

Results for Broad SMQ MACE

As shown earlier, the SMQ MACE endpoint is a broad endpoint so the event rate for SMQ MACE was notably greater than the rate observed for Custom MACE. In comparing SMQ MACE events from the ST period (Table 7.69 below) to Custom MACE events, it is important to note that a disproportionately large number of subjects represented in the SMQ MACE analysis had a PT of “blood creatine phosphokinase increased”. Fifty of the 58 first SMQ MACE events for the saxagliptin group and 14 of the 25 SMQ MACE events for the comparator group were creatine phosphokinase (CPK) increases. Of note, CPK was measured routinely in all patients at select clinic visits. Therefore this PT alone, which may easily not represent an important cardiovascular event, comprised a significant number of events in the broad SMQ analysis. This was also true for the ST+LT period where additional events of increased CPK were observed; again the majority of first Broad SMQ MACE events for the saxagliptin group and about half of the events for comparator were recorded as increased CPK.

Table 7.69. SMQ MACE: Observed Preferred Terms

ST Treatment Period					
System Organ Class (%)	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Comparator
Preferred Term (%)	N=937	N=1269	N=1000	N=3356	N=1251
Total Subjects with an Event	16 (1.7)	18 (1.4)	19 (1.9)	58 (1.7)	25 (2.0)
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)
Investigations	14 (1.5)	17 (1.3)	16 (1.6)	52 (1.5)	14 (1.1)
Blood Creatine Phosphokinase Increased	14 (1.5)	16 (1.3)	15 (1.5)	50 (1.5)	14 (1.1)
Electrocardiogram ST Segment Abnormal	0	1 (<0.1)	0	1 (0.1)	0
Blood Creatine Phosphokinase MB Increased	0	0	1 (0.1)	1 (0.1)	0
Nervous System Disorders	1 (0.1)	1 (<0.1)	2 (0.2)	4 (0.1)	5 (0.4)
Cerebrovascular Accident	1 (0.1)	1 (<0.1)	0	2 (<0.1)	1 (<0.1)
Carotid Artery Stenosis	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)
Cerebrovascular Disorder	0	0	0	0	1 (<0.1)
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	0
Transient Ischemic Attack	1 (0.1)	0	0	1 (<0.1)	3 (0.2)
Vascular Disorders	1 (0.1)	0	1 (0.1)	2 (<0.1)	0
Infarction	1 (0.1)	0	1 (0.1)	2 (<0.1)	0

Source: Applicant's "Response to Letter from the FDA, 11-Jan-2009", Table 2.1

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Table 7.70. ST + LT Treatment Period

SOC (%)	Saxa 2.5 mg N=937	Saxa 5 mg N=1269	Saxa 10 mg N=1000	All Saxa N=3356	Comparator N=1251
PT (%)					
Total Subjects with an Event	28 (3.0)	37 (2.9)	30 (3.0)	100 (3.0)	41 (3.3)
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)
Investigations	19 (2.0)	29 (2.3)	18 (1.8)	71 (2.1)	19 (1.5)
Blood Creatine Phosphokinase Increased	19 (2.0)	28 (2.2)	17 (1.7)	69 (2.1)	19 (1.5)
Electrocardiogram ST Segment Abnormal	0	1 (<0.1)	0	1 (<0.1)	0
Blood Creatine Phosphokinase MB Increased	0	0	1 (0.1)	1 (<0.1)	0
Nervous System Disorders	5 (0.5)	6 (0.5)	6 (0.6)	17 (0.5)	10 (0.8)
Cerebrovascular Accident	3 (0.3)	2 (0.2)	3 (0.3)	8 (0.2)	2 (0.2)
Carotid Artery Stenosis	0	1 (<0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)
Cerebellar Hemorrhage	0	1 (<0.1)	0	1 (<0.1)	0
Cerebral Hematoma	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Cerebral Infarction	1 (0.1)	1 (<0.1)	0	2 (<0.1)	0
Carotid Arteriosclerosis	0	0	0	0	1 (<0.1)
Carotid Artery Disease	1 (0.1)	0	0	1 (<0.1)	0

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Cerebrovascular Disorder	0	0	0	0	0	1 (<0.1)
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Ischemic Stroke	0	0	1 (0.1)	1 (<0.1)	0	0
Transient Ischemic Attack	1 (0.1)	0	0	1 (<0.1)	5 (0.4)	0
Vascular Disorders	2 (0.2)	0	1 (0.1)	3 (<0.1)	0	0
Infarction	2 (0.2)	0	1 (0.1)	3 (<0.1)	0	0

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

As for the Custom MACE endpoint, no dose response was seen for the SMQ MACE endpoint (Table 7.71 below) where again a higher percentage of events is seen for comparators than for any dose of saxagliptin overall and for most of the studies individually.

