (8.4% vs. 7.1%), sinusitis (3.1% vs. 0.5%), and viral infection (1.6% vs 0%). There were no infection-related discontinuations. SAEs related to infection were reported for 2 saxagliptin-treated subjects (0.5% each) and 2 placebo subjects (1.1% each).

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
<b>ST Period, Excluding Rescue</b>					
<b>Pooled Monotherapy</b> (CV181011, CV181038)	30.4% (75/247)	29.8% (75/252)	38.8% (38/98)	31.5% (188/597)	23.7% (40/169)
<b>Add-on Combination</b>					
+ Met (CV 181014)	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)
<b>Up to Week 24, Regardless of Rescue Status</b>					
<b>Placebo-controlled</b>	36.4%	35.9%	40.1%	36.7%	34.8%
<b>Pooled Safety</b>	(321/882)	(317/882)	(112/279)	(750/2043)	(278/799)

Source: Summary of Clinical Safety, Table 2.3.3.1A

Table 7.36 summarizes the frequencies of AEs in the SOC of Infections and Infestations during the ST period of the Initial Combination Study with metformin. The highest frequency of AEs was seen in the saxagliptin 10 mg monotherapy group, while the lowest was seen in the saxagliptin 10mg + metformin group. AEs that were more frequent (>1%) in the all saxagliptin group versus placebo were: URI (3.5% vs. 1.8%), bronchitis (2.2% vs. 0%), and rhinitis (1.4% vs. 0.3%). No infection-related AE led to discontinuation. There were 4 infection-related SAEs in saxagliptin-treated subjects (0.4%). There were no SAEs in the metformin alone-treated subjects.

Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	All Saxa	Met
22.80%	20.10%	26.60%	23.20%	23.50%
(73/320)	(65/323)	(89/335)	(227/978)	(77/328)

Source: Summary of Clinical Safety, Table 2.3.3.1B

Table 7.37 summarizes subjects with infection-related SAEs or events that led to discontinuation of study drug during the ST periods of the Core Phase 3 studies.

<b>Table 7.37. Subjects with Infection-related SAEs or Events Leading to Discontinuation of Study Drug During ST Period of Core Phase 3 Studies</b>			
<b>Subject</b>	<b>AE/SAE/</b>	<b>Onset</b>	<b>Action/</b>
<b>Age/Gender/Drug (Dose)</b>	<b>PT/Intensity</b>	<b>Day/ Duration</b>	<b>Relationship (as assessed by Investigator)</b>
<b>Pooled Monotherapy, Excluding Rescue</b>			
CV181011-9-147	SAE/	Day 84/	Continued/
56/M/Saxa 2.5 mg	Gastroenteritis/Moderate Pyelonephritis/Moderate	4 days	Unrelated
CV181011-142-670	SAE/	Day 15/	Discontinued/
68/F/Saxa 2.5 mg	Hepatitis C/Moderate	Unknown	Unrelated
CV181038-85-572	SAE/	Day 54/	Continued/
	Pneumococcal sepsis/Very severe	1 day	Unrelated
CV181038-67-164	SAE/	Day 94/	Continued/
56/M/Saxa 2.5 mg	Cellulitis/Severe	15 days	Probably related
CV181038-67-346	AE/	Day 156/	Discontinued/
54/M/Saxa 2.5 mg	Tinea pedis/Moderate	28 days	Unrelated
<b>Add-on Combination, Excluding Rescue</b>			
<b>+ Met (CV181014)</b>			
CV181014-25-1463	AE/	Day 22/	Discontinued/
68/F/Saxa 2.5 mg	Viral infection/Moderate	6 days	Unlikely
CV181014-134-1022	SAE	Day 48/	Discontinued/
62/F/Saxa 2.5 mg	Diverticulitis/Very severe	16 days	Unlikely
CV181014-176-883	SAE/	Day 33/	Discontinued/
74/F/Saxa 2.5 mg	Breast abscess/Mild	11 days	Unrelated
CV181014-135-535	SAE/	Day 161/	Continued/
58/F/Saxa 5 mg	C. difficile colitis/Mild	19 days	Unrelated
CV181014/45/280	SAE/	Day 37/	Continued/
45/F/Placebo	Pneumonia/Mild	39 days	Unrelated
<b>+ SU (CV181040)</b>			
CV181040-129-1391	SAE/	Day 70/	Continued/
41/F/Saxa 2.5 mg	Appendicitis/Moderate	2 days	Unrelated
CV181040-36-716	SAE/	Day 75/	Continued/
64/M/Saxa 5 mg	Cellulitis orbital/Moderate	19 days	Unrelated
CV181040-36-573	SAE/	Day 50/	Continued/
71/F/Placebo	Pyelonephritis/Moderate	9 days	Unrelated
<b>+ TZD (CV181013)</b>			
CV181013-252-242	SAE/	Day 68/	Continued/
44/M/Saxa 2.5 mg	Perianal abscess/Severe	8 days	Unrelated
CV181013-37-75	SAE/	Day 47/	Interrupted/
21/F/Saxa 5 mg	Gastroenteritis/Severe	3 days	Unlikely
CV181013-150-584	SAE/	Day 153/	Interrupted/
55/M/Placebo	Staphylococcal infection/Severe	7 days	Unrelated
CV181013-212-1065	SAE/	Day 20/27/	Interrupted/

44/M/Placebo	Meningitis aseptic/Severe	9 days total	Unrelated
<b>Initial Combination</b>			
CV181039-4-109	SAE/	Day 79/	Continued/
57/F/Saxa 5 mg + Met	Gastroenteritis/Moderate	2 days	Unrelated
CV181039-140-1056	SAE/	Day 132/	Continued/
45/F/Saxa 5 mg + Met	Erysipelas/Moderate	11 days	Unrelated
CV181039-117-1850	SAE/	Day 5/	Continued/
44/M/Saxa 10 mg + Met	Scrotal Abscess/Moderate	9 days	Unrelated
CV181039-54-526	SAE/	Day 86/	Continued/
48/M/Saxa 10 mg	Appendicitis/Moderate	5 days	Unrelated

Source: Summary of Clinical Safety, Table 2.3.3.3

#### Classification of Infections

The Sponsor attempted to classify the type of organism causing each infection-related AE. The relationship between infections and lymphocyte decreases has already been discussed under Section 7.3.5. To do this, individual AEs in the SOC of Infections and Infestations in each of the Core Phase 3 studies were reviewed in a blinded fashion using supplemental CRFs that investigators used to collect additional information. Those that could not be classified were considered indeterminate, and these were the most common classification for infections (18.7% for saxagliptin vs. 16.9% for placebo). A summary of this analysis is shown below for the Placebo-controlled pooled safety population.

	Number (%) of Subjects				
	Saxa 2.5 mg N=822	Saxa 5 mg N=822	Saxa 10 mg N=279	All Saxa N=2043	Placebo N=799
Total Subjects with Events	321 (36.4)	317 (35.9)	112 (40.1)	750 (36.7)	278 (34.8)
Indeterminate	163 (18.5)	162 (18.4)	57 (20.4)	382 (18.7)	135 (16.9)
Viral	121 (13.7)	100 (11.3)	50 (17.9)	271 (13.3)	108 (13.5)
Bacterial	101 (11.5)	96 (10.9)	23 (8.2)	220 (10.8)	81 (10.1)
Fungal	12 (1.4)	25 (2.8)	9 (3.2)	46 (2.3)	26 (3.3)
Other	12 (1.4)	13 (1.5)	3 (1.1)	28 (1.4)	11 (1.4)

Source: Summary of Clinical Safety, Table 2.3.3.2A

#### Conclusions:

- Infections were the most common types of AE across the Core Phase 3 studies.
- Infection-related AEs were generally more common in saxagliptin-treated subjects compared to placebo.
- Relatively few of these AEs were SAEs or led to study discontinuation.

- The most common and most frequent infection-related AEs varied by study with no predominant PT common to all Phase 3 studies.

**Hypoglycemia**

All reported hypoglycemic AEs were based upon a pre-defined list of MedDRA PTs and included: hypoglycemia, blood glucose decreased, and blood glucose abnormal. The frequency of confirmed hypoglycemia AEs (discussed below) was much lower than all reported hypoglycemic AEs. Table 7.39 summarizes all reported hypoglycemic AEs (including unconfirmed cases) by pooled monotherapy, individual add-on combination studies, and the pooled placebo-controlled population for the ST period (prior to rescue). Table 7.40 summarizes this data for the initial combination study with metformin. In the pooled monotherapy analysis, subjects in the saxagliptin 10 mg group had the highest frequency (8.2% versus 4.1% placebo) of hypoglycemic AEs, followed by the saxagliptin 5 mg group (5.6%). This differs from the initial combination study with metformin, where the saxagliptin 10 mg group had a lower frequency of hypoglycemic AEs. In the add-on combination studies, treatment with sulfonylureas was associated with the highest frequency of hypoglycemic AEs (14% for all saxagliptin), including subjects in the placebo group (10.1%).

**Reviewer comment:** Sulfonylureas are well-known to be associated with hypoglycemia when used as monotherapy or in combination with other oral antidiabetic drugs.

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
<b>ST Period, Excluding Rescue</b>					
Pooled Monotherapy (CV181011, CV181038)	4.0% (10/247)	5.6% (14/252)	8.2% (8/98)	5.4% (32/597)	4.1% (7/169)
<b>Add-on Combination</b>					
+ 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)
<b>Up to Week 24, Regardless of Rescue Status</b>					
Placebo-controlled	7.6%	7.8%	5.4%	7.4%	6.8%
<b>Pooled Safety</b>	<b>(67/882)</b>	<b>(69/882)</b>	<b>(15/279)</b>	<b>(151/2043)</b>	<b>(54/799)</b>

Source: Summary of Clinical Safety, Table 2.3.1.1A

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

Source: Summary of Clinical Safety, Table 2.3.1.1B

One hypoglycemic AE, reported in a subject in the saxagliptin 5 mg group in the add-on combination study with glyburide, led to study discontinuation. None of the reported events required medical assistance. Confirmed cases of hypoglycemia are presented later in this section.

**Reviewer comment:** Although these cases include unconfirmed hypoglycemia, it is interesting to note that in the pooled monotherapy analysis, the saxagliptin 10 mg group had the highest frequency of hypoglycemic AEs. It should also be noted that this group had the smallest sample size. Subjects receiving saxagliptin 10 mg in CV181014 were not observed to have this imbalance in hypoglycemic AEs, but in fact had the lowest of all groups, including placebo. Given this variability, it can not be concluded that saxagliptin 10 mg is associated with a higher risk of hypoglycemia.

Phase 2b (CV181008)

During the double-blind period of the 0-40mg cohort, 26 saxagliptin-treated subjects (8.9%) and 2 placebo-treated subjects (3.0%) had hypoglycemic AEs. The proportions of subjects with hypoglycemic AEs ranged from 4.8% to 7.7% for the saxagliptin 10-40 mg groups. In the 0, 100 mg cohort, 5 saxagliptin-treated subjects (11.4%) had hypoglycemic AEs.

Confirmed Hypoglycemic AEs—ST Periods

Hypoglycemia was defined as symptoms of hypoglycemia associated with a fingerstick value ≤50 mg/dL. As summarized in the table below, there were no confirmed hypoglycemic AEs in the monotherapy studies. In the add-on combination studies, confirmed events were generally low. The highest frequency (2.4%) was seen in the saxagliptin 2.5 mg group of the add-on study to sulfonylurea. In the initial combination study with metformin (data not shown), there were 2 cases of confirmed hypoglycemia in the saxagliptin 10 mg + metformin group (0.6% versus 0.3% in the placebo group).

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
<b>ST Period, Excluding Rescue</b>					
Pooled Monotherapy (CV181011, CV181038)	0	0	0	0	0
<b>Add-on Combination</b>					
+ Met (CV181014)	0.5% (1/192)	0.5% (1/191)	0.6% (1/181)	0.5% (3/564)	0.6% (1/179)
+ SU (CV181040)	2.4% (6/248)	0.8% (2/253)	N/A	1.6% (8/501)	0.7% (2/267)
+ TZD	0.5%	0	N/A	0.3%	0

(CV181013)	(1/195)	(0/186)	(1/381)	(0/184)
<b>Up to Week 24, Regardless of Rescue Status</b>				
<b>Placebo-controlled</b>	0.8%	0.5%	0.4%	0.6%
<b>Pooled Safety</b>	(7/882)	(4/882)	(1/279)	(12/2043)

Phase 2b (CV181008)

No subjects in the 0 to 40 mg cohort had confirmed hypoglycemia. Two subjects in the saxagliptin 100 mg group had confirmed hypoglycemia during the double-blind period. Neither event required medical assistance.

Liver-related Abnormalities

Liver injury has been observed in the clinical development program of another DPP-4 inhibitor, vildagliptin. The Sponsor's clinical assessment of the safety of saxagliptin with respect to drug induced liver injury (DILI) included an analysis of change from baseline, marked abnormalities (MAs), shift tables, and combinations of laboratory parameters that could indicate DILI. As discussed and agreed upon in the pre-NDA meeting, the Sponsor used 2 methods to define Hy's Law: one requiring an alkaline phosphatase <2 ULN and a second without the alkaline phosphatase requirement.

Change from baseline

In all populations, including the ST + LT periods of the placebo-controlled studies as well as the initial combination study with metformin, there were no consistent or clinically meaningful changes from baseline at all time points in liver tests (including ALT, AST, total bilirubin, and alkaline phosphatase).

Marked Abnormalities

Since the frequency of MAs for liver abnormalities was low among individual studies, the Sponsor used a pooled assessment. Below is a table of MAs for LFTs in all phase 2/3 studies.

<b>Table 7.42. Marked Laboratory Abnormalities of LFTs up to Week 24 Regardless of Rescue Status--Placebo-controlled Pooled Safety</b>					
Parameter	n/N, (%)				
	Saxa 2.5 mg N=882	Saxa 5 mg N=882	Saxa 10 mg N=279	All Saxa N=2043	Placebo N=799
<b>AST</b>					
>3xULN	4/872 (0.5%)	2/875 (0.2%)	3/278 (1.1%)	9/2025 (0.4%)	5/792 (0.6%)
>5xULN	2/872 (0.2%)	0	2/278 (0.7%)	4/2025 (0.2%)	1/792 (0.1%)
>10xULN	1/872	0	0	1/2025 (0%)	0
>20xULN	0	0	0	0	0
<b>ALT</b>					
>3xULN	5/872 (0.6%)	4/875 (0.5%)	2/278 (0.7%)	11/2025 (0.5%)	7/792 (0.9%)

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>5xULN	2/872 (0.2%)	0	0	2/2025 (0.1%)	2/792 (0.3%)
>10xULN	1/872 (0.1%)	0	0	1/2025 (0%)	0
>20xULN	0	0	0	0	0
<b>Total bilirubin</b>					
>2 mg/dL	1/872 (0.1%)	2/875 (0.2%)	2/278 (0.7%)	5/2025 (0.2%)	1/792 (0.1%)
>1.5xULN	2/872 (0.2%)	2/875 (0.2%)	2/278 (0.7%)	6/2025 (0.3%)	2/792 (0.3%)
>2xULN	1/872 (0.1%)	1/875 (0.1%)	0	2/2025 (0.1%)	0
<b>Alkaline Phosphatase</b>					
>3x pre-RX and ULN	0	2/875 (0.2%)	0	2/2025 (0.1%)	0
	80/372	24/875		55/2025	
>1.5xULN	(3.4%)	(2.7%)	1/278 (0.4%)	(2.7%)	29/792 (3.7%)
<i>Abbreviations: AST=aspartate aminotransferase, ALT=alanine aminotransferase; RX=treatment; ULN=upper limit of normal</i>					

**Reviewer comment: Since liver-related MAs were low, pooling across the Phase 2/3 studies was a reasonable approach.**

There did not appear to be any imbalances in MAs for LFTs across groups. There were no subjects with AST or ALT > 20 ULN during the ST + LT period (regardless of rescue). Four saxagliptin-treated subjects had AST and/or ALT values > 10 x ULN. These subjects are described here:

- Subject CV181011-142-670 in the saxagliptin 2.5 mg group had elevations in AST and ALT related to an SAE of acute hepatitis C. Study drug was discontinued on Day 56.

**Reviewer comment: This event was unrelated to study drug.**

- Subject CV181039-156-750 was a 60 year old female in the saxagliptin 10 mg group with abnormalities that led to discontinuation of study drug on Day 273. Levels were as follows:

	Day 1	Day 269	Day 281	Day 288	Day 302
AST (nl: 10-36 U/L)	20 U/L	372	39	26	n/a
ALT (nl: 6-37 U/L)	26	474	125	44	26
Alkaline phosphatase (nl: 40-100)	98	293	291	183	103
Bilirubin (0.2-1.2)	0.7	2	1.2	0.8	n/a

The subject had no signs or symptoms, and since laboratory tests normalized, a hepatic ultrasound was not done. This AE was considered by the Investigator to be possibly related to study drug.

**Reviewer comment: It is plausible that this event was study drug-related.**

- Subject CV181014-157-389 was a 56 year old male in the saxagliptin 2.5mg + metformin group. He was diagnosed with Hepatitis A on Day 511. The hepatitis resolved on Day 547. The subject continued in the study. His labs were as follows:

	Day 1	Day 526	Day 541	Day 708
AST (nl: 0-43)	24	258	23	24
ALT (nl: 0-43)	33	815	39	26
Bilirubin (nl: 0.3-1.2mg/dL))	0.70	2.6	0.90	0.70

**Reviewer comment: This event was unrelated to study drug.**

Subject CV181008-40-805 was a 64 year old female in the saxagliptin 100 mg group. She had peak elevations of AST and ALT of 194 U/L and 343 U/L, respectively, on Day 43. She was taking concomitant pravastatin until Day 50. Liver tests decreased on subsequent labs, with Day 84 measurement of 36 U/L and 44 U/L. She completed participation in the study.

**Reviewer comment: Given that the values normalized with its discontinuation, it is likely that the AST/ALT elevations were a result of pravastatin.**

The Sponsor also performed a combined analysis across the ST and ST+LT periods of the phase 2/3 studies, specifically investigating the frequencies of concomitant rises of ALT or AST > 3 x ULN in conjunction with an elevated total bilirubin > 2 x ULN (Hy's Law). Two subjects, summarized below, met these criteria. Both had a total bilirubin > 3 ULN.

- Subject CV181011-142-670 was a subject in the saxagliptin 2.5mg group, described above, with Hepatitis C.
- Subject CV181039-193-688 was a 55 year old female in the metformin group whose liver test elevations were attributed to pancreatic neoplasm. This subject died on Day 268.

Shift Tables:

In the placebo-controlled Pooled Safety analysis, there were no clear patterns of shift from baseline for either AST or ALT to the highest value during the double-blind period up to Week 24, regardless of rescue, across all treatment groups. This is summarized in the tables below.

Treatment Group	Baseline Value	Highest Value--Number (%) of Subjects			Total
		≤3xULN	>3 to ≤5xULN	>5xULN	
Saxa 2.5 mg N=882	≤3xULN	867 (99.5)	2 (0.2)	2 (0.2)	871 (100)
	>3 to ≤5xULN	1 (100.0)	0 (0)	0 (0)	1 (100)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)

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	Total	868 (99.5)	2 (0.2)	2 (0.2)	872 (100)
Saxa 5 mg N=882	≤3xULN	873 (99.8)	2 (0.2)	0 (0)	875 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	873 (99.8)	2 (0.2)	0 (0)	875 (100)
Saxa 10 mg N=279	≤3xULN	275 (98.9)	1 (0.4)	2 (0.7)	278 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	275 (98.9)	1 (0.4)	2 (0.7)	278 (100)
All Saxa N=2043		2015			
	≤3xULN	(99.6)	5 (0.2)	4 (0.2)	2024 (100)
	>3 to ≤5xULN	1 (100.0)	0 (0)	0 (0)	1 (100)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	2016			
		(99.6)	5 (0.2)	4 (0.2)	2025 (100)
Placebo N=799	≤3xULN	787 (99.4)	4 (0.5)	1 (0.1)	792 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	787 (99.4)	4 (0.5)	1 (0.1)	792 (100)

Source: Summary of Clinical Safety, Appendix 8.1.3.2

**Table 7.44. ALT--Shift Table from Baseline to Highest Value Occurring After 24 Weeks of Double-Blind Treatment, for Placebo-controlled Pooled Safety**

Treatment Group	Baseline Value	Highest Value--Number (%) of Subjects			
		≤3xULN	>3 to ≤5xULN	>5xULN	Total
Saxa 2.5 mg N=882	≤3xULN	866 (99.4)	3 (0.3)	2 (0.2)	87 (100)
	>3 to ≤5xULN	1 (100.0)	0 (0)	0 (0)	1 (100)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	867 (99.4)	3 (0.3)	2 (0.2)	872 (100)
Saxa 5 mg N=882	≤3xULN	871 (99.5)	4 (0.5)	0 (0)	875 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	871 (99.5)	4 (0.5)	0 (0)	875 (100)
Saxa 10 mg N=279	≤3xULN	276 (99.3)	2 (0.7)	0 (0)	278 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	276 (99.3)	2 (0.7)	0 (0)	278 (100)

<b>Table 7.44. ALT--Shift Table from Baseline to Highest Value Occurring After 24 Weeks of Double-Blind Treatment, for Placebo-controlled Pooled Safety</b>					
	Total	276 (99.3)	2 (0.7)	0 (0)	278 (100)
All Saxa N=2043	≤3xULN	2013 (99.5)	9 (0.4)	2 (0.1)	2024 (100)
	>3 to ≤5xULN	1 (100.0)	0 (0)	0 (0)	1 (100)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	2014 (99.5)	9 (0.4)	2 (0.1)	2025 (100)
Placebo N=799	≤3xULN	784 (99.1)	5 (0.6)	2 (0.3)	791 (100)
	>3 to ≤5xULN	0 (0)	1 (100.0)	0 (0)	1 (100)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	784 (99.0)	6 (0.8)	2 (0.3)	792 (100)

*Source: Summary of Clinical Safety, Appendix 8.1.3.1*

Similar to the data above, in the Initial Combination Study with metformin, there were no clear patterns of shift from baseline for either AST or ALT to the highest value during the double-blind period up to Week 24, regardless of rescue, across all treatment groups. This is summarized in the tables below.

<b>Table 7.45. ALT--Shift Table from Baseline to Highest During Double-blind Treatment Period up to Week 24, Regardless of Rescue Status for CV181039</b>					
Treatment Group	Baseline Value	Highest Value--Number (%) of Subjects			Total
		≤3xULN	>3 to ≤5xULN	>5xULN	
Saxa 5 mg + Met N=320	≤3xULN	313 (99.1)	3 (0.9)	0 (0)	316 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	313 (99.1)	3 (0.9)	0 (0)	316 (100)
Saxa 10 mg + Met N=323	≤3xULN	316 (99.4)	1 (0.3)	1 (0.3)	318 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	316 (99.4)	1 (0.3)	1 (0.3)	318 (100)
Saxa 10 mg N=335	≤3xULN	324 (99.7)	1 (0.3)	0 (0)	325 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	324 (99.7)	1 (0.3)	0 (0)	325 (100)
All Saxa	≤3xULN	953 (99.4)	5 (0.5)	1 (0.1)	959 (100)

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N=978	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	953 (99.4)	5 (0.5)	1 (0.1)	959 (100)
Met N=328	≤3xULN	317 (99.1)	3 (0.9)	0 (0)	320 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
Total	317 (99.1)	3 (0.9)	0 (0)	320 (100)	

Source: Integrated Summary of Safety, Appendix 8.1.4.1

Table 7.46. AST--Shift Table from Baseline to Highest During Double-blind Treatment Period up to Week 24, Regardless of Rescue Status for CV181039					
Treatment Group	Baseline Value	Highest Value--Number (%) of Subjects			
		≤3xULN	>3 to ≤5xULN	>5xULN	Total
Saxa 5 mg + Met N=320	≤3xULN	314 (99.4)	2 (0.6)	0 (0)	316 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	314 (99.4)	2 (0.6)	0 (0)	316 (100)
Saxa 10 mg + Met N=323	≤3xULN	317 (99.7)	1 (0.3)	0 (0)	318 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	317 (99.7)	1 (0.3)	0 (0)	318 (100)
Saxa 10 mg	≤3xULN	324 (99.7)	1 (0.3)	0 (0)	325 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	324 (99.7)	1 (0.3)	0 (0)	325 (100)
All Saxa N=978	≤3xULN	955 (99.6)	4 (0.4)	0 (0)	959 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	955 (99.6)	4 (0.4)	0 (0)	959 (100)
Met N=328	≤3xULN	317 (99.1)	3 (0.9)	0 (0)	320 (100)
	>3 to ≤5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	>5xULN	0 (0)	0 (0)	0 (0)	0 (0)
	Total	317 (99.1)	3 (0.9)	0 (0)	320 (100)

Source: Integrated Summary of Safety, Appendix 8.1.4.2

#### Discontinuations due to Liver Abnormalities

A subject in Study CV181040 discontinued because of elevated LFTs. This narrative can be found in Section 7.3.2.

**120 Day Safety Update:** In the placebo-controlled Pooled Safety analysis, a total of 11 new subjects had marked LFT laboratory abnormalities (8 saxagliptin-treated and 3 placebo). No additional saxagliptin-treated subjects had AST and/or ALT values > 10ULN between the cutoff date for the NDA and the cutoff date for the 120-day Safety Update. Two subjects discontinued the study because of elevated liver enzymes. One subject, CV181038-60-436, a 35 year old man treated with saxagliptin 2.5 mg (Days 1-78), 5 mg (Days 179-214), and 10 mg (starting Day 215), discontinued due to elevated ALT on Day 208 (150 U/L, normal: 6 to 48 U/L). A second subject, CV181039-34-218, a 57 year old male in the saxagliptin 10 mg/metformin group, had liver test elevations on Day 520 (ALT 75U/L, normal: 6 to 37; AST 44U/L, normal: 10 to 36). Study drug was discontinued on Day 523, and the event was reported as resolved on Day 527.

An additional subject, CV181038-55-781, a 72 year old male treated with saxagliptin 2.5mg from Days 1-84 and 5mg from Days 85, met the criteria for possible Hy's Law cases. He experienced an elevation of ALT, AST, and total bilirubin on Day 345 (403U/L, 119 U/L, and 2.4mg/dL, respectively). He had an AE of chronic cholecystitis on Day 338, and a diagnosis of acute calculous cholecystitis was made on Day 350. Study drug was disrupted on Day 351, a cholecystectomy was performed on Day 357, and study drug resumed on Day 361. All LFTs were normal on Day 435.

Of the 8 saxagliptin-treated subjects mentioned above with marked LFT abnormalities, 4 subjects (1 in the 2.5 mg group, 3 in the 5 mg group) had normalization of laboratory values and continued on study drug. Narratives for the other subjects are provided here. None of these MAs resulted in study discontinuation.

- Subject CV181011-52-1002, a 40 year old male in the saxagliptin 2.5 mg group, had a MA of AST at 145 U/L on Day 801, the subject's final visit due to the Investigator's retirement from practice. He had a history of diverticulitis and partial bowel removal. Other liver tests were normal, but CPK was elevated at 13,560 U/L with no predisposing factors. Creatinine was normal. No additional laboratory values were available after Day 801.
- Subject CV181040-38-946, a 55 year old female in the saxagliptin 5 mg group, had an AST of 139 U/L and ALT of 133 U/L on Day 542. On Day 564, these levels were noted to have decreased some, but levels obtained on Day 645 showed an AST and ALT of 156 U/L and 112 U/L, respectively. At the time of the safety update, ultrasound examination was pending.
- Subject CV181013-182-600, a 63 year old male in the saxagliptin 2.5 mg group, had an elevated ALT from Day 1-Day 442, ranging from 52-143 U/L. On Day 533 (last study visit), his ALT level was more than 3 times the ULN. This remained elevated at follow-up on Day 608. Bilirubin levels were normal. No AEs were reported in connection with this elevation.
- Subject CV181040-37-221, a 38 year old female in the saxagliptin 5 mg group, had an AST and ALT of 137 U/L and 292 U/L, respectively, on the finally study visit on Day 533. No additional values were available.

In the 120 Day Safety Update, the Sponsor noted that because of changes in the normal ranges ALT and AST at one laboratory site in CV181014, some subjects who were reported as having MAs for AST/ALT in the NDA no longer meet the criteria for MA. For

AST, this includes one subject in the 10 mg group who had an MA >5xULN that is now counted in the AST> 3xULN category, and 1 placebo subject with a previously reported MA of AST>3 xULN that is no longer counted as an MA. For ALT, this correction affects 1 subject in the 2.5mg group with an MA of ALT> 5xULN now counted in the ALT>3 xULN category, and 2 placebo subjects with previous MAs of ALT> 3 ULN that are no longer counted as having a MA.

Conclusion regarding Liver Test Abnormalities:

- In all populations studied, there were no consistent or clinically meaningful changes from baseline at all time points in liver tests.
- Marked abnormalities were generally infrequent, and no imbalances across dose groups were seen.
- Overall, in the initial NDA submission as well as the 120-day safety update, there were 3 cases that met the definition of Hy's Law. Of the 2 cases that were reported in the initial submission, one was diagnosed with hepatitis C and the other with pancreatic neoplasm. The third subject, diagnosed with acute cholecystitis, underwent surgery and subsequently had normal liver tests as he continued on study drug.

**Thrombocytopenia**

This section discusses the laboratory abnormalities related to thrombocytopenia as well as the AEs of thrombocytopenia. Thrombocytopenia was observed in the Clinical Pharmacology Studies (discussed in Section 4.4.2) and is therefore discussed here as a possible safety concern. Table 7.47 below presents the percent change from baseline in the Pooled Monotherapy Analysis at key time points. It should be noted that Study CV181038 incorporated up-titration of study drug, and that this may complicate data interpretation. Overall, there did not appear to be a trend of dose-relatedness, although subjects in the 10 mg dose were observed to have the largest mean decrease in percent change from baseline in platelets.

	Treatment Group	N=	Percent Change from Baseline			
			Mean	SE	Median	95% CI
6 months (Week 24)	Saxa 2.5mg	195	-2.8	1.08	-3.8	-4.9, -0.7
	Saxa 5mg	187	-2.1	0.98	-2.7	-4.1, -0.2
	Saxa 10mg	73	-4.7	1.59	-5.8	-7.8, -1.5
	All Saxa	455	-2.8	0.66	-3.5	-4.1, -1.5
	Placebo	132	-1.5	1.12	-2.1	-3.7, 0.7
12 months (Week 50)	Saxa 2.5mg	96	-2.7	-1.54	-4.4	-5.7, 0.4
	Saxa 5mg	98	-3.2	1.29	-5.5	-5.8, -0.7
	Saxa 10mg	66	-3.6	1.17	-4.0	-6.0, -1.3
	All Saxa	260	-3.1	0.8	-4.6	-4.7, -1.5

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	Placebo	77	2.2	1.75	2.9	-1.3, 5.7
18 months (Week 76)	Saxa 2.5mg	50	-0.9	2.64	-1.6	-6.2, 4.4
	Saxa 5mg	60	1.1	2.24	-1.7	-3.4, 5.6
	Saxa 10mg	62	-2.2	1.38	-3.0	-4.9, 0.6
	All Saxa	172	-0.7	1.2	-1.7	-3.0, 1.7
	Placebo	49	1.0	2.0	0.4	-3.0, 5.1
24 months (Week 102)	Saxa 2.5mg	23	5.7	4.57	0.0	-3.8, 15.2
	Saxa 5mg	34	-1.0	2.35	-0.5	-5.8, 3.7
	Saxa 10mg	39	-1.4	2.09	0.0	-5.6, 2.8
	All Saxa	96	0.4	1.63	0.0	-2.8, 3.7
	Placebo	25	5.3	3.72	4.6	-2.3, 13

Source: Summary of Clinical Safety, Table 3.2A

Abbreviations: CI=confidence interval

Overall, the percent decrease in platelets ranged from approximately 1-5% throughout all time points. Sample sizes were markedly smaller at 24 months, limiting the data interpretation at this important time point. Overall, there appeared to be small percent changes in platelet counts compared to placebo. The following table presents an analysis of platelet count for the placebo-controlled Pooled Safety analysis through Week 24 regardless of rescue.