Table 7.71. Incidence of SMQ MACE by Dose of Saxagliptin and by Study

ST Treatment Period					
	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa n/N (%)	Comparator n/N (%)
Pooled	16/937 (1.7)	18/1269 (1.4)	19/1000 (1.9)	58/3356 (1.7)	25/1251 (2.0)
CV181008	1/55 (1.8)	3/47 (6.4)	0/63 (0)	9/315 (2.9)	1/108 (0.9)
CV181011	0/102 (0)	2/106 (1.9)	1/98 (1.0)	3/306 (1.0)	2/95 (2.1)
CV181013	5/195 (2.6)	5/186 (2.7)	NA	10/381 (2.6)	3/184 (1.6)
CV181014	5/192 (2.6)	1/191 (0.5)	5/181 (2.8)	11/564 (2.0)	3/179 (1.7)
CV181038	2/145 (1.4)	1/146 (0.7)	NA	3/291 (1.0)	1/74 (1.4)
CV181039	NA	0/320	13/658 (2.0)	13/978 (1.3)	6/328 (1.8)
CV181040	3/248 (1.2)	6/253 (2.4)	NA	9/501 (1.8)	8/267 (3.0)
CV181041	NA	0/20	NA	0	1/16 (6.3)
ST + LT Treatment Period (120 Day Safety Update Database)					
	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa n/N (%)	Comparator n/N (%)
Pooled	28/397 (3.0)	37/1269 (2.9)	30/1000 (3.0)	100/3356 (3.0)	41/1251 (3.3)
CV181008	1/55 (1.8)	3/47 (6.4)	0/63 (0)	9/315 (2.9)	1/108 (0.9)
CV181011	0/102 (0)	4/106 (3.8)	2/98 (2.0)	6/306 (2.0)	4.95 (4.2)
CV181013	9/195 (4.6)	10/186 (5.4)	NA	19/381 (5.0)	4/184 (2.2)
CV181014	6/192 (3.1)	6/191 (3.1)	9/181 (5.0)	21/564 (3.7)	6/179 (3.4)
CV181038	3/145 (2.1)	1/146 (0.7)	NA	4/291 (1.4)	2/74 (2.7)
CV181039	NA	2/320 (0.6)	19/658 (2.9)	21/978 (2.1)	11/328 (3.4)
CV181040	9/248 (3.6)	11/253 (4.3)	NA	20/501 (4.0)	12/267 (4.5)
CV181041	NA	0/20 (0)	NA	0/20 (0)	1/16 (6.3)

The results for SMQ MACE, for both ST and ST+LT, show essentially no treatment difference with estimates of 0.85 to 0.96. The upper bounds for the 95% confidence intervals are less than or equal to 1.52 for all analyses so this data satisfies the 1.8 boundary but not the 1.3 boundary set by the guidance.

The interpretation of the SMQ MACE results compared to the Custom MACE results are complicated by the inclusion of the events defined by increased CPK in the SMQ endpoint. As noted earlier, the primary difference between the two endpoints is the inclusion of these events. Because more events of increased CPK occurred in the saxagliptin group than the comparator group (ST+LT: 2.1% versus 1.4%, respectively), the inclusion of these events shifts the estimate to the right (Custom MACE point estimate of 0.5→SMQ point estimate of 0.96).

Table 7.72. Overall Results for SMQ MACE

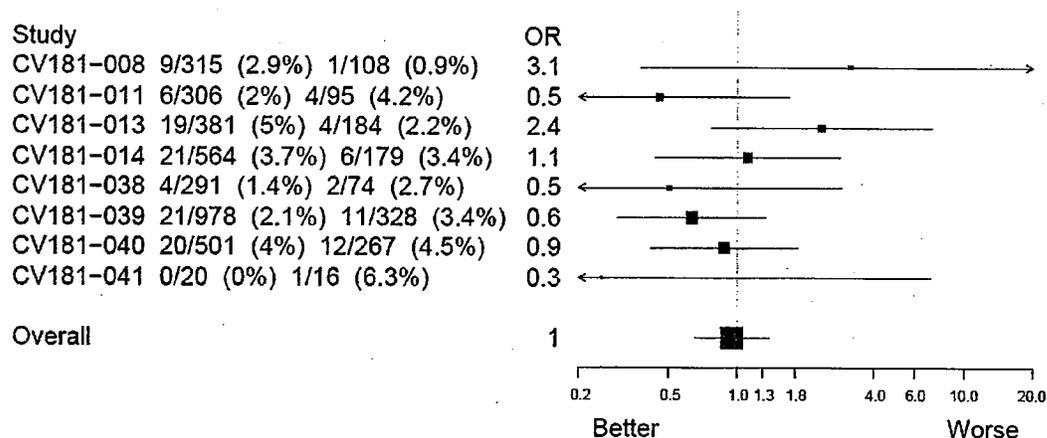
	Saxagliptin (N=3356)	Comparator (N=1251)
Patient-years		
ST	1295	458
ST+LT	3753	1289
Events (%)		
ST	58 (1.8%)	25 (2.0%)
ST+LT	100 (3.1%)	41 (3.2%)
Events/1000 pt-years		
ST	46	54
ST+LT	28	32
Study-stratified Estimate of Treatment Difference¹ (95% CI)		
Odds Ratio – Exact method		
ST	0.90 (0.55, 1.52)	
ST+LT	0.96 (0.65, 1.42)	
Incidence Rate Ratio		
ST	0.85 (0.52, 1.42)	
ST+LT	0.89 (0.61, 1.31)	
Risk Difference		
ST	-0.2% (-1.1%, +0.7%)	
ST+LT	-0.1% (-1.3%, +1.0%)	

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

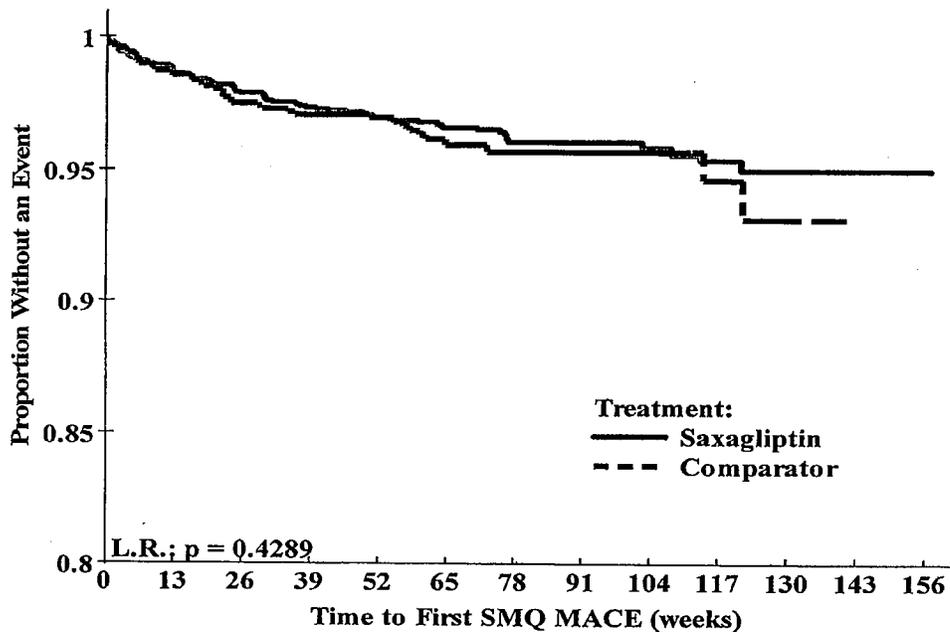
The forest plot for SMQ MACE (Figure 7.3 below) shows the contribution of each study to the overall estimate of risk and that no single study shows significant increased or decreased risk of MACE events due to saxagliptin. The Kaplan-Meier curve also provides further support for no treatment difference.

Figure 7.3. Forest Plot of SMQ MACE Odds Ratio Results – ST+LT



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

Figure 7.4. Kaplan-Meier Plot of SMQ MACE Results – ST+LT



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

Conclusions regarding MACE events:

- The MACE results produced by FDA and the Sponsor met the Guidance criterion of an upper bound on the 95% CI of the odds ratio of the less than 1.8.
- The Custom MACE results showed upper bounds for the CI less than 1.3, regardless of analytical approach.

The results of the advisory committee meeting are discussed in detail in Section 9.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Pooled Monotherapy Studies

Table 7.73 Summarizes the most common AEs ($\geq 2\%$) by PT during the ST period for the Pooled Monotherapy Analysis. Hypoglycemic events are excluded from this analysis and have been discussed separately in Section 7.3.5. Overall, the proportion of subjects with AEs during the ST

period was higher in all saxagliptin treatment groups (64.4%, 65.65%, and 76.5% in the saxagliptin 2.5, 5, and 10 mg groups, respectively) compared to placebo (59.8%). The most frequent AEs across all treatment groups were URI and headache.