**Table 7.48. Mean and Percent Change from Baseline in Platelet Counts ( $\times 10^9$  c/L) -  
-ST + LT Period-- Placebo-controlled Pooled Safety Analysis at Week 24  
Regardless of Rescue**

	Treatment Group	N=	Percent Change from Baseline			
			Mean	SE	Median	95% CI
6 months (Week 24)	Saxa 2.5mg	432	-2.3	0.63	-3.4	-3.6, -1.1
	Saxa 5mg	434	-1.7	0.82	-2.8	-3.3, -0.0
	Saxa 10mg	131	-2.1	1.23	-3.8	-4.5, 0.3
	All Saxa	997	-2.0	0.48	-3.1	-2.9, -1.1
	Placebo	390	-1.5	0.67	-1.9	-2.8, -0.1

**Change from Baseline**

	Treatment Group	N=	Mean Change from Baseline			
			Mean	SE	Median	95% CI
6 months (Week 24)	Saxa 2.5mg	432	-7.9	1.67	-8.5	-11.2, -4.6
	Saxa 5mg	434	-7.3	1.86	-7.0	-10.9, -3.6
	Saxa 10mg	131	-8.7	3.42	-10.0	-15.5, -1.9
	All Saxa	997	-7.7	1.18	-8.0	-10.0, -5.4
	Placebo	390	-6.1	1.87	-5.0	-9.8, -2.4

Source: Summary of Clinical Safety, Table 3.2B

Abbreviation: CI=confidence interval

At 24 weeks, the percent change from baseline in platelet count (upper panel) was low and generally comparable between saxagliptin treatment groups as well as compared to placebo. In addition, the decreases in actual platelet count are shown in the bottom panel. Again, decreases between treatment groups as well as compared to placebo were similar. For subjects with available platelet data at Week 24, the mean platelet counts at baseline in each treatment group ranged from  $261.3 \times 10^9$  c/L to  $266.3 \times 10^9$  c/L. In each group the 95% CI excluded zero.

The Sponsor also conducted an outlier analysis of subjects with a pre-specified reduction of  $\geq 10\%$ ,  $\geq 20\%$ , and  $\geq 30\%$  from baseline in platelet count at time points presented in the tables above. This was done for all Core Phase 3 studies. Few subjects remained in the 24 month analyses, and therefore these will not be discussed.

MAs of low platelet count in the individual studies were infrequent, ranging from 0-1 subject in any treatment group of any study.

#### Thrombocytopenic Adverse Events

AEs of thrombocytopenia were identified by matching AEs to a pre-defined list of PTs that were thought to reflect a diagnosis of thrombocytopenia. This list was reviewed and appears adequate. Using these, the frequency of AEs in the placebo-controlled studies was low (0-0.8%) across all saxagliptin treatment groups and were comparable to placebo.

In the Pooled Monotherapy analysis none of the thrombocytopenia AEs were considered serious or resulted in discontinuation of study drug.

In the add-on combination studies, there was one SAE and one AE that resulted in discontinuation of study drug. These are summarized here:

- Subject CV181040-68-280 was a 59 year old female in the saxagliptin 5mg group who had a platelet count of  $168 \times 10^9$  on Day 126 (baseline value of  $358 \times 10^9$ ). Subsequent counts on Day 132 and Day 274 were  $233 \times 10^9$  c/L and  $244 \times 10^9$  c/L, respectively. She was reported to have an AE of herpes zoster between Days 275 and 330. Study drug was continued. On Day 365, a CBC revealed an isolated decreased platelet count of  $7 \times 10^9$  c/L; she was asymptomatic. Study drug was discontinued on Day 366. She was hospitalized and bone marrow biopsy revealed myelodysplastic syndrome. She was started on prednisone and platelet count at discharge (Day 377) was  $88 \times 10^9$  c/L. Despite the biopsy results, in view of the subject's response to therapy, the consulting hematologist's diagnosis was Idiopathic Thrombocytopenic Purpura. The subject remained asymptomatic. Platelet counts on Day 432 (66 days after last dose of study drug) and Day 439 (73 days after last dose of study drug) remained decreased at  $88 \times 10^9$  c/L and  $126 \times 10^9$  c/L, respectively. Per information obtained after database lock, platelet count was  $161 \times 10^9$  c/L on Day 540 while on daily prednisone.

**Reviewer comment: Due to the complicated history, it remains unclear if the thrombocytopenia was indeed related to study drug or to the preceding viral illness.**

- Subject CV181014-174-624 was a 50 year old male in the saxagliptin 5mg group who had an AE of thrombocytopenia on Day 15 ( $109 \times 10^9$  c/L). He had a history of

thrombocytopenia. His pre-randomization counts were below normal (Day -14,  $141 \times 10^9$  c/L; Day 1,  $117 \times 10^9$  c/L). Study drug was discontinued and the event resolved on Day 41.

**Reviewer comment: Given the subject's history of thrombocytopenia and the very small decrease from baseline that could have been attributed to laboratory variation alone, it is unlikely that this event was study drug-related.**

In the initial combination study with metformin, there were again very few events of thrombocytopenia for subjects treated with saxagliptin (0.2%) or metformin (0.3%). One event resulted in study discontinuation, described here:

- Subject CV181039-201-732 was a 60 year old male in the saxagliptin 10mg monotherapy group who had an AE of decreased platelet count on Day 54 ( $120 \times 10^9$  c/L; baseline,  $178 \times 10^9$  c/L). Study drug was discontinued on Day 68, and the event resolved on Day 75.

**Reviewer comment: This AE may have been drug-related.**

### Creatine Kinase Elevations

Tables 7.49-7.53 summarize the changes in creatine kinase (CK) from baseline to Week 24 for the pooled monotherapy studies, the individual add-on combination studies, and the ICM study. CK measurements were performed routinely in these studies at clinic visits.

In the monotherapy studies, all groups were observed to have some increase in CK over time. The steepest mean change was seen in the saxagliptin 10 mg group, although there was wide variation within this group. The overall incidence of MAs in the monotherapy studies was low (data not shown).

	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
n (%)	188 (76)	197 (78)	70 (71)	455 (76)	126 (75)
Mean±SE	18.4±7.25	9.5±4.32	48.5±45.18	19.2±7.78	5.6±5.87
Median	10.0	4.0	4.5	7.0	3.0
95% CI	(4.1, 32.7)	(1, 18)	(-41.6, 138.7)	(3.9, 34.5)	(-6, 17.3)

Source: Integrated Summary of Safety, Appendix 8.2.1

In the ICM study, the saxagliptin 10 mg + metformin group had the steepest change, with a mean decrease of 49.5 u/L.

	Saxa 5 mg + Met N=320	Saxa 10 mg + Met N=323	Saxa 10 mg N=335	All Saxa N=978	Metformin N=328
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n (%)	270 (84)	262 (78)	245 (73)	777 (79)	252 (77)
Mean±SE	6.6±5.98	-49.5±44.71	17.5±4.10	-8.9±15.29	-1.9±4.91
Median	3.5	2.0	7.0	4.0	0.0
95% CI	(-5.2, 18.4)	(-137.5, 38.6)	(9.4, 25.6)	(-38.9, 21.2)	(-11.6, 7.7)

Source: Integrated Summary of Safety, Appendix 8.2.1

In the add-on combination study with metformin, there were no clinically significant changes in mean CK over time.

	Saxa 2.5 mg + Met N=192	Saxa 5 mg + Met N=191	Saxa 10 mg + Met N=181	Placebo + Met N=179
n (%)	157 (82%)	155 (81%)	147 (81%)	124 (69%)
Mean±SE	10.1±4.69	1.6±3.55	1.3±5.67	-2.2±3.65
Median	2.0	0.0	2.0	-2.5
95% CI	(0.79, 19.32)	(-5.39, 8.62)	(-9.87, 12.55)	(-9.47, 4.99)

Source: Clinical Study Report, CV181014, Appendix 7.15

In the add-on combination study with glyburide, small increases from baseline were seen in the 2 saxagliptin-treated groups.

	Saxa 2.5 mg + Gly N=248	Saxa 5mg + Gly N=253	Placebo + Gly N=267
n (%)	207 (83%)	213 (84%)	211 (79%)
Mean±SE	11.4±6.31	17.8±8.06	-5.4±6.64
Median	7.0	8.0	3.0
95% CI	(-1.01, 23.87)	(-1.91, 33.7)	(-18.53, 7.65)

Source: Clinical Study Report, Study CV181040, Appendix 7.15

In the add-on combination study with TZD, clinically significant changes in CK were not observed over time.

	Saxa 2.5 mg + TZD N=195	Saxa 5mg + TZD N=186	Placebo + TZD N=184
n (%)	163 (87)	149 (80)	142 (77)
Mean±SE	0.3±4.66	11.2±6.98	5.4±6.03
Median	7.0	7.0	-2.0
95% CI	(-8.87, 9.54)	(-2.64, 24.96)	(-6.5, 17.35)

Source: Clinical Study Report, Study CV181013, Appendix 7.15

In addition to analyzing changes in CK from baseline over time, the Sponsor specifically analyzed MAs for CK, defined as >5 x ULN, for the ST and LT periods of both the Core Phase 3 studies and the pooled Phase 2/3 studies. Overall, in the Core Phase 3 studies, MAs for CK were uncommon. Still, the highest numbers of MAs for CK were seen in the add-on to TZD study. Specifically, the 5 mg group in this study had a total of 5 subjects (2.7%) with MAs of CK, versus 2 subjects (1%) in the 2.5 mg group and none in the comparator. Since this study had the highest number of MAs for CK, narratives for subjects with AEs of CK in Study CV181013 are included below.

Table 7.54 summarizes the MAs of CK in the ST + LT Periods for all Phase 2/3 studies. There was a slightly higher incidence in the 5 mg group (1.4%) versus other groups, although the incidence with the 2.5 mg dose (1.0%) and 10 mg dose (0.9%) were comparable to that with placebo.

<b>Table 7.54. Marked Abnormalities of Creatine Kinase--ST + LT Periods--All Phase 2/3 Studies</b>						
		n/N, (%)				
		Saxagliptin			Placebo	Metformin
Parameter	2.5 mg N=937	5 mg N=1269	10 mg N=1066	All Saxa N=3422	N=923	N=328
>5 x ULN	9/926 (1.0)	17/1255 (1.4)	9/1046 (0.9)	38/3376 (1.1)	10/912 (1.1)	2/319 (0.6)

Source: Summary of Clinical Safety, Table 3.4B

Narratives for Subjects with AEs for Blood CPK Increased in Study CV181013:

- Subject CV181013-253-972, a 45 year old male in the saxagliptin 2.5 mg group (background pioglitazone 30 mg), was noted to have increased CPK on Day 18 (from baseline 168 U/L to 706 U/L). An AE was not reported at that time. On Day 88, the subject was noted to have a CPK level of 1043 U/L and study drug was interrupted on Day 89. On Day 89, CPK level was 262 U/L. Study drug was restarted on Day 99. On Day 146, again the subject was reported as having an increased CPK (306 U/L). Study drug was discontinued permanently. CPK levels subsequently normalized.

**Reviewer comment: Given the temporal relationships described, it is possible that this subject's CPK elevations were drug-related. No inciting factors were noted.**

- Subject CV181013-182-955, a 49 year old male in the saxagliptin 5 mg group (background pioglitazone 45 mg), was reported to have increased CPK (2985 U/L) on Day 45. His CPK was elevated at 625 U/L at baseline. The subjects reported having recently taken a second job which required more activity. Study drug was discontinued on Day 50. On Day 51, CPK was 766 U/L. The subject discontinued the study.

**Reviewer comment:** Given the elevated CPK at baseline, it is difficult to attribute the CPK elevation to saxagliptin alone. However, a role of saxagliptin cannot be excluded based on the dramatic elevation on Day 45, together with the decrease from the peak level.

- Subject CV181013-2-782, a 55 year old male in the saxagliptin 5 mg group (background pioglitazone 45 mg) was reported to have increased CPK (419 U/L) on Day 113. The subject had a history of hypercholesterolemia and was being treated with atorvastatin. His baseline CPK was mildly elevated (215 U/L, normal 24-195). He reported that his daily physical activity increased dramatically. Study drug was permanently discontinued on Day 116. CPK level on Day 141 was 844 U/L.

**Reviewer comment:** It does not appear that these CPK elevations were related to saxagliptin.

- Subject CV181013-165-424, a 63 year old male in the saxagliptin 5 mg group (background pioglitazone 45 mg) had a CPK of 1408 U/L on Day 43. He had been taking lovastatin for several years and had a baseline CPK of 363 U/L. No action was taken. On Day 87, CPK level was 1531 U/L. Study drug was held on Day 91. On Day 93, CPK was 673 U/L and study drug was resumed. CPK levels remained elevated at 500-942 U/L.

**Reviewer comment:** Saxagliptin may have contributed to the baseline CPK elevations in this subject.

- Subject CV181013-233-430, a 62 year old male treated with saxagliptin 5 mg had a CPK level of 1377 U/L on Day 141. Baseline CPK level was elevated at 316 U/L. Study drug was not interrupted, and repeat CPK on Day 145 was 242 U/L.

**Reviewer comment:** There appeared to be no definite causal relationship between saxagliptin and the transient further elevation of CPK.

### Hypersensitivity

Because of post-marketing reports of hypersensitivity reactions associated with Januvia, the only FDA-approved DPP-4 inhibitor, a pre-defined list of PTs intended to identify all AEs related to a hypersensitivity reaction were created after database locks for Studies CV181011 and CV181014. These were meant to represent a broader collection of PTs than the MedDRA PT of hypersensitivity. This list of 65 PTs included all terms related to angioedema (a higher level term in MedDRA). The following tables show the frequencies of hypersensitivity AEs in the placebo-controlled and initial combination studies with metformin, respectively.

	2.5 mg	5 mg	10 mg	All Saxa	Placebo
<b>Pooled Monotherapy</b> (CV181011, CV181038)	3.2% (8/247)	3.2% (8/252)	3.1% (3/98)	3.2% (19/597)	1.8% (3/169)
<b>Add-on Combination</b> + Met	1.0%	2.6%	3.3%	2.3%	0%

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 NDA 22,350 (Submission 000)  
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(CV181014)	(2/192)	(5/191)	(6/181)	(13/564)	(0/179)
+ SU	2.4%	0.4%	N/A	1.4%	0%
(CV181040)	(6/248)	(1/253)		(7/501)	(0/267)
+ TZD	1.5%	2.2%	N/A	1.8%	0.5%
(CV181013)	(3/195)	(4/186)		(7/381)	(1/184)

Source: Summary of Clinical Safety, Table 2.3.9A

Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	All Saxa	Met
0.6%	0.3%	0.6%	0.5%	0.6%
(2/320)	(1/323)	(2/335)	(2/978)	(2/328)

Source: Summary of Clinical Safety, Table 2.3.9B

Pooled Monotherapy

In the Pooled Monotherapy analysis, the frequency of hypersensitivity AEs in the saxagliptin treatment groups was 3.1-3.2% versus 1.8% in the placebo group. There were no SAEs associated with hypersensitivity. The AEs were comprised of 10 PTs. There were only three PTs with a frequency of ≥1%. These are detailed here in Table 7.57.

	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
PT (%)					
Hypersensitivity	2 (0.8)	8 (3.2)	3 (3.1)	19 (3.2)	3 (1.8)
Urticaria	5 (2.0)	1 (0.4)	1 (1.0)	7 (1.2)	1 (0.6)
Drug Hypersensitivity	0	0	0	0	2 (1.2)

Source: Integrated Summary of Safety, Appendix 7.8.1

None of the hypersensitivity AEs led to discontinuation of study drug in saxagliptin-treated subjects. One subject in the placebo group discontinued study drug because of a hypersensitivity AE:

- Subject CV181011-84-252 was a 39 year old female in the placebo group who had circumoral edema and urticaria on Day 119. The event required treatment (unspecified), and study drug was discontinued.

Study CV181014

In the add-on combination study with metformin, frequencies of hypersensitivity AEs were higher in all saxagliptin treatment groups, with a possible dose relationship, including 3.3% in

the 10 mg group versus 0% in the placebo group. The most frequently reported PTs are summarized below. None of the AEs led to discontinuation of study drug. There were no SAEs associated with hypersensitivity.

**Table 7.58. Hypersensitivity Reactions Adverse Events with a Frequency  $\geq 1\%$ -- Summary by Pre-specified PT During ST + LT Treatment Period for Study CV181014**

	Saxa 2.5 mg + Met	Saxa 5 mg + Met	Saxa 10 mg + Met	All Saxa	Placebo + Met
PT (%)	N=192	N=191	N=181	N=564	N=179
Hypersensitivity	1 (0.5)	3 (1.6)	1 (0.6)	5 (0.9)	0
Urticaria	0	1 (0.5)	2 (1.1)	3 (0.5)	0

Source: Integrated Summary of Safety, Appendix 7.8.6

#### Study CV181040

In the add-on combination study with SU, frequencies of hypersensitivity AEs were 2.4%, 0.4%, and 0% in the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. Urticaria was the most frequent PT reported.

**Table 7.59. Hypersensitivity Reactions Adverse Events with a Frequency  $\geq 1\%$ --Summary by Pre-specified PT During St + LT Treatment Period for Study CV181040**

	Saxa 2.5 mg + Gly	Saxa 5 mg + Gly	All Saxa	Placebo + Gly
PT (%)	N=248	N=253	N=501	N=267
Urticaria	3 (1.2)	1 (0.4)	4 (0.8)	0

Source: Integrated Summary of Safety, Appendix 7.8.7

There were no SAEs associated with hypersensitivity. Two saxagliptin-treated subjects had hypersensitivity AEs that led to discontinuation of study drug. These subjects are described here:

- Subject CV181040-100-1169 was a 52 year old male in the saxagliptin 2.5 mg group who had urticaria on Day 219. The event was characterized as moderate and required no treatment. This subject also had 2 prior resolved AEs of urticaria on Days 188 and 194. Neither required treatment. The Investigator characterized the event as certainly related to study drug.
- Subject CV181040-49-1894 was a 55 year old female in the saxagliptin 5 mg group who had urticaria on Day 28. The event was characterized as moderate and required treatment (unspecified). The Investigator characterized the event as possibly related to study drug.

#### Study CV181013

In the add-on combination study with TZD, the frequencies of hypersensitivity AEs were 1.5%, 2.2%, and 0.5% of subjects in the saxagliptin 2.5mg, 5mg, and placebo groups, respectively. No

single PT occurred with a frequency  $\geq 1\%$ . There were no SAEs associated with hypersensitivity. None led to discontinuation of study drug.

Study CV181039

In the initial combination study with metformin, the frequency of hypersensitivity AEs was low (0.3-0.6%). No single PT occurred with a frequency  $\geq 1\%$ . There were no SAEs associated with hypersensitivity. None led to discontinuation of study drug.

Non-Core Studies

In Study CV181008 (Phase 2b), the frequencies of hypersensitivity AEs were 1.8%, 2.1%, 3.2%, 0%, 3.8%, and 1.5% in the saxagliptin 2.5, 5, 10, 20, 40 mg and placebo groups, respectively. Several individual PTs occurred with a frequency  $\geq 1\%$  in the -40 mg cohort; however sample sizes were very small. None were reported in the 100 mg cohort.

PT (%)	Saxa 2.5 mg N=55	Saxa 5 mg N=47	Saxa 10 mg N=63	Saxa 20 mg N=54	Saxa 40 mg N=52	All Saxa N=271	Placebo N=67
Total Subjects with an Event	1 (1.8)	1 (2.1)	2 (3.2)	0	2 (3.8)	6 (2.2)	1 (.5)
Face Edema	0	0	0	0	2 (3.8)	2 (0.7)	0
Drug Hypersensitivity	1 (1.8)	0	0	0	0	1 (0.4)	0
Eyelid Edema	0	0	1 (1.6)	0	0	1 (0.4)	0
Gingival Swelling	0	0	1 (1.6)	0	0	1 (0.4)	0
Hypersensitivity	0	1 (2.1)	0	0	0	1 (0.4)	0
Periorbital Edema	0	0	0	0	1 (1.9)	1 (0.4)	0
Angioedema	0	0	0	0	0	0	1 (1.5)

Source: Integrated Summary of Safety, Appendix 7.8.3.1

There were no SAEs associated with hypersensitivity. One subject withdrew because of a hypersensitivity AE:

- Subject CV181008-126-98 was a 69 year old female in the saxagliptin 40mg group who had face edema on Day 93. The event required no treatment. The Investigator characterized it as possible related to study drug.

In Study CV181041 (MOA), no saxagliptin-treated subjects had a hypersensitivity AE.

Angioedema

Angioedema is briefly mentioned here as a subset of hypersensitivity reactions. The PT of angioedema was reported in 2 subjects (1 saxagliptin; 1 placebo) across the Phase 2/3 program. They are described here:

- Subject CV181038-60-419 was a 58 year old female in the saxagliptin 2.5 mg group with angioedema on Day 27. She had a history of chronic idiopathic urticaria and angioneurotic edema that pre-dated exposure to saxagliptin. The event required treatment (unspecified), but study drug was continued.
- Subject CV181008-116-169 was a 56 year old female in the placebo group with angioneurotic edema on Day 44. She had a history of idiopathic angioedema (shell fish). The event required treatment (unspecified) and resulted in interruption of study drug.

#### Localized Edema

Because symptomatic edema of the hands and feet has been clinically observed with another DPP-4 inhibitor, subjects were monitored for similar findings in this clinical development program. The Sponsor created a pre-defined list of lower level terms (LLTs) that reflect a diagnosis of localized edema. Table 7.61 summarizes the frequencies of localized edema, based on the pre-defined list, during the ST periods of the Core phase 3 studies.

With the exception of the add-on combination study to TZD, the studies had generally low rates of localized edema reported. This includes very low rates in the initial combination with metformin study (0.3% all saxagliptin vs. 0 metformin, data not shown).

In Study CV181013 (add-on to TZD), none of the events were SAEs or resulted in study discontinuation. The placebo group in this study had a higher frequency of localized edema AEs compared to the placebo groups in other studies. The frequency of these AEs was highest in the saxagliptin 5 mg group (7.0% vs. 2.7% in placebo subjects). The LLTs that comprised the 13 events observed in the 5 mg group were: pedal edema, eyelid edema, and periorbital swelling. There was only one AE of isolated foot swelling. This occurred in a female subject in 2.5 mg group on Day 169. This was treated with furosemide and reportedly resolved.

**Reviewer comment:** The package insert for Avandia® states that edema (not specifically localized edema) was noted in 4.8% of subjects treated with Avandia® in their monotherapy studies and, higher frequencies were observed in their combination studies (including sulfonylurea). The frequency observed in Study CV181013 in the placebo group (2.7%) is compatible with, although somewhat lower than, the Avandia® data. Although one would expect higher frequencies of edema AEs in a TZD add-on study compared to the other studies, it is notable that the combination of the TZD with saxagliptin resulted in a higher than expected frequency of this AE in the proposed 5 mg dose group.

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
<b>ST Period, Excluding Rescue</b>					
Pooled Monotherapy (CV181011, CV181038)	1.2% (3/247)	1.2% (3/252)	1.0% (1/98)	1.2% (7/597)	1.2% (2/169)
<b>Add-on Combination</b>					
+ Met (CV181014)	0 (0/192)	1.6% (3/191)	0.6% (1/181)	0.7% (4/564)	1.1% (2/179)

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+ 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)
<b>Up to Week 24, Regardless of Rescue Status</b>					
<b>Placebo-controlled</b>	0.9%	2.3%	0.7%	1.5%	1.1%
<b>Pooled Safety</b>	<b>(8/882)</b>	<b>(20/882)</b>	<b>(2/279)</b>	<b>(30/2043)</b>	<b>(9/799)</b>

Source: Summary of Clinical Safety, Table 2.3.6A

Localized edema events were also observed in the Phase 2b study (CV181008). Although localized edema was not reported in the 0, 100 mg cohort, events were seen in the 0-40 mg cohort. These AEs included: hand swelling, pedal edema, periorbital edema, swelling of eyelid, swelling of feet, swelling of fingers. These were seen in 3 subjects (4.8%) in the saxagliptin 10 mg group, 1 subject (1.9%) in the 20 mg group, 1 subject (1.9%) in the 40 mg group, and 1 subject in the placebo group.

#### Falls, Accidents, or Trauma-related AEs

The Sponsor created a pre-defined MedDRA PT list to identify subjects with falls, accidents, or trauma-related AEs in the ST+LT periods of the Phase 2/3 program. The Sponsor also reviewed the hypoglycemia AEs for all subjects with an AE of fall, accident, or trauma to evaluate if a temporal relationship existed.

Overall, 52 subjects reported a fall, accident, or trauma-related AE: 41 events (1.0%) among saxagliptin-treated subjects and 11 events (0.9%) among placebo/metformin subjects. Of the subjects who experienced such an AE, 6 (14.6%) of saxagliptin- and 3 (27.3%) of placebo-treated subjects also had an AE of hypoglycemia reported at some point during the study. All hypoglycemic AEs were reported in add-on combination studies. However, a temporal relationship was not found.

One subject (CV181013-74-386) who died as a result of an automobile accident was described under Deaths (Section 7.3.1). The event was considered not likely to be related to study drug.

#### Cardiovascular safety

As requested by the Division, the Sponsor analyzed cardiovascular events by type (ischemia-related, heart rate/rhythm-related, heart failure-related, and other) for the controlled Phase 2/3 database using standardized MedDRA queries (SMQs) for ischemic heart disease. Results of this analysis are shown below. Proportions of subjects with AEs in the Saxagliptin treatment groups and placebo appeared comparable across all 4 categories. The "all saxagliptin" group that the Sponsor created includes not only the 2.5 mg, 5 mg, and 10 mg treatment groups, but also the 20, 40, and 100 mg saxagliptin treatment groups from Phase 2b Study CV181008, increasing the denominator in this category by 150 subjects.

**Table 7.62. Summary of Cardiovascular Events by Event Type and by PT During ST + LT Treatment Period**

SOC (%) PT (%)	Saxa 2.5mg N=937	Saxa 5mg N=1269	Saxa 10mg N=1000	All Saxa <sup>a</sup> N=3356	Comparator <sup>b</sup> N=1251
<b>Total Subjects with an Event</b>	<b>50 (5.3)</b>	<b>54 (4.3)</b>	<b>40 (4.0)</b>	<b>144 (4.3)</b>	<b>60 (4.8)</b>
<b>1. Ischemic Heart Disease</b>	<b>13 (1.4)</b>	<b>15 (1.2)</b>	<b>9 (0.9)</b>	<b>37 (1.1)</b>	<b>20 (1.6)</b>
Coronary Artery Disease	5 (0.5)	6 (0.5)	3 (0.3)	14 (0.4)	5 (0.4)
Acute Myocardial Infarction	1 (0.1)	3 (0.2)	0	4 (0.1)	3 (0.2)
Angina Pectoris	2 (0.2)	3 (0.2)	3 (0.3)	8 (0.2)	7 (0.6)
Myocardial Ischemia	4 (0.4)	3 (0.2)	1 (0.1)	8 (0.2)	1 (<0.1)
Myocardial Infarction	0	1 (<0.1)	2 (0.2)	3 (<0.1)	3 (0.2)
Angina Unstable	1 (0.1)	0	0	1 (<0.1)	3 (0.2)
Coronary Artery Insufficiency	1 (0.1)	0	0	1 (<0.1)	0
<b>2. Cardiac Failure</b>	<b>7 (0.7)</b>	<b>4 (0.3)</b>	<b>4 (0.4)</b>	<b>15 (0.4)</b>	<b>7 (0.6)</b>
Cardiac Failure	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Cardiac Failure Congestive	2 (0.2)	1 (<0.1)	0	3 (<0.1)	4 (0.3)
Cardiogenic Shock	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Diastolic Dysfunction	3 (0.3)	1 (<0.1)	2 (0.2)	6 (0.2)	1 (<0.1)
Cardiac Failure Acute	0	0	1 (0.1)	1 (<0.1)	0
Dilatation Ventricular	1 (0.1)	0	0	1 (<0.1)	0
Left Ventricular Dysfunction	1 (0.1)	0	1 (0.1)	2 (<0.1)	0
Left Ventricular Failure	0	0	0	0	1 (<0.1)
Ventricular Hypokinesia	0	0	1 (0.1)	1 (<0.1)	0
<b>3. Cardiac Arrhythmias</b>	<b>31 (3.3)</b>	<b>30 (2.4)</b>	<b>25 (2.5)</b>	<b>86 (2.6)</b>	<b>30 (2.4)</b>
Sinus Bradycardia	1 (0.1)	5 (0.4)	1 (0.1)	7 (0.2)	3 (0.2)
Atrial Fibrillation	6 (0.6)	4 (0.3)	1 (0.1)	11 (0.3)	3 (0.2)
AV Block First Degree	1 (0.1)	4 (0.3)	0	5 (0.1)	2 (0.2)
Ventricular Extrasystoles	3 (0.3)	4 (0.3)	1 (0.1)	8 (0.2)	3 (0.2)
Palpitations	9 (1.0)	3 (0.2)	6 (0.6)	18 (0.5)	3 (0.2)
Bundle Branch Block Left	1 (0.1)	2 (0.2)	3 (0.3)	6 (0.2)	2 (0.2)
Bundle Branch Block Right	1 (0.1)	2 (0.2)	0	3 (<0.1)	2 (0.2)
Sinus Tachycardia	1 (0.1)	2 (0.2)	3 (0.3)	6 (0.2)	0
Supraventricular Extrasystoles	2 (0.2)	2 (0.2)	2 (0.2)	6 (0.2)	0
Supraventricular Tachycardia	2 (0.2)	2 (0.2)	1 (0.1)	5 (0.1)	0
Tachycardia	3 (0.3)	2 (0.2)	5 (0.5)	10 (0.3)	7 (0.6)
Arrhythmia	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
AV Block Complete	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
AV Block Second Degree	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Extrasystoles	3 (0.3)	1 (<0.1)	1 (0.1)	5 (0.1)	1 (<0.1)
Sinus Arrhythmia	0	1 (<0.1)	0	1 (<0.1)	0
AV Block	0	0	1 (0.1)	1 (<0.1)	0
Bradycardia	0	0	0	0	1 (<0.1)
Bundle Branch Block	0	0	1 (0.1)	1 (<0.1)	0
Conduction Disorder	1 (1.0)	0	0	1 (<0.1)	0
Ventricular Arrhythmia	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)

**Table 7.62. Summary of Cardiovascular Events by Event Type and by PT During ST + LT Treatment Period**

<b>4. Other</b>	<b>8 (0.9)</b>	<b>8 (0.6)</b>	<b>6 (0.6)</b>	<b>22 (0.7)</b>	<b>7 (0.6)</b>
Left Ventricular Hypertrophy	4 (0.4)	5 (0.4)	3 (0.3)	12 (0.4)	1 (<0.1)
Mitral Valve Incompetence	2 (0.2)	2 (0.2)	1 (0.1)	5 (0.1)	3 (0.2)
Aortic Valve Disease	1 (0.1)	1 (<0.1)	0	2 (<0.1)	0
Left Atrial Dilatation	4 (0.4)	1 (<0.1)	2 (0.2)	7 (0.2)	1 (<0.1)
Pericarditis	0	1 (<0.1)	0	1 (<0.1)	0
Aortic Valve Incompetence	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)
Aortic Valve Stenosis	0	0	1 (0.1)	1 (<0.1)	0
Atrial Hypertrophy	1 (0.1)	0	0	1 (<0.1)	0
Cardiovascular Disorder	0	0	1 (0.1)	1 (<0.1)	0
Dilatation Atrial	1 (0.1)	0	0	1 (<0.1)	0
Heart Valve Incompetence	0	0	0	0	2 (0.2)
Hypertensive Heart Disease	0	0	1 (0.1)	1 (<0.1)	0
Left Atrial Hypertrophy	1 (0.1)	0	0	1 (<0.1)	1 (<0.1)
Mitral Valve Disease	1 (0.1)	0	0	1 (<0.1)	0
Mitral Valve Prolapse	0	0	0	0	1 (<0.1)
Mitral Valve Sclerosis	1 (0.1)	0	0	1 (<0.1)	0
Tricuspid Valve Incompetence	0	0	0	0	1 (<0.1)

From Sponsor's Response to FDA day 74 Letter

<sup>a</sup> Includes the 2.5, 5, and 10mg saxagliptin treatment groups as well as the 20, 40, and 100mg saxagliptin treatment groups from Phase 2b Study CV181008.