Table 7.73. Most Common AEs (Incidence $\geq 2\%$)--Summary by PT During Short-term Treatment Period for Pooled Monotherapy

Preferred Term	Placebo N=169	All Saxa N=597	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98
Upper Resp. Tract Infection	17 (10.1)	53 (8.9)	21 (8.5)	21 (8.3)	11 (11.2)
Headache	9 (5.3)	34 (5.7)	9 (3.6)	14 (5.6)	11 (11.2)
Nasopharyngitis	8 (4.7)	29 (4.9)	12 (4.9)	11 (4.4)	6 (6.1)
Urinary Tract Infection	6 (3.6)	28 (4.7)	12 (4.9)	12 (4.8)	4 (4.1)
Sinusitis	3 (1.8)	25 (4.2)	11 (4.5)	8 (3.2)	6 (6.1)
Diarrhea	4 (2.4)	22 (3.7)	11 (4.5)	5 (2.0)	6 (6.1)
Pain in Extremity	5 (3.0)	21 (3.5)	10 (4.0)	8 (3.2)	3 (3.1)
Arthralgia	3 (1.8)	19 (3.2)	5 (2.0)	9 (3.6)	5 (5.1)
Cough	4 (2.4)	16 (2.7)	9 (3.6)	5 (2.0)	2 (2.0)
Peripheral edema	5 (3.0)	16 (2.7)	9 (3.6)	5 (2.0)	2 (2.0)
Musculoskeletal Pain	1 (0.6)	16 (2.7)	6 (2.4)	6 (2.4)	4 (4.1)
Rash	1 (0.6)	15 (2.5)	7 (2.8)	5 (2.0)	3 (3.1)
Influenza	1 (0.6)	14 (2.3)	4 (1.6)	5 (2.0)	5 (5.1)
Nausea	2 (1.2)	14 (2.3)	5 (2.0)	7 (2.8)	2 (2.0)
Hypertension	5 (3.0)	13 (2.2)	5 (2.0)	6 (2.4)	2 (2.0)
Dizziness	8 (4.7)	13 (2.2)	3 (1.2)	9 (3.6)	1 (1.0)
Vomiting	1 (0.6)	13 (2.2)	5 (2.0)	7 (2.8)	1 (1.0)
Back pain	8 (4.7)	12 (2.0)	3 (1.2)	9 (3.6)	0
Insomnia	4 (2.4)	12 (2.0)	5 (2.0)	6 (2.4)	1 (1.0)
Depression	2 (1.2)	12 (2.0)	4 (1.6)	5 (2.0)	3 (3.1)
Pharyngitis	4 (2.4)	10 (1.7)	5 (2.0)	4 (1.6)	1 (1.0)
Bronchitis	0	10 (1.7)	7 (2.8)	2 (0.8)	1 (1.0)
Dyspepsia	0	10 (1.7)	8 (3.2)	1 (0.4)	1 (1.0)
Fatigue	1 (0.6)	10 (1.7)	3 (1.2)	5 (2.0)	2 (2.0)
Sinus Congestion	2 (1.2)	10 (1.7)	3 (1.2)	5 (2.0)	2 (2.0)
Contusion	1 (0.6)	9 (1.5)	7 (2.8)	1 (0.4)	1 (1.0)
Muscle Spasms	3 (1.8)	8 (1.3)	3 (1.2)	2 (0.8)	3 (3.1)
Myalgia	2 (1.2)	7 (1.2)	5 (2.0)	1 (0.4)	1 (1.0)
Constipation	5 (3.0)	7 (1.2)	3 (1.2)	4 (1.6)	0
Gastritis	0	7 (1.2)	2 (0.8)	2 (0.8)	3 (3.1)
Toothache	1 (0.6)	7 (1.2)	5 (2.0)	2 (0.8)	0

Table 7.73. Most Common AEs (Incidence $\geq 2\%$)--Summary by PT During Short-term Treatment Period for Pooled Monotherapy