<sup>b</sup> Includes placebo groups as well as the metformin monotherapy group from CV181039.

The table below includes narratives of subjects with Cardiovascular SAEs, Deaths, and AEs leading to discontinuation. The Sponsor was also asked to provide narratives for all subjects with potential cardiac PTs that may have been classified under other SOCs, such as "chest pain" and PTs related to abnormal EKGs. Using this method, the Sponsor identified an additional 2 subjects (CV181040-149-862 in the saxagliptin 2.5mg group and CV181014-183-1096 in the placebo group) who had no AE in the Cardiac SOC, but had cardiac procedures. The Sponsor recognized that these could have been coded differently, and these subjects were discussed in Section 7.1.2

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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

Subject	Event	Demographics	Treatment group	Duration of exposure prior to event	Sponsor PT	Division PT	Brief narrative
CV181011-142-778	SAE	49yo female	Saxagliptin 5mg	16 days	Supraventricular tachycardia	Same	The subject, who had no previous history of cardiovascular disease, experienced palpitations and EKG performed at the study center showed SVT with a heart rate of 181 beats/min. She was sent to the ER, where the event resolved and the subject was asymptomatic. The event did not recur, and the subject continued in the trial. The Investigator believes the event was possibly related to study drug.
CV181011-46-176	AE leading to discontinuation	34yo male	Saxagliptin 2.5mg	158 days	Tachycardia	Same	The subjects experienced concurrent events of tachycardia and acute left leg pain. EKGs were normal. No further information was provided. The Investigator considered the events possible and probably related to study drug.
CV181011-6-72	SAE	51yo male	Saxagliptin 5mg	44 days	Atrial fibrillation	Same	The subject, who had a history of left ventricular hypertrophy (LVH) and "heart flutter", presented to the ER with a feeling of an irregular heartbeat, and he was hospitalized. The subjects was treated with diltiazem and metoprolol and converted back to normal sinus rhythm (NSR). Cardiac enzymes were normal. The subject continued in the trial with no recurrence of atrial fibrillation. The Investigator considered the event unrelated to study drug.
CV181011-10-459	SAE	62yo man	Saxagliptin 2.5mg	234 days	Chest pain	Same	The subject, who had a medical history of coronary artery disease (CAD) and coronary

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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

CV181011-32-968	SAE	70yo female	Saxagliptin 5mg	58 days	Non-cardiac chest pain	Same	<p>artery bypass graft (CABG), was hospitalized for chest pain on Day 234. Study drug was interrupted for 2 days and the subject was treated with atenolol. On Day 277, the subject again developed chest pain as well as acute coronary syndrome. He was treated with isosorbide dinitrate, atenolol, and aspirin. A cardiac catheterization showed multiple stenoses and 3 stents were placed. Study drug was again briefly interrupted and he was started on clopidogrel. He continued in the study. The Investigator considered the event unrelated to study drug.</p> <p>The subject presented to the ER with chest pain and hypertension and was admitted. Study drug was interrupted. EKG and CPK were normal. All events resolved on Day 60. She resumed study drug on Day 61, although consent was withdrawn on Day 67. The Investigator considered the event unrelated to study drug.</p>
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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

Subject ID	SAE, AE leading to discontinuation	56yo male	Saxagliptin 5mg	210 days	Acute myocardial infarction, Cerebrovascular Accident (CVA)	Same	The subject, with a history of CAD and percutaneous coronary intervention, presented to the ER with chest pain and was diagnosed with acute myocardial infarction (AMI). Cardiac catheterization showed an occluded right coronary artery for which stents were placed. Study medication was interrupted. The event resolved the same day. On Day 211, the subject became aphasic and a CT showed a large left pontine infarction (CVA). The subject was discontinued from the study, and the event was ongoing at the time of last report. The Investigator considered both events unrelated to study drug
CV181011-37-532	SAE, AE leading to discontinuation	56yo male	Saxagliptin 5mg	210 days	Acute myocardial infarction, Cerebrovascular Accident (CVA)	Same	The subject, with a history of CAD and percutaneous coronary intervention, presented to the ER with chest pain and was diagnosed with acute myocardial infarction (AMI). Cardiac catheterization showed an occluded right coronary artery for which stents were placed. Study medication was interrupted. The event resolved the same day. On Day 211, the subject became aphasic and a CT showed a large left pontine infarction (CVA). The subject was discontinued from the study, and the event was ongoing at the time of last report. The Investigator considered both events unrelated to study drug
CV181011-72-590	SAE, AE leading to discontinuation	61yo male	Saxagliptin 2.5mg	343 days	Cardiac failure congestive	Same	The subject was taken to the ER with acute onset shortness of breath (SOB), where he was found to be tachypneic and hypotensive. He was diagnosed with pneumonia and congestive heart failure (CHF). He underwent a cardiac catheterization but results were not provided. The CHF resolved, and the subject was discharged on Day 352. The Investigator considered the events unrelated to study drug.
CV181011-109-178	SAE	52yo male	Saxagliptin 10mg	115 days	Chest pain	Same	The subject, with a history of stable angina, had thoracic pain that was unrelieved with sublingual nitroglycerin. He went to the ER, and EKG cardiac enzymes were normal. A stress test was negative. The subject was discharged 2 days later. The Investigator considered the event unrelated to study drug.

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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

Subject ID	SAE	64yo male	Saxagliptin 5mg	103 days	CVA	Same	Description
CV181011-114-144	SAE	64yo male	Saxagliptin 5mg	103 days	CVA	Same	The subject arrived at the ER with paresis and paresthesia of the left hand and was diagnosed with a CVA. Study drug was discontinued on Day 105 and never resumed. Imaging showed right carotid stenosis, and the subject underwent a right carotid endarterectomy. He was discharged on Day 155, at which time the event was considered resolved. The Investigator considered the event unrelated to study drug. The subject was removed from the study on Day 152 because he no longer met study criteria.
CV181011-174-950	SAE	70yo male	Saxagliptin 5mg	515 days	Coronary artery disease	Same	On Day 515, he was hospitalized due to 3-vessel CAD and underwent coronary artery bypass with saphenous vein grafts. Study drug was restarted on Day 520.
CV181011-128-746	SAE	51yo male	Placebo + Metformin 500mg (rescue started Day 465)	676 days	Chest pain, tachycardia	same	This subject experienced tachycardia that resolved with treatment. On Day 677, the Investigator reported SAEs of tachycardia and chest pain. In the ER, he was noted to have a HR of 208 beats/minute and was admitted. He was treated medically. Cardiac enzymes were negative, and a coronary angiogram on Day 678 showed no blockages. He was discharged the same day.
CV181011-165-310	SAE	73yo female	Placebo + Metformin 500mg	Day 529	Unstable angina	Same	This subject, with a history of CAD, was hospitalized due to shortness of breath and chest pain that was characterized as "unstable angina" and was unrelieved with nitroglycerin spray at home. Cardiac enzymes were negative, and EKG was normal. She was treated with medical therapy, and coronary angiography on Day 532 showed multi-vessel disease. Medical

**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

CV181014-13-126	SAE	54yo male	Saxagliptin 5mg + Metformin 2000mg	514 days	Myocardial infarction	Same	<p>treatment was continued, and she was discharged the same day.</p> <p>This subject was reported to have an MI on Day 514, but had discontinued study drug on Day 474 following instructions from his primary care physician. He underwent triple bypass surgery on Day 515. The subject later informed the Investigator that he had enrolled in another clinical study and refused to follow-up. The outcome of the event could not be confirmed. The Investigator considered the event unrelated to study drug.</p>
CV181014-46-180	SAE	68yo male	Saxagliptin 10mg + Metformin 2000mg + Pioglitazone 15mg (rescue started Day 549)	70 days	Coronary artery disease	Same	<p>This subject was hospitalized on Day 70 for coronary stent placement and received 2 coronary stents without complications. Study drug was resumed on Day 74.</p>
CV181014-56-701	SAE	50yo female	Saxagliptin 10mg + Metformin 1500mg + Pioglitazone 15mg (rescue started Day 50)	342 days	CVA	Same	<p>The subject presented with headache and left sided weakness. She also lost consciousness for 30 minutes. She was diagnosed with a CVA. Her condition improved and she was discharged from the hospital 5 days after onset. The Investigator judged the event as unrelated to study drug.</p>
CV181014-75-189	SAE, AE leading to discontinuation	74yo female	Saxagliptin 5mg + Metformin 2000mg + Pioglitazone 15mg (rescue started Day 227)	Day 688	Cardiac failure congestive	Same	<p>This subject, with a history of CAD and prior MI, was admitted with a diagnosis of CHF. EKG results are unavailable, but cardiac enzymes were normal. An EKG on Day 226 was normal, and a subsequent EKG on Day 704 showed an old infarction. Study drug was discontinued on Day 689. The event resolved on Day 692. The Investigator judged the event as related to</p>

**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

CV181014-114-368	SAE	56yo female	Saxagliptin 10mg + Metformin 2000mg	Day 16	Supraventricular tachycardia (SVT)	Same	<p>pioglitazone, but not related to saxagliptin or metformin.</p> <p>This subject presented to her physician with palpitations and was diagnosed with SVT with a HR of 140. Several hours later she developed substernal chest tightness radiating to the right neck and was sent to the ER. EKG showed junctional tachycardia with a HR of 150 and incomplete right bundle branch block (RBBB). Study drug was interrupted. She was treated with adenosine and symptomatically improved, and repeat EKG showed NSR with the incomplete RBBB. Troponin level was 0.498 (unknown units, normal range undetectable) and CK of 86U/L (normal range 10-80U/L). No further episodes were reported, but the hospital discharge date is unknown. Study drug was resumed on Day 18. The Investigator considered the event unrelated to study drug.</p>
CV181014-118-332	SAE, AE leading to discontinuation	53yo male	Saxagliptin 5mg + Metformin 2000mg	Day 443	Coronary artery disease	Same	<p>A pre-operative EKG was abnormal, and the subject was sent for cardiac catheterization on Day 443, which revealed multi-vessel disease. The subject subsequently underwent coronary artery bypass grafting on Day 446.</p>
CV181014-143-997	SAE	52yo male	Saxagliptin 2.5mg + Metformin 1500mg + Pioglitazone 15mg (rescue added Day 534)	Day 337	Coronary artery insufficiency	Same	<p>This subject, who had an AE of mild chest pain on Day 173 (coronary arteriography done on Day 230 showed 100% occlusion of right coronary artery), presented to the ER with chest pain and abdominal pain on Day 337. Echocardiogram was unchanged from baseline, and cardiac enzymes were negative. Coronary arteriography on Day</p>

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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

CV181014-167-638	SAE, AE leading to discontinuation	59yo female	Saxagliptin 10mg + Metformin 1500mg + Pioglitazone 15mg (rescue added Day 218)	Day 220	CVA	Same	<p>339 was unchanged from that performed on Day 230. Additional medical therapy was added. The Investigator considered the event unrelated to study drug.</p> <p>This subject, who had a history of CVA, was reported to have a CVA when she presented with left hemiparesis. Study medication was discontinued on Day 221. She was discharged on Day 234, at which time the event was considered resolved with sequela (unspecified). The Investigator considered the event unrelated to study drug.</p>
CV181014-171-1380	SAE	56yo female	Saxagliptin 10mg + Metformin 2500mg	Day 537	CVA	Same	<p>This subject presented with severe headache and vomiting on Day 537, and she was diagnosed with hypertensive crisis. She was discharged from the hospital on Day 540. Her headaches worsened and she was readmitted to the hospital on Day 541. A CT of the brain suggested subarachnoid hemorrhage, and CVA was diagnosed. Her condition improved, and she was discharged from the hospital on Day 573. The Investigator considered the event unrelated to study drug.</p>
CV181014-174-696	SAE	58yo male	Saxagliptin 5mg + Metformin 2500mg +	Day 119	Coronary artery disease (CAD)	Same	<p>This subject, who was first reported to have CAD on Day 92, was reported again to have CAD on Day 119. He was hospitalized for coronary revascularization on Day 119. Study drug was discontinued from Days 119-131. The subject did well. The Investigator considered the event unrelated to study drug.</p>
CV181014-175-839	SAE	54yo male	Saxagliptin 5mg + Metformin 1500mg	Day 210	Myocardial Infarction (MI)	Same	<p>This subject, with a prior history of CAD, was reported to have chest pain; an EKG showed an acute MI in the inferior wall.</p>

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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

CV181014-13-254	SAE, Death	48yo male	Placebo + Metformin 2000mg (background)	Day 405	Cardiac Failure Congestive	Same	<p>Percutaneous coronary intervention and stent placement was performed in the anterior descending artery the same day. Study drug was interrupted. The event was considered resolved on Day 212, and study drug was resumed on Day 213. The subject was reported to have another SAE of CAD on Day 266, and myocardial revascularization was performed on that day. He was discharged 6 days later. The Investigator considered both events unrelated to study drug.</p> <p>The subject was found dead at home. No autopsy was performed. The Investigator concluded CHF as the cause of death.</p>
CV181014-107-994	SAE	44yo male	Placebo + Metformin 2000mg (background) + Pioglitazone (15mg (rescue started Day 279))	Day 40	Myocardial Infarction, Unstable Angina	Same	<p>The subject presented to the ER with chest pain and was reported to have an MI. Cardiac catheterization and stenting were performed the same day. He was discharged from the hospital with the event resolved on Day 51. On Day 492, he experienced an SAE of unstable angina. He presented with chest pain, and cardiac enzymes were negative. He was discharged on Day 493.</p>
CV181014-167-700	SAE	54yo male	Placebo + Metformin 1500mg (background) + Pioglitazone 15mg (rescue added Day 541)	Day 13	Angina Pectoris	Same	<p>This subject consulted a cardiologist and an EKG showed subtle ischemic changes on the inferior side. The subject was hospitalized for coronary angiography, which revealed multi-vessel disease, from Days 14-15. On Day 21, he underwent bypass surgery without complications. The event resolved on Day 25.</p>
CV181014-171-1341	SAE, Death	35yo male	Placebo + Metformin	Day 157	Cardiogenic Shock,	Same	<p>The subject experienced an MI and died while awaiting assistance in the ER. An</p>

**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

CV181014-183-1096	AE leading to discontinuation, AE related to abnormal EKG	60yo male	Placebo + Pioglitazone 15mg (rescue added Day 466) + Metformin 2500mg (background)	Day 622	Abnormal EKG	Coronary artery disease	Myocardial Infarction	autopsy was not performed. Cardiogenic shock was listed as the primary cause of death.	This subject, with no history of cardiac disease, experienced dyspnea which was felt to be of cardiac origin. He underwent coronary angiography on Day 668, which demonstrated "severe both principal nodes illness". Angioplasty was performed on Day 668, and no further details were provided.	
CV181040-149-862	SAE, AE related to chest pain	64yo female	Saxagliptin 2.5mg + Glyburide 7.5mg (background)	Day 141	Chest pain	Coronary artery disease		This subject, who had no history of cardiac disease, was reported as having an SAE of chest pain. She was hospitalized and underwent an arteriogram with stent placement. Study drug was interrupted from Day 142-145. She was discharged on Day 145. She was readmitted with chest pain on Day 146. Angiography was repeated and results were pending. She was discharged on Day 147.		
CV181038-047-0636	SAE	38yo male	Saxagliptin 2.5mg/5mg qam	Day 53	Chest pain	Same		This subject, with a history of prior MI, PTCA, and unstable angina, presented to the ER on Day 53 with chest pain. Cardiac enzymes were normal. On Day 55 he underwent cardiac catheterization, which showed non-severe multi-vessel disease. Medical therapy was continued, Study drug was interrupted from Days 53-55. The Investigator considered the event unrelated to study drug.		
CV181038-055-455	SAE	69yo female	Saxagliptin 2.5mg qam	Day 47	Chest pain	Same		This subject had a history of prior MI and CHF and was admitted for unstable angina. She was treated with medical therapy and the event resolved on Day 67. Study drug was continued.		