Preferred Term	Placebo N=169	All Saxa N=597	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98
Paraesthesia	4 (2.4)	7 (1.2)	4 (1.6)	2 (0.8)	1 (1.0)
Sciatica	0	7 (1.2)	4 (1.6)	1 (0.4)	2 (2.0)
Pyrexia	0	7 (1.2)	3 (1.2)	1 (0.4)	3 (3.1)
Contact Dermatitis	0	7 (1.2)	6 (2.4)	1 (0.4)	0
Pain	2 (1.2)	6 (1.0)	2 (0.8)	2 (0.8)	2 (2.0)
Pharyngolaryngeal Pain	5 (3.0)	6 (1.0)	1 (0.4)	3 (1.2)	2 (2.0)
Hematuria	1 (0.6)	6 (1.0)	1 (0.4)	3 (1.2)	2 (2.0)
Blood Pressure Increased	0	5 (0.8)	2 (0.8)	1 (0.4)	2 (2.0)
GERD	0	5 (0.8)	1 (0.4)	2 (0.8)	2 (2.0)
Eczema	2 (1.2)	5 (0.8)	5 (2.0)	0	0
Gastroenteritis Viral	0	4 (0.7)	1 (0.4)	0	3 (3.1)
Lower Resp. Tract Infection	0	4 (0.7)	2 (0.8)	0	2 (2.0)
Burning Sensation	1 (0.6)	4 (0.7)	0	2 (0.8)	2 (2.0)
Anxiety	0	4 (0.7)	0	2 (0.8)	2 (2.0)
Ear pain	0	4 (0.7)	1 (0.4)	1 (0.4)	2 (2.0)
Palpitations	1 (0.6)	3 (0.5)	1 (0.4)	0	2 (2.0)
Rash Papular	0	3 (0.5)	0	1 (0.4)	2 (2.0)
Carpal Tunnel Syndrome	0	3 (0.5)	1 (0.4)	0	2 (2.0)
Pneumonia	0	2 (0.3)	0	0	2 (2.0)

Source: Summary of Clinical Safety, Table 2.1.1.1A

Abbreviations: GERD=Gastroesophageal Reflux Disease

Table 7.74 presents the most common and more frequent AEs in the monotherapy studies. Events were included in this table if the frequency of AEs was $\geq 2\%$ in either the All Saxa or placebo group and there was an absolute difference of more than 1% in either direction between any saxagliptin group and the placebo group. The following AEs were more frequent ($\geq 1\%$ difference) in the all saxagliptin group compared to placebo: urinary tract infection, sinusitis, influenza, vomiting, nausea, diarrhea, arthralgia, musculoskeletal pain, and rash. Focusing on specific dose groups, the saxagliptin 10 mg group had the highest frequency of upper respiratory tract infection, sinusitis, influenza, diarrhea, arthralgia, musculoskeletal pain, and headache, when compared with any other group (saxagliptin or placebo). The group receiving saxagliptin 5 mg, the proposed dose, had the highest frequency of vomiting and nausea compared with any group. The following AEs were also more frequent ($>1\%$ difference) in the saxagliptin 5 mg group compared to placebo: urinary tract infection, sinusitis, influenza, vomiting, nausea, arthralgia, musculoskeletal pain, and rash.

Table 7.74. Most Common AEs (≥2%) and More Frequent (>1%) with Any Saxagliptin Group or Placebo During ST Period for Monotherapy Populations					
SOC/PT (Number and % of subjects)	Placebo-controlled Studies				
	Pooled Monotherapy				
	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
Infections and Infestations					
Upper resp. tract infection	21 (8.5)	21 (8.3)	11 (11.2)	53 (8.9)	17 (10.1)
Urinary tract infection	12 (4.9)	12 (4.8)	4 (4.1)	28 (4.7)	6 (3.6)
Sinusitis	11 (4.5)	8 (3.2)	6 (6.1)	25 (4.2)	3 (1.8)
Influenza	4 (1.6)	5 (2.0)	5 (5.1)	14 (2.3)	1 (0.6)
Pharyngitis	5 (2.0)	4 (1.0)	1 (1.0)	10 (1.7)	4 (2.4)
Gastrointestinal Disorders					
Vomiting	5 (2.0)	7 (2.8)	1 (1.0)	13 (2.2)	1 (0.6)
Nausea	5 (2.0)	7 (2.8)	2 (2.0)	14 (2.3)	2 (1.2)
Diarrhea	11 (4.5)	5 (2.0)	6 (6.1)	22 (3.7)	4 (2.4)
Constipation	3 (1.2)	4 (1.6)	0 (0.0)	7 (1.2)	5 (3.0)
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	5 (2.0)	9 (3.6)	5 (5.1)	19 (3.2)	3 (1.8)
Back pain	3 (1.2)	9 (3.6)	0 (0.0)	12 (2.0)	8 (4.7)
Pain in extremity	10 (4.0)	8 (3.2)	3 (3.1)	21 (3.5)	5 (3.0)
Musculoskeletal pain	6 (2.4)	6 (2.4)	4 (4.1)	16 (2.7)	1 (0.6)
Nervous System Disorders					
Headache	9 (3.6)	14 (5.6)	11 (11.2)	34 (5.7)	9 (5.3)
Dizziness	3 (1.2)	9 (3.6)	1 (1.0)	13 (2.2)	8 (4.7)
Paraesthesia	4 (1.6)	2 (0.8)	1 (1.0)	7 (1.2)	4 (2.4)
Vascular Disorders					
Hypertension	5 (2.0)	6 (2.4)	2 (2.0)	13 (2.2)	5 (3.0)
Investigations					
Blood Creatine Phosphokinase Increased	2 (0.8)	2 (0.8)	1 (1.0)	5 (0.8)	3 (1.8)
Skin and Subcutaneous Tissue Disorders					
Rash	7 (2.8)	5 (2.0)	3 (3.1)	15 (2.5)	1 (0.6)
Respiratory, Thoracic, and Mediastinal Disorders					
Cough	9 (3.6)	5 (2.0)	2 (2.0)	16 (2.7)	4 (2.4)
Pharyngolaryngeal Pain	1 (0.4)	3 (1.2)	2 (2.0)	6 (1.0)	5 (3.0)