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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

Subject ID	SAE	Subject	Saxagliptin	Days	Event	Outcome	Notes
CV181038-079-748	SAE	62yo female	Saxagliptin 2.5 mg/5 mg qam	Days 15, 174, and 181	Atrial fibrillation	Same	Subject with history of paroxysmal atrial fibrillation with multiple episodes of atrial fibrillation. Study drug was continued.
CV181038-23-297	SAE	68yo male	Saxagliptin 2.5 mg	Day 182	CAD	Same	This subject had a history of CAD and failed a routine stress test. He was hospitalized for coronary catheterization and 3 stents were placed. During another planned coronary stent placement on Day 213, the cardiologist advised the subject to first take pioglitazone for one month to soften plaque. He was then discontinued from the study because of concomitant pioglitazone therapy.
CV181038-51-543	SAE, other significant medical event	55yo female	Saxagliptin 2.5 mg	Day 197	Chest pain	Same	She was reported to have an AE of chest pain. All tests, including EKG, were normal. The subject continued in the study.
CV181038-87-811	SAE, AE leading to discontinuation	54yo female	Placebo	Day 84	Coronary Artery Disease	Myocardial Infarction	This subject was hospitalized with vomiting and chest pain. EKG showed T wave inversions in the inferior leads and ST elevation in V2-V4. She was treated with medical therapy. She was discharged from this hospital on Day 91 with the diagnosis of "extensive AW STEMI". The event was considered resolved on Day 162. After database lock, the Investigator reported the SAE as "Extensive Anterior Wall ST elevation".
CV181040-100-1810	SAE, Death, AE leading to discontinuation	68yo male	Saxagliptin 5mg + Glyburide 7.5mg (background)	Day 213	Acute MI, Atrioventricular Block Complete, Cardiogenic Shock	Same	This subject was found by his family to be diaphoretic, nauseous, and vomiting. He was hypotensive and bradycardic in the ER, and EKG showed ST segment elevation in leads II and III with a third degree AV block. Cardiac catheterization showed complete obstruction of the RCA. A pacemaker was placed on Day 213, but the subject remained hypotensive in the ICU. The subject

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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

CV181040-132-815	SAE	35yo male	Saxagliptin 2.5mg + Glyburide 7.5mg	Day 280	AMI	Same	expired on Day 214, and the cause of death was reported as cardiogenic shock. The last dose of study drug was taken on Day 212. The Investigator considered the events unrelated to study drug. The subject presented to the ER with chest pain, and the EKG showed acute posterior/inferior wall MI. Cardiac enzymes were elevated. The subject received medical care. Study drug was interrupted from Days 281-283. The subject was discharged from the hospital on Day 297. The Investigator considered the event not likely related to study drug.
CV181040-71-1612	SAE	70yo male	Saxagliptin 2.5mg + Glyburide 7.5mg	Day 52	Myocardial ischemia	Same	This subject, with a history of ischemic heart disease, was hospitalized on Day 52 for an elective coronary angiogram. This subject had PCI performed. On Day 57, the subject resolved on Day 59. The Investigator judged the event not related to study medication.
CV181040-149-862	SAE	64yo female	Saxagliptin 2.5mg + Glyburide 7.5mg	Day 141	Chest pain	Coronary artery disease	This subject was admitted for chest pain and underwent an arteriogram with stent placement. She was discharged on Day 145. Study drug was interrupted from Days 142-145. She was then readmitted on Day 146 with a recurrence of chest pain. The arteriogram was repeated (results not provided) and discharged on Day 147. The Investigator judged the event as not related to study drug.
CV181040-39-240	SAE	50yo male	Saxagliptin 2.5mg + Glyburide 7.5mg	Day 399	CAD	Same	This subject, with a history of myocardial ischemia, was hospitalized for an elective CABG, which was performed on Day 400 without complications. The subject was

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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

CV181040-71-1293	SAE	54yo female	Saxagliptin 2.5mg + Glyburide 7.5mg	Day 195	Myocardial ischemia	Same	discharged on Day 407, at which time study drug was resumed. The Investigator judged the event as possibly related to study drug. This subject, with a history of chest pain, underwent a cardiac catheterization on Day 195. The results were normal.
CV181040-10-439	SAE	48yo male	Placebo + Glyburide 2.5mg + Glyburide 7.5mg (background) + Metformin 1000mg (rescue started Day 64)	Day 418	AMI	Same	This subject, with no history of cardiac disease, awoke in the middle of the night with diaphoresis, dizziness, and right shoulder pain. In the hospital he was diagnosed with an AMI with a dysrhythmia. A cardiac catheterization with stent placement was performed. A cardiac electrophysiologic study was performed with ablation of an irritant pathway. The event resolved on Day 422.
CV181040-36-276	SAE	51yo male	Placebo + Glyburide 2.5mg + Glyburide 7.5mg (background)	Day 66	MI	Same	The subject experienced 2 episodes of chest pain with dyspnea. This occurred the following day. In the hospital an EKG showed Q waves in inferior leads. Cardiac enzymes were elevated, and a diagnosis of inferior wall MI was made. The event resolved on Day 67. Study drug was not interrupted.
CV181040-37-1006	SAE, other significant medical event	59yo male	Placebo + Glyburide 2.5mg + Glyburide 7.5mg (background)	Day 165	CVA	Same	This subject, with a history of CVA, was reported to have paresis, dysphagia, and severe hypertension. The diagnosis of CVA was made. CT suggested an ischemic stroke within the suprasellar cistern. On Day 175, the event resolved with sequelae and he was discharged. The subject discontinued the study due to transport difficulties following his CVA.
CV181040-47-1823	SAE	58yo female	Placebo + Glyburide 2.5mg + Glyburide	Day 190, Day 303	Chest Pain, CAD	Same	On Day 190, a non-serious AE of chest pain was reported. Study drug was discontinued. On Day 303, an SAE of CAD was reported.

**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

CV181040-68-1424	SAE, Death	58yo male	7.5mg (background) + Metformin 1000mg (rescue added Day 121)	Day 112	Sudden Cardiac Death	Same	This subject was hospitalized with a 2 month history of chest pain. An angiogram showed non-significant coronary artery disease.
CV181040-127-89	SAE, Death	62yo female	Placebo + Glyburide 2.5mg + Glyburide 7.5mg (background)	Day 201	Hemorrhagic Stroke	Same	This subject, who had a history of CAD and CVA, woke up complaining of chest pain and collapsed. CPR was initiated but he was pronounced dead on arrival at the hospital. The cause of death was acute MI.
CV181041-3-90	SAE	55yo male	Placebo + Metformin 500mg	Day 179	Unstable angina	Same	This subject, with a history of two prior strokes, developed acute left hemiplegia. A CT showed a large right parietal hemorrhage. On Day 209 her neurologic condition deteriorated and she died on Day 211.
CV181013-25-38	SAE	43yo male	Saxagliptin 2.5mg + Rosiglitazone 4mg (background)	Day 3	CVA, TIA	Same	This subject presented to the ER with chest discomfort, dyspnea, and diaphoresis, which was diagnosed as unstable angina. EKG was reportedly normal. A nuclear stress test was "markedly positive". Cardiac catheterization revealed multi-vessel disease, and the subject underwent bypass surgery on Day 182. He was discharged from the hospital on Day 187.
CV181013-154-964	SAE	60yo female	Saxagliptin 2.5mg + Pioglitazone 30mg (background)	Day 120	Chest pain	Same	The subject was reported as having a CVA on Day 3. Study drug was discontinued on Day 4, and he was given medical therapy. The event resolved with sequelae on Day 7, and study drug was resumed on Day 8.
CV181013-	SAE	63yo female	Saxagliptin 5mg +	Day 48	Chest pain	Same	The subject was reported to have chest pain and was hospitalized. Cardiac enzymes were negative, and acute coronary syndrome was ruled out. The subject continued in the study.

**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

Subject ID	SAE, AE leading to discontinuation	Age and Sex	Treatment	Day	Medical History	Outcome	Notes
231-663			Rosiglitazone 8mg (background)				radiating to the right arm. All tests were normal. The subject continued in the study.
CV181013-101-59	SAE, AE leading to discontinuation	46yo male	Placebo + Rosiglitazone 8mg (background)	Day 34	Angina Pectoris	Same	This subject presented to the hospital with angina pectoris, describing a 5-week history of chest pain and SOB on exertion and at rest, but relieved with nitroglycerin. Cardiac catheterization revealed a 90% ostial LAD stenosis.
CV181013-178-39	SAE	44yo male	Placebo + Rosiglitazone 4mg (background) + Metformin 1000mg (rescue added Day 452)	Day 530	Coronary Artery Disease, AMI	Same	This subject had an episode of severe SOB. EKG was read as "Q waves...suggestive of a septal infarct". Cardiac enzymes were elevated. The following day, a cardiac catheterization was performed, which showed 30-40% blockage in the RCA and 60% in the LAD. The event was considered resolved on Day 531.
CV181013-240-812	SAE	68yo male	Placebo + Rosiglitazone (background) + Metformin 500mg (rescue added Day 356)	Day 159	Coronary Artery Disease	Same	This subject was reported to have "chronic obstructive" CAD. Cardiac catheterization on Day 161 was performed, and bypass surgery was performed on Day 188. The event resolved with sequela (unspecified) on Day 198.
CV181013-256-804	SAE	58yo female	Placebo + Pioglitazone 30mg (background) + Metformin 500mg (rescue added Day 218)	Day 141	Coronary Artery Disease	Same	This subject had sudden onset epigastric discomfort radiating to the chest. EKG showed infero-lateral wall ischemia. Cardiac enzymes were negative. She was treated with ranitidine, which relieved her discomfort. Both events were considered resolved on Day 145.
CV181013-258-1107	SAE, AE leading to discontinuation	63yo female	Placebo + Pioglitazone 30mg (background)	Day 82	Congestive Cardiac Failure	Same	This subject awoke from sleep due to difficulty breathing. In the ER she was diagnosed with CHF. She received medical therapy and improved after 2 hours. The event was considered resolved on Day 87.
CV181013-76-451	SAE	73 year old male	Placebo + Pioglitazone 45mg	Day 116	TIA	Sponsor did not	N/A

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**Table 7.63. Narratives of Subjects with CV SAEs, Deaths, and AEs leading to discontinuation in Core Phase 3 Studies**

							provide narrative	
CV181039-3-1908	SAE, AE leading to discontinuation	67yo male	Saxagliptin 10mg/Metformin 500mg	Day 99	MI	Same	The subject was reported to have an inferior acute MI. Cardiac enzymes were positive and EKG showed a left bundle branch block (LBBB) with ST elevation in the inferior leads (baseline KEG showed LBBB). On the same day, cardiac catheterization showed 3-vessel coronary artery disease with critical lesions in the left anterior descending artery and left circumflex artery, as well as a critical acute-appearing thrombotic lesion in the distal right coronary artery. Treatment was given, but was not specified. On Day 99, study drug was discontinued and the subject withdrew from the study.	
CV181039-151-1044	SAE	54yo male	Saxagliptin 10mg/Metformin 500mg	Day 63	Hemorrhagic stroke	Same	The subject awoke with slurred speech and left-sided paralysis. A CT scan in the hospital showed an acute hemorrhage in the right external capsule. A repeat CT on Day 65 showed stable hemorrhage. On Day 68, he was discharged from the hospital with a shallow left residual nasolabial fold. Study drug was not interrupted. The Investigator judged the event as not likely related to study drug.	
CV181039-1-210	SAE, AE leading to discontinuation	51yo female	Saxagliptin 10mg/Metformin 500mg	Day 184	Acute cardiac failure	Same	This subject was reported to have acute-on-chronic diastolic heart failure and was hospitalized. On Day 212, the subject was discontinued from the study. The Investigator judged the event as not likely related to study drug.	
CV181039-47-165	SAE	57yo female	Saxagliptin 10mg + placebo	Day 234	Atrioventricular block	Same	This subject was hospitalized with atypical chest pain. EKG was significant for new 1 <sup>st</sup> degree AV block. Labs were not available.	

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CV181039-075-2877	SAE	51yo female	Saxagliptin 10mg + Metformin + Pioglitazone (rescue added Day 63)	Day 140	Severe Myocardial Infarction	Same	The subjects underwent permanent pacemaker implantation. Study drug was not interrupted. She was discharged to home on Day 236. The Investigator judged the event as not related to study drug. The subject was hospitalized with an MI. Study drug was not interrupted, and the subject was transferred to a rehabilitation unit on Day 162. Additional information is pending. The Investigator characterized the event as not related to study drug.
CV181039-148-943	Death	57yo male	Saxagliptin 10mg + Placebo	Day 294	Arteriosclerosis Coronary Artery Disease	Same	According to a relative, this subject died suddenly. The cause of death was atherosclerotic cardiovascular disease. The Investigator judged the event as not related to study drug.
CV181039-156-751	SAE	71yo female	Saxagliptin 5mg/Metformin 500mg + Pioglitazone (rescue added Day 89)	Day 294	Acute Myocardial Infarction, Cerebral Infarction	Same	This subject had discontinued the study on Day 269 for lack of efficacy. On Day 294, he had sudden onset of epigastric pain associated with vomiting and difficulty breathing. An EKG reveals sinus tachycardia with interventricular conduction defect, CXR showed bilateral pleural effusion, and echocardiogram showed global hypokinesia. Cardiac enzymes were positive. On Day 295, the subject had a cerebrovascular infarction. The subject was intubated for one day. The event reportedly resolved with sequelae on Day 295. The Investigator judged both events as not likely related to study drug.
CV181039-232-2798	SAE, Death	55yo male	Saxagliptin 10mg/Metformin 500mg	Day 254	Sudden Death	Same	This subject, who had no history of ischemic heart disease or peripheral vascular disease, was reported to have sudden cardiac death. There was no medical observation of the death and no

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	SAE	64yo male	Saxagliptin 10mg + Placebo + Pioglitazone 15mg (rescue began Day 244)	Day 221	Ischemic Stroke	Same	medical assistance was performed.
CV181039-237-2639	SAE, Death	65yo male	Placebo + Metformin 500mg	Day 144	Cardiac Failure	Same	This subject experienced dyslalia and vertigo and was hospitalized on Day 222. An MRI indicated ischemic stroke. The event resolved with sequelae of right paresis, and the subject was discharged on Day 225. Study drug was interrupted on Day 221 and restarted on Day 222. The subject, with no history of CHF, complained of stomach pain on Day 143 and was found dead in his home the next day. An autopsy was performed, and the cause of death was noted as "left ventricular failure".
CV181039-140-1597	SAE, Death	60yo male	Placebo + Metformin 500mg	Day 6	AMI	Same	This subject, with a history of prior MI, felt severe chest pain. He became unconscious during transport and EKG showed asystole.
CV181039-141-1059	SAE, Death	62yo male	Placebo + Metformin	Day 130	CVA	Same	This subject presented with torpor, aphasia and was hospitalized for stroke. A CT and MRI noted a right cerebral hematoma and brain edema. On Day 131, he underwent burr hole surgical drainage of an intracerebral hematoma. On Day 133 he was transferred to the ICU, and he was found to have a hematoma relapse on Day 135. On the same day, the subject had acute cardiovascular and respiratory insufficiency and could not be resuscitated. An autopsy confirmed the cause of death as acute cerebral circulation impairment of the hemorrhagic type.