Source: Summary of Clinical Safety, Table 2.1.1.1B

The following AEs appeared to have a possible dose-dependency: influenza, arthralgia, and headache.

Add-on Combination Studies

Table 7.75 presents the common AEs for the 3 add-on combination studies. Table 7.76 presents only the most common and frequent AEs versus placebo.

Add-on to Metformin: The overall frequency of AEs during the ST period (excluding rescue) was 78.1%, 69.6%, 71.8%, and 64.8% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. The most frequently reported AEs in saxagliptin-treated subjects were: nasopharyngitis, headache, diarrhea, URI, influenza, and UTI.

Add-on to SU: The overall frequency of AEs during the ST period was 71.4%, 70.4%, and 74.2% in the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. The most frequently reported AEs in saxagliptin-treated subjects were: UTI, headache, nasopharyngitis, URI, back pain, and hypertension.

Add-on to TZD: The overall frequency of AEs during the ST period was 61.5%, 74.2%, and 66.3% in the 2.5 mg, 5 mg, and placebo groups. The most frequently reported AEs in saxagliptin-treated subjects were: URI, peripheral edema, UTI, headache, and hypertension.

Table 7.75. Most Common AEs (Incidence ≥2%)--Summary PT During ST Period for the Add-on Combination Studies					
Add-on to Metformin (CV181014)					
	Placebo + Met	All Saxa	Saxa 2.5 mg + Met	Saxa 5 mg + Met	Saxa 10 mg + Met
Nasopharyngitis	14 (7.8)	49 (8.7)	18 (9.4)	13 (6.8)	19 (9.9)
Headache	13 (7.3)	45 (8.0)	18 (9.4)	11 (5.8)	16 (8.8)
Diarrhea	20 (11.2)	40 (7.1)	19 (9.9)	22 (5.8)	10 (5.5)
URI	9 (5.0)	37 (6.6)	13 (6.8)	9 (4.7)	15 (8.3)
Influenza	13 (7.3)	34 (6.0)	12 (6.3)	12 (6.3)	10 (5.5)
UTI	8 (4.5)	29 (5.1)	10 (5.2)	10 (5.2)	9 (5.0)
Arthralgia	5 (2.8)	25 (4.4)	8 (4.2)	8 (4.2)	9 (5.0)
Back pain	12 (6.7)	24 (4.3)	11 (5.7)	5 (2.6)	8 (4.4)
Hypertension	6 (3.4)	20 (3.5)	11 (5.7)	4 (2.1)	5 (2.8)
Cough	6 (3.4)	19 (3.4)	10 (5.2)	6 (3.1)	3 (1.7)
Vomiting	5 (2.8)	19 (3.4)	9 (4.7)	6 (3.1)	4 (2.2)
Dyspepsia	6 (3.4)	19 (3.2)	4 (2.1)	10 (5.2)	4 (2.2)
Nausea	7 (3.9)	17 (3.0)	6 (3.1)	4 (2.1)	7 (3.9)
Pain in extremity	10 (5.6)	17 (3.0)	5 (2.6)	4 (2.1)	8 (4.4)
Abdominal pain upper	3 (1.7)	15 (2.7)	5 (2.5)	6 (3.1)	4 (2.2)

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Table 7.84. Change from Baseline to Week 24 According to Urinalysis Parameter and Treatment Group for Pooled Monotherapy

	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
Microalbumin (mg/dL)	-1.247±0.896 -0.100 (-3.014, 0.520)	-0.788±0.766 -0.100 (-2.299, 0.723)	-2.239±2.272 -0.100 (-6.765, 2.288)	-1.209±0.613 -0.100 (-2.414, 0.005)	-0.017±0.333 -0.000 (-0.675, 0.641)
Creatinine (mg/dL)	-6.232±5.724 -4.000 (-17.52, 5.059)	1.259±5.360 -5.000 (-9.310, 11.827)	0.718±7.566 3.000 (-14.37, 15.808)	-1.905±3.509 -3.000 (-8.799, 4.990)	-1.953±6.100 -3.000 (-14.02, 10.117)
pH	0.064±0.034 0.000 (-0.003, 0.132)	0.080±0.035 0.000 (0.011, 0.148)	-0.136±0.071 0.000 (-0.277, 0.005)	0.039±0.024 0.000 (-0.008, 0.085)	0.026±0.047 0.000 (-0.066, 0.118)

Source: Response to FDA Question Received on 18-March-2009
 Plus-minus values are means±SD. Values with parentheses are median (min, max).

7.4.1.2.1.2 Add-on Combination Studies

7.4.1.2.1.2.1 Hematology

Add-on to Metformin

Table 7.85 summarizes the changes from baseline to Week 24 for hematology parameters for Study CV181014. Lymphocytes and platelets have previously been addressed in Section 7. For all parameters, there were no clinically significant changes over time.

Table 7.85. Change from Baseline to Week 24 According to Hematology Parameter and Treatment Group for Study CV181014				
	Saxa 2.5 mg + Met	Saxa 5 mg + Met	Saxa 10 mg + Met	Placebo + Met
	N=137	N=140	N=131	N=103
Basophils (10 ³ c/uL)	-0.02±0.01 0.0 (0, 0)	-0.02±0.01 0.0 (0, 0)	-0.01±0.00 0.0 (0, 0)	-0.02±0.01 0.0 (0, 0)
Eosinophils (10 ³ c/uL)	-0.03±0.03 0 (-0.1, 0)	-0.02±0.02 0 (-0.1, 0)	-0.02±0.01 0 (-0.1, 0)	0.01±0.01 0 (0, 0)
Hemoglobin (g/dL)	-0.22±0.07 -0.20 (-0.4, -0.1)	-0.24±0.06 -0.30 (-0.4, -0.1)	-0.25±0.07 -0.15 (-0.4, -0.1)	-0.12±0.07 -0.10 (-0.3, 0)
Hematocrit (%)	-0.31±0.21 0 (-0.7, 0.1)	-0.32±0.21 0 (-0.7, 0.1)	-0.36±0.22 0 (-0.8, 0.1)	-0.20±0.26 0 (-0.7, 0.3)
Monocytes (10 ³ c/uL)	0.01±0.02 0 (0, 0)	0.01±0.02 0 (0, 0)	0.00±0.01 0 (0, 0)	0.01±0.01 0 (0, 0)
Neutrophils (10 ³ c/uL)	0.02±0.10 0.10 (-0.2, 0.2)	0.22±0.15 0.10 (-0.1, 0.5)	0.18±0.10 0.10 (0, 0.4)	0.00±0.12 0.06 (-0.2, 0.3)

Source: Clinical Study Report, CV181014, Appendix 7.5

Add-on to Sulfonylurea

Table 7.86 summarizes the changes from baseline to Week 24 for hematology parameters for Study CV181014. Lymphocytes and platelets have previously been addressed in Section 7. For all parameters, there were no clinically significant changes over time.

Table 7.86. Change from Baseline to Week 24 According to Hematology Parameter and Treatment Group for Study CV181040			
	Saxa 2.5 mg + Gly	Saxa 5 mg + Gly	Placebo + Gly
	N=248	N=253	N=267
Basophils (10 ³ c/uL)	-0.01±0.002	0±0.002	0±0.002

	0 (-0.01, -0.002)	0 (-0.004, 0.003)	0 (-0.006, 0.003)
Eosinophils (10 ³ c/uL)	-0.03±0.012 -0.02 (-0.051, -0.003)	-0.02±0.016 0 (-0.056, 0.008)	-0.02±0.011 -0.01 (-0.042, 0.003)
Hemoglobin (g/dL)	-0.01±0.063 0 (-0.13, 0.117)	-0.11±0.056 -0.10 (-0.223, -0.002)	0±0.057 0 (-0.117, 0.109)
Hematocrit (%)	-0.2±0.22 -0.3 (-0.59, 0.29)	-0.4±0.18 -0.4 (-0.73, -0.04)	-0.20±0.19 -0.3 (-0.6, 0.15)
Monocytes (10 ³ c/uL)	-0.02±0.011 -0.01 (-0.04, 0.003)	0.01±0.011 0.01 (-0.009, 0.032)	0.01±0.013 0.01 (-0.012, 0.038)
Neutrophils (10 ³ c/uL)	-0.06±0.072 0.02 (-0.201, 0.082)	0.09±0.091 0.02 (-0.091, 0.268)	0.02±0.089 -0.04 (-0.154, 0.197)
<i>Source: Clinical Study Report, CV181040, Appendix 7.5</i>			