**Reviewer comment: The Division requested the Sponsor to explain why the following subject, who appeared to have had an obvious MACE event, was not coded as such. Details of these subjects are found in the table above.**

- **CV181038-87-811 (placebo group): The Investigator reported the SAE as “extensive anterior wall ST elevation myocardial infarction” after the database lock. Although the initial MACE analysis sent to the Division did not include this as a MACE event, the Sponsor agreed that this event be classified as a MACE event.**

### **MACE ANALYSIS**

The Sponsor was also requested to perform a composite MACE analysis (cardiovascular death, non-fatal MI, and non-fatal stroke) using the controlled Phase 2/3 database. The results of this analysis, including the total numbers of randomized subjects with at least 1 MACE event in the Phase 2b/3 program, are shown in the table below. In order to perform this analysis, the Sponsor used their own list of selected PTs to search all AEs in the Phase 2b/3 clinical database (as of cutoff of NDA filing). This list was extracted from a pre-specified list of PTs developed for analyses of CV events for the NDA submission and was formulated as a subset of select MedDRA SMQs. The original pre-specified list was intended to identify CV AEs which were acute, ischemic, and clinically relevant. A subset of PTs from this list was then used to identify MACE events, which include stroke, myocardial infarction, and CV death. In general, in order to be chosen for the MACE list, PTs were required to represent events that were acute, symptomatic, and thromboembolic in nature. In addition, a clinical review of all deaths was performed to identify additional MACE events. The pooled Phase 2b/3 population, as well as each individual Phase 2b/3 study, was evaluated. The 10 mg open-label experience from Study CV181011 was not included in the analysis below. However, no MACE events were identified in subjects from the 10 mg open-label cohort of CV181011 and no deaths from any cause were reported in this cohort.

Addition terms were identified by the Sponsor that required clinical review prior to classification as a MACE event. These terms included: “infarction” unqualified, “silent MI”, and cerebral or coronary events which included the term “occlusion”, and serious cardiac rhythm disturbances. This addition review yielded 2 subjects who were identified with the PT “infarction”. These subjects, one in the 2.5 mg saxagliptin + Glyburide group in Study CV181040 and another in the saxagliptin 10 mg group in Study CV181039, both had abnormal EKGs at baseline, with additional abnormalities noted at other visits that were not related to a specific clinical event. Therefore, these 2 subjects could not be confidently classified as having MACE events and were therefore not included in the MACE frequency table below.

Finally, in order to include a subject that died from a CV-related condition coded with a PT absent from the MACE PT list, a review of all deaths in Phase 2b/3 studies was performed. Every reported death in the Phase 2b/3 program was assessed to ascertain whether the underlying cause was CV related based on the descriptive PT and a review of the case details. Deaths were classified as CV-related if the associated PTs either: 1) fell under the SOC Cardiac Disorders; 2) were stroke-related; 3) were suggestive of sudden death; or 4) were related to other vascular events. The output used to summarize MACE events was then compared against this assessment

to determine if any CV deaths were not included in the initial output. In the Phase 2b/3 program, there were 16 deaths reported as of the cutoff dates for the NDA submission. Of these 16, 11 were considered CV-related. Of these 11, 7 were already accounted for in the programmed output. There were 4 remaining deaths (2 in the saxagliptin 10 mg group and 2 in the comparator group) that were not categorized as MACE events. Nevertheless, they are included in the table below. Based on this analysis, there did not appear to be an increased rate of MACE events in the saxagliptin groups, particularly the lower dose groups. Among the saxagliptin groups, subjects treated with 10 mg had the highest number of MACE events. The total subject-years of exposure in the comparator group was 1015 compared with 2941 in the “all saxa” group. Therefore the overall pool had a ratio of approximately 3 subjects on saxagliptin to 1 on comparator.

**Table 7.64. Summary of MACE Events for Controlled Phase 2b/3 Pooled Population and by Phase 2b and 3 Studies**

Population	Number (%)				
	Saxa 2.5mg N=937	Saxa 5mg N=1269	Saxa 10mg N=1000	All Saxa* N=3356	Comparator** N=1251
Pooled 2b/3	2 (0.2)	5 (0.4)	10 (1.0)	17 (0.5)	12 (1.0)
CV181008			None		
CV181011	0	2 (1.9)	0	2 (0.7)	0
CV181013	1 (0.5)	0	N/A	1 (0.3)	1 (0.5)
CV181014	0	1 (0.5)	4 (2.2)	5 (0.9)	3 (1.7)
CV181038			None		
CV181039	N/A	1 (0.3)	6 (0.9)	7 (0.7)	3 (0.9)
CV181040	1 (0.4)	1 (0.4)	N/A	2 (0.4)	5 (1.9)
CV181041			None		

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

Source: Sponsor's "Response to FDA day 74 Letter dated 12-Sep-2008", Ques. 7, Table 1

### **Diabetes Mellitus Guidance**

In July 2008, the Endocrine and Metabolic Drugs Advisory Committee voted in favor of requiring applicants to conduct long-term clinical trials or to provide equivalent evidence in ruling out an unacceptable cardiovascular safety risk for drugs and biologics developed for the treatment of type 2 diabetes. After internal discussions following that meeting, the FDA issued a Guidance entitled “Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”. This Guidance (which is included in the FDA briefing document for the saxagliptin advisory committee meeting) makes recommendations for changes in the clinical development program for drugs and biologics under development for the treatment of type 2 diabetes in order to evaluate the cardiovascular safety of the investigational therapy.

The Guidance conveys the following important points:

- An independent cardiovascular endpoints committee should be established to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possible other endpoints.
- Phase 2 and phase 3 clinical trials should be appropriately designed and conducted so that a meta-analysis can be performed at the time of data analysis. This includes enrolling subjects with a higher risk of cardiovascular events.
- It is likely that the controlled trials will need to last more than the typical 3 to 6 months duration to obtain sufficient numbers of events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these drugs that are used as chronic therapies.
- For completed studies, a comparison of the incidence of important cardiovascular events occurring with the study drug versus the control group should be performed. Sponsors should show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. This can be done by several methods: a meta-analysis of the phase 2 and phase 3 clinical trials or an additional single, large safety trial should be conducted before NDA/BLA submission.
- If the upper bound of the two-sided 95 percent confidence interval is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be done by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed required postmarketing safety trial.
- If the premarketing application contains data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk is less than 1.3, a postmarketing cardiovascular trial may not be necessary.

The New Drug Application for saxagliptin was under review within the Division at the time the Guidance was issued. Nonetheless, FDA has publicly communicated that unapproved drugs that were in late stage development and those that were under FDA review at the time the guidance was issued, will also be asked to provide adequate evidence of cardiovascular safety before approval. The remainder of this document describes FDA's method of making this assessment.

#### **Definitions of Major Adverse Cardiovascular Events (MACE)**

During the initial review of this NDA and another NDA that was the subject of the April 2-3, 2009 advisory committee meetings, requests for MACE analyses were sent to the respective applicants. While results of these analyses were somewhat informative, it was noted that the individual terms chosen to represent "MACE" differed widely between the two sponsors. The Division determined that more uniform MACE analyses were imperative to evaluating cardiovascular risk for these anti-diabetic products.

Post hoc adjudication of all events was not possible due to inadequate information. Therefore, it was decided to instead use a collection of MedDRA preferred terms for myocardial infarction

and stroke, as originally coded, with the addition of cardiovascular deaths. Two endpoints were chosen, one intended to broadly capture all possible strokes and myocardial infarctions; and one intended to include those terms which seemed likely to be chosen as the term to describe an event that truly was a myocardial infarction or a stroke. The broad endpoint was a composite endpoint of cardiovascular death, and all preferred terms in the Standardized MedDRA Queries (SMQ) for “Myocardial Infarction” and “Central Nervous System Haemorrhages and Cerebrovascular Accidents.” This endpoint is referred to as the “Broad SMQ MACE”. The more specific endpoint, referred to as the “Custom MACE”, is a subset of the “Broad SMQ MACE”. This endpoint was developed by collaboration of three FDA clinical reviewers. Without considering which events had actually occurred, each clinical reviewer independently reviewed the list of all possible terms included in the “Broad SMQ MACE”. The clinical reviewer then considered each term, with this question in mind: “If I had a patient who actually had a myocardial infarction or a stroke, is this a Preferred Term that I might actually have chosen for such an event?”, with the goal of selecting only those Preferred Terms that seemed more likely to represent events that would be a myocardial infarction or a stroke. The interest was also that these events likely represent acute events with a mechanism of atherosclerotic plaque development followed by plaque rupture/thrombosis (as opposed to events with non-atherosclerotic mechanisms, e.g. rupture of congenital aneurysm). The three reviewers’ lists were compared, and any terms for which there was not unanimous agreement to include or exclude were open for discussion. Consensus was reached on which terms were included. The clinical reviewer acknowledges that this is an imperfect process; other reasonable physicians may have chosen a different set of terms. Also, although the MedDRA SMQs are broad, they may not be all-inclusive. For example, the MedDRA Broad Myocardial Infarction SMQ does not contain the terms “cardiac arrest” or “circulatory collapse”.

A comprehensive list of preferred terms that defined the two individual endpoints described above is organized alphabetically in Table 9.2 in the Appendix. In addition, this table includes the preferred terms used in the initial MACE analysis conducted by the applicant (“Prior BMS MACE”) submitted prior to FDA’s Information Request for the uniform MACE analyses.

The saxagliptin database was queried for these terms with the first event for each patient counted as a MACE event. Only these first events were analyzed by both the applicant and by FDA.

In addition to events identified through MedDRA preferred terms, all data for subjects who died were assessed retrospectively to ascertain if the underlying cause was CV-related based on the descriptive preferred term and a review of case details. Deaths were classified as CV-related if the associated preferred terms either: 1) fell under the System-Organ-Class of Cardiac Disorders; 2) were stroke-related; 3) were suggestive of sudden death; or 4) were related to other vascular events. This approach yielded six such CV deaths among saxagliptin-treated patients; four of these occurred in the ST+LT period as reported in the NDA submission. The two additional CV deaths, determined by a clinical review of all deaths, occurred between the NDA submission and the 120-Day Safety Update cutoff dates. These two deaths were not initially identified as MACE events because of ambiguity related to their last dose of study drug at the time of the interim database lock. It was later confirmed that both subjects were taking study drug until the fatal event.

There were 10 CV-related deaths among the comparator-treated patients (6 patients treated with placebo and 4 patients treated with metformin). One subject in the placebo group of Study CV181038 had an “extensive anterior wall ST elevation myocardial infarction” that was not reported as a MACE event before database lock. This subject was not included in the FDA MACE analyses. Note that inclusion of this one event would weigh in favor of saxagliptin but the impact would be trivial given the small sample size and the low event rates of the study. Note that the applicant has included this event in some analyses.

As already described, the database for the analysis of MACE is composed of 8 Phase 2b/3 studies; Studies CV181008, CV181011, CV181013, CV181014, CV181038, CV181039, CV181040, and CV181041. Seven of these eight studies are placebo- controlled and one is metformin-controlled (Study CV181039).

Analyses were performed of the following:

1. short-term (ST), 24-week periods
2. short-term (ST) plus long-term (LT) periods (120-day Safety Update database).

The ST data excludes data collected after glycemic rescue; while the ST + LT data includes data following initiation of rescue therapy. All patients (rescued patients and trial completers) who continued into the long-term period remained on double-blind, randomized treatment. In the monotherapy trials (CV181011 and CV181018), placebo-treated patients who completed the ST period without being rescued, were given double-blind metformin in addition to placebo during the LT period. The majority of randomized patients continued into the long-term period of the study; 78% of saxagliptin-treated patients and 76% of comparator-treated patients. In the long-term period, rescued patients were also being treated with open-label rescue anti-diabetic medication. It is reasonable to assess safety from the ST+LT data because blinded treatment is continued. One must assume however that the add-on open-label rescue medication would not differentially impact the collection of safety data. The latter may be problematic given that the use of rescue was significantly different between saxagliptin and comparator. Nonetheless, there is value in the LT safety evaluation because it compares saxagliptin to a background of standard anti-diabetic therapies, while attempting to maintain some degree of balance in glycemic control between treatment groups. Therefore, looking at both ST data and ST+LT data is informative.

### **Results for Custom Mace**

All events that satisfied the definition of a Custom MACE event are shown in Table 7.65 below; the top part of the table shows the ST period events and the bottom, the ST+LT events. The number of events for each preferred term (PT) is the number of first events for that particular PT so patients are counted once on each line of the table.

Looking at the individual PTs, there is no evidence of dose response and no single PT is dominant.

**Table 7.65. Custom MACE: Observed Preferred Terms**

<b>ST Treatment Period</b>					
<b>System-Organ-Class (%)</b>	<b>Saxa 2.5 mg</b>	<b>Saxa 5 mg</b>	<b>Saxa 10 mg</b>	<b>All Saxa</b>	<b>Comparator</b>
<b>Preferred Term (%)</b>	<b>N=937</b>	<b>N=1269</b>	<b>N=1000</b>	<b>N=3356</b>	<b>N=1251</b>
<b>Total Subjects with an Event</b>	<b>1 (0.1)</b>	<b>1 (&lt;0.1)</b>	<b>2 (0.2)</b>	<b>4 (0.1)</b>	<b>7 (0.6)</b>
<b>Cardiac Disorders</b>	<b>0</b>	<b>0</b>	<b>1 (0.1)</b>	<b>1 (&lt;0.1)</b>	<b>5 (0.4)</b>
Acute Myocardial Infarction	0	0	0	0	1 (<0.1)
Cardiac Failure	0	0	0	0	1 (<0.1)
Cardiogenic Shock	0	0	0	0	1 (<0.1)
Myocardial Infarction	0	0	1 (0.1)	1 (<0.1)	3 (0.2)
<b>General Disorders and Administration</b>					
<b>Site Conditions</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.1)</b>
Sudden Cardiac Death	0	0	0	0	1 (<0.1)
<b>Nervous System Disorders</b>	<b>1 (0.1)</b>	<b>1 (&lt;0.1)</b>	<b>1 (0.1)</b>	<b>3 (&lt;0.1)</b>	<b>1 (&lt;0.1)</b>
Cerebrovascular Accident	1 (0.1)	1 (<0.1)	0	2 (<0.1)	1 (<0.1)
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	0

Source: Applicant's "Response to Letter from the FDA, 11-Jan-2009, Table 2.2"

<b>ST + LT Treatment Period</b>					
<b>System Organ Class (%)</b>	<b>Saxa 2.5mg</b>	<b>Saxa 5mg</b>	<b>Saxa 10mg</b>	<b>All Saxa</b>	<b>Comparator</b>
<b>Preferred Term (%)</b>	<b>N=937</b>	<b>N=1269</b>	<b>N=1000</b>	<b>N=3356</b>	<b>N=1251</b>
<b>Total Subjects with an Event</b>	<b>6 (0.6)</b>	<b>6 (0.5)</b>	<b>11 (1.1)</b>	<b>23 (0.7)</b>	<b>17 (1.4)</b>
<b>Cardiac Disorders</b>	<b>2 (0.2)</b>	<b>4 (0.3)</b>	<b>4 (0.4)</b>	<b>10 (0.3)</b>	<b>12 (1.0)</b>
Acute Myocardial Infarction	2 (0.2)	3 (0.2)	0	5 (0.1)	5 (0.4)
Atrioventricular Block Complete	0	1 (<0.1)	0	1 (<0.1)	0
Cardiogenic Shock	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Myocardial Infarction	0	1 (<0.1)	2 (0.2)	3 (<0.1)	5 (0.4)
Arteriosclerosis Coronary Artery	0	0	1 (0.1)	1 (<0.1)	0
Cardiac Arrest	0	0	1 (0.1)	1 (<0.1)	0
Cardiac Failure	0	0	0	0	1 (<0.1)
Cardiac Failure Congestive	0	0	0	0	1 (<0.1)
<b>General Disorders and Administration</b>					
<b>Site Conditions</b>	<b>0</b>	<b>1 (&lt;0.1)</b>	<b>1 (0.1)</b>	<b>2 (&lt;0.1)</b>	<b>2 (0.2)</b>
Sudden Death	0	1 (<0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)
Sudden Cardiac Death	0	0	0	0	1 (<0.1)
<b>Nervous System Disorders</b>	<b>4 (0.4)</b>	<b>3 (0.2)</b>	<b>5 (0.5)</b>	<b>12 (0.4)</b>	<b>3 (0.2)</b>
Cerebrovascular Accident	3 (0.3)	2 (0.2)	3 (0.3)	8 (0.2)	2 (0.2)
Cerebral Infarction	1 (0.1)	1 (<0.1)	0	2 (<0.1)	0
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)

Ischemic Stroke	0	0	1(0.1)	1 (<0.1)	0
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Applicant's "Response to Letter from the FDA, 11-Jan-2009", Table 2.4

Event rates of Custom MACE were low across all groups and there is no evidence of a dose response in individual studies or for the studies pooled. Overall, the rate in the comparator group (0.6%) exceeded that of all saxagliptin-treated subjects (0.1%). In particular, cardiac disorders were seen more frequently in the comparator group (0.4%) compared to the saxagliptin groups (<0.1%). The rates of events in nervous system disorders were comparable for all groups.

These findings changed only slightly when looking at Custom MACE for the ST and LT treatment periods (Table 7.66 below). Using both periods, the comparator rate (1.4%) still exceeded that of all saxagliptin groups (0.7%). Once again, cardiac disorders were seen more frequently in the comparator group (1.0% versus 0.3% for saxagliptin-treated subjects). Also, similar to the analysis of the ST period, nervous system disorders appeared comparable across all groups.

**Table 7.66. Incidence of Custom MACE by Dose of Saxagliptin and by Study**

<b>ST Treatment Period</b>					
	<b>Saxa 2.5 mg n/N (%)</b>	<b>Saxa 5 mg n/N (%)</b>	<b>Saxa 10 mg n/N (%)</b>	<b>All Saxa n/N (%)</b>	<b>Comparator n/N (%)</b>
Pooled	1/937 (0.1)	1/1269 (<0.1)	2/1000 (0.2)	4/3356 (0.1)	7/1251 (0.6)
CV181008	0/55 (0)	0/47 (0)	0/63 (0)	0/315 (0)	0/108 (0)
CV181011	0/102 (0)	1/106 (0.9)	0/98 (0)	1/306 (0.3)	0/95 (0)
CV181013	1/195 (0.5)	0/186 (0)	NA	1/381 (0.3)	0/184 (0)
CV181014	0/192 (0)	0/191 (0)	0/181 (0)	0/564 (0)	2/179 (1.1)
CV181038	0/145 (0)	0/146 (0)	NA	0/291 (0)	0/74 (0)
CV181039	NA	0/320 (0)	2/658 (0.3)	2/978 (0.2)	3/328 (0.9)
CV181040	0/248 (0)	0/253 (0)	NA	0/501 (0)	2/267 (0.7)
CV181041	NA	0/20 (0)	NA	0/20 (0)	0/16 (0)
<b>ST+LT Treatment Period</b>					
	<b>Saxa 2.5 mg n/N (%)</b>	<b>Saxa 5 mg n/N (%)</b>	<b>Saxa 10 mg n/N (%)</b>	<b>All Saxa n/N (%)</b>	<b>Comparator n/N (%)</b>
Pooled	6/937 (0.6)	6/1269 (0.5)	11/1000 (1.1)	23/3356 (0.7)	17/1251 (1.4)
CV181008	0/55 (0)	0/47 (0)	0/63 (0)	0/315 (0)	0/108 (0)
CV181011	0/102 (0)	2/106 (1.9)	0/98 (0)	2/306 (0.7)	1 (1.1)
CV181013	3/195 (1.5)	1/186 (0.5)	NA	4/381 (1.0)	1/184 (0.5)
CV181014	1/192 (0.5)	1/191 (0.5)	4/181 (2.2)	6/564 (1.1)	4/179 (2.2)
CV181038	0/145 (0)	0/146 (0)	NA	0/291 (0)	0/74 (0)
CV181039	NA	1/320 (0.3)	7/658 (1.1)	8/978 (0.8)	5/328 (1.5)
CV181040	2/248 (0.8)	1/253 (0.4)	NA	3/501 (0.6)	6/267 (2.2)
CV181041	NA	0/20 (0)	NA	0/20 (0)	0/16 (0)

The lack of a dose response suggested that the saxagliptin doses may be combined for an overall analysis stratified on study.

The Custom MACE results (Table 7.67 below) show reduced risk of a CV event due to saxagliptin compared to control (predominantly placebo) with some analyses (incidence rate ratio and odds ratio for the ST period) showing statistically significant reductions of more than 50%. However, the event rates are low with a total of 11 events in the ST period and a total of 40 events in the ST+LT period and the risk difference is small (<1%) and is not statistically significant.

The results for Custom MACE changed little with analysis population (ST versus ST+LT) or with statistical method; in all cases the upper bound of the 95% confidence interval is less than 1.3. According to the guidance, meeting a boundary of 1.3 may suggest that a post-marketing study for assessing CV safety is not necessary.

**Table 7.67. Overall Results for Custom MACE**

	<b>Saxagliptin (N=3356)</b>	<b>Comparator (N=1251)</b>
<b>Patient-years</b>		
ST	1295	458
ST+LT	3753	1289
<b>Events (%)</b>		
ST	4 (0.1%)	7 (0.6%)
ST+LT	23 (0.7%)	17 (1.3%)
<b>Events/1000 patient-years</b>		
ST	3	15
ST+LT	6	13
<b>Study-stratified Estimate of Treatment Difference<sup>1</sup> (95% CI)</b>		
<b>Odds Ratio – Exact method</b>		
ST	0.21 (0.04, 0.8)	
ST+LT	0.52 (0.26, 1.04)	
<b>Incidence Rate Ratio</b>		
ST	0.20 (0.04, 0.79)	
ST+LT	0.48 (0.24, 0.96)	
<b>Risk Difference</b>		
ST	-0.4% (-1.0%, +0.1%)	
ST+LT	-0.6% (-1.3%, +0.1%)	

1- Odds ratios under 1 and risk differences less than 0 favor saxagliptin.

Source: Joint Clinical and Statistical Briefing Document for Endocrinologic and Metabolic Drugs Advisory Committee meeting, NDA 22,350

**Table 7.68. Custom MACE: Observed Preferred Terms**

<b>ST Treatment Period</b>					
<b>System-Organ-Class (%)</b>	<b>Saxa 2.5 mg</b>	<b>Saxa 5 mg</b>	<b>Saxa 10 mg</b>	<b>All Saxa</b>	<b>Comparator</b>
<b>Preferred Term (%)</b>	<b>N=937</b>	<b>N=1269</b>	<b>N=1000</b>	<b>N=3356</b>	<b>N=1251</b>
<b>Total Subjects with an Event</b>	<b>1 (0.1)</b>	<b>1 (&lt;0.1)</b>	<b>2 (0.2)</b>	<b>4 (0.1)</b>	<b>7 (0.6)</b>
Cardiac Disorders	0	0	1 (0.1)	1 (<0.1)	5 (0.4)
Acute Myocardial Infarction	0	0	0	0	1 (<0.1)
Cardiac Failure	0	0	0	0	1 (<0.1)
Cardiogenic Shock	0	0	0	0	1 (<0.1)
Myocardial Infarction	0	0	1 (0.1)	1 (<0.1)	3 (0.2)
General Disorders and Administration					
Site Conditions	0	0	0	0	1 (<0.1)
Sudden Cardiac Death	0	0	0	0	1 (<0.1)
Nervous System Disorders	1 (0.1)	1 (<0.1)	1 (0.1)	3 (<0.1)	1 (<0.1)
Cerebrovascular Accident	1 (0.1)	1 (<0.1)	0	2 (<0.1)	1 (<0.1)
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	0

Source: Applicant's "Response to Letter from the FDA, 11-Jan-2009, Table 2.2

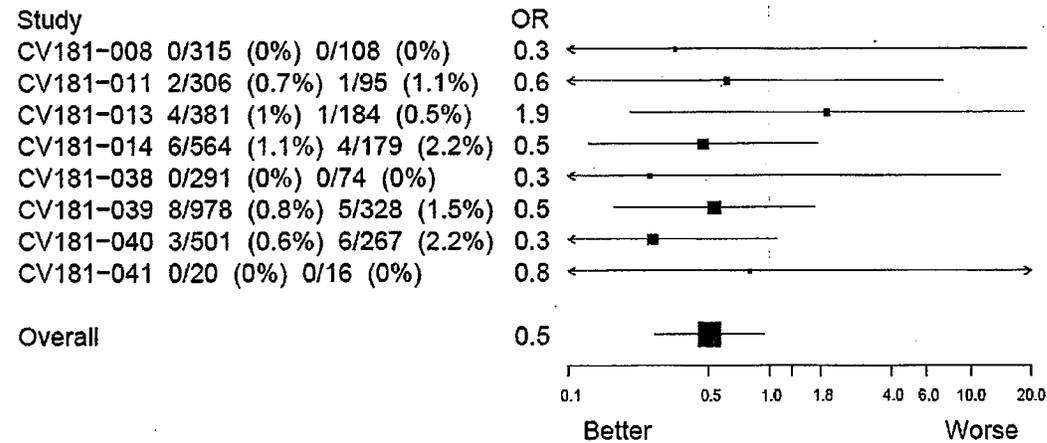
<b>ST + LT Treatment Period</b>					
<b>System Organ Class (%)</b>	<b>Saxa 2.5mg</b>	<b>Saxa 5mg</b>	<b>Saxa 10mg</b>	<b>All Saxa</b>	<b>Comparator</b>
<b>Preferred Term (%)</b>	<b>N=937</b>	<b>N=1269</b>	<b>N=1000</b>	<b>N=3356</b>	<b>N=1251</b>
<b>Total Subjects with an Event</b>	<b>6 (0.6)</b>	<b>6 (0.5)</b>	<b>11 (1.1)</b>	<b>23 (0.7)</b>	<b>17 (1.4)</b>
Cardiac Disorders	2 (0.2)	4 (0.3)	4 (0.4)	10 (0.3)	12 (1.0)
Acute Myocardial Infarction	2 (0.2)	3 (0.2)	0	5 (0.1)	5 (0.4)
Atrioventricular Block Complete	0	1 (<0.1)	0	1 (<0.1)	0
Cardiogenic Shock	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Myocardial Infarction	0	1 (<0.1)	2 (0.2)	3 (<0.1)	5 (0.4)
Arteriosclerosis Coronary Artery	0	0	1 (0.1)	1 (<0.1)	0
Cardiac Arrest	0	0	1 (0.1)	1 (<0.1)	0
Cardiac Failure	0	0	0	0	1 (<0.1)
Cardiac Failure Congestive	0	0	0	0	1 (<0.1)
General Disorders and Administration					
Site Conditions	0	1 (<0.1)	1 (0.1)	2 (<0.1)	2 (0.2)
Sudden Death	0	1 (<0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)
Sudden Cardiac Death	0	0	0	0	1 (<0.1)
Nervous System Disorders	4 (0.4)	3 (0.2)	5 (0.5)	12 (0.4)	3 (0.2)
Cerebrovascular Accident	3 (0.3)	2 (0.2)	3 (0.3)	8 (0.2)	2 (0.2)
Cerebral Infarction	1 (0.1)	1 (<0.1)	0	2 (<0.1)	0
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)
Ischemic Stroke	0	0	1(0.1)	1 (<0.1)	0

Applicant's "Response to Letter from the FDA, 11-Jan-2009", Table 2.4

A forest plot (Figure 7.1) of the results by study and overall for the ST+LT period show consistently favorable results for saxagliptin (with the exception of Study CV181013). In addition, the Kaplan-Meier curve (Figure 5 on the following page) illustrates that the event rate differences persist through the LT period.

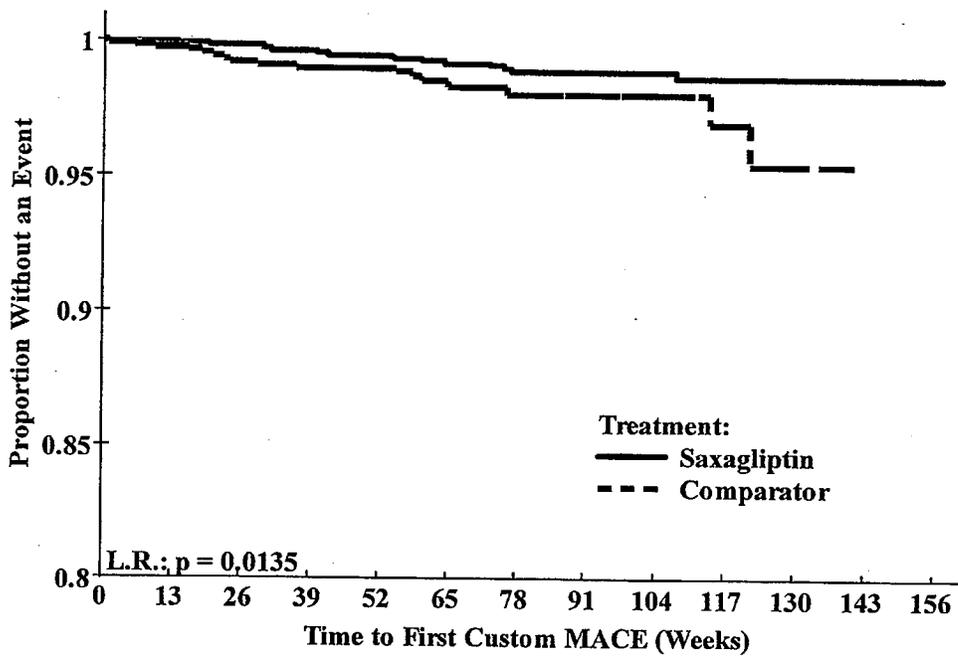
**Figure 7.1. Forest Plot of Custom MACE Results – ST+LT**

Odds Ratios



Source: Joint Clinical and Statistical Briefing Document for Endocrinologic and Metabolic Drugs Advisory Committee meeting, NDA 22,350

Figure 7.2. Kaplan-Meier Plot of Custom MACE Results – ST+LT



Source: Joint Clinical and Statistical Briefing Document for Endocrinologic and Metabolic Drugs Advisory Committee meeting, NDA 22,350