Add-on to TZD

Table 7.87 summarizes the changes from baseline to Week 24 for hematology parameters for Study CV181013. Lymphocytes and platelets have previously been addressed in Section 7. For all parameters, there were no clinically significant changes over time.

Table 7.87. Change from Baseline to Week 24 According to Hematology Parameter and Treatment Group for Study CV181013			
	Saxa 2.5 mg + TZD	Saxa 5 mg + TZD	Placebo + TZD
Basophils (10 ³ c/uL)	0.00±0.002 0 (-0.003, 0.004)	0.00±0.001 0 (-0.004, 0.001)	0.00±0.002 0 (-0.002, 0.005)
Eosinophils (10 ³ c/uL)	0.00±0.011 0 (-0.022, 0.021)	0.00±0.014 -0.01 (-0.032, 0.023)	-0.01±0.011 0 (-0.036, 0.009)
Hematocrit (%)	-0.16±0.17 -0.6 (-0.98, -0.29)	-0.5±0.20 -0.4 (-0.95, -0.14)	-0.5±0.21 -0.5 (-0.87, -0.04)
Hemoglobin (g/dL)	-0.19±0.055 -0.10 (-0.296, -0.078)	-0.15±0.065 -0.15 (-0.281, -0.024)	-0.19±0.066 -0.10 (-0.318, -0.057)
Monocytes (10 ³ c/uL)	-0.02±0.009 -0.01 (-0.034, 0.001)	-0.01±0.012 0 (-0.028, 0.018)	-0.030±0.011 -0.04 (-0.048, -0.003)
Neutrophils (10 ³ c/uL)	-0.01±0.089 0.11 (-0.182, 0.169)	0.04±0.103 -0.01 (-0.166, 0.242)	-0.07±0.105 -0.04 (-0.278, 0.136)
<i>Source: Clinical Study Report, CV181013, Appendix 7.6</i>			

7.4.1.2.1.2.2 Chemistry

Add-on to Metformin

Table 7.88 summarizes the changes from baseline to Week 24 for chemistry parameters for Study CV181013. Liver function tests and CPK have previously been addressed in Section 7. For all parameters, there were no clinically significant changes 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
Sodium (mEq/L)	1.1±0.2 1.0 (0.4, 1.4)	1.0±0.2 1.0 (0.8, 1.7)	1.2±0.2 1.0 (0.5, 1.6)	0.7±0.3 1.0 (-0.3, 1.1)
Potassium (mEq/L)	0.0±0 0.0 (0, 0.1)	0.1±0 0.0 (0, 0.1)	0.1±0 0.1 (0, 0.1)	0.1±0 0.1 (0, 0.2)
Chloride (mEq/L)	1.1±0.3 1.0 (0.5, 1.7)	1.6±0.3 1.0 (1.0, 2.2)	1.1±0.3 1.0 (0.5, 1.6)	0.5±0.4 0.0 (-0.2, 1.2)
BUN (mg/dl)	0.9±0.4 0.3 (0.2, 1.6)	0.2±0.3 0.3 (-0.4, 0.8)	0.6±0.3 0.5 (-0.1, 1.2)	0.0±0.4 0.3 (-0.8, 0.7)
Creatinine (mg/dL)	0±0 0.0 (0, 0)	0±0 0.0 (0, 0)	0±0 0.0 (0, 0)	0±0 0 (-0.1, 0)
Alkaline phosphatase (u/L)	-7.8±1.2 -7.0 (-10.2, -5.3)	-6.2±1.1 -5.5 (-8.3, -4.1)	-4.1±1.0 -3.0 (-6.1, -2.1)	-2.1±1.2 -1.5 (-4.4, 0.7)
Total Bilirubin (mg/dL)	0±0 0.0 (0, 0)	0±0 0.0 (0, 0)	0±0 0.0 (-0.1, 0)	0±0 0.0 (-0.1, 0)

Source: Clinical Study Report, CV181014, Appendix 7.7

Add-on to Sulfonylurea

Table 7.89 summarizes the changes from baseline to Week 24 for chemistry parameters for Study CV181013. Liver function tests and CPK have previously been addressed in Section 7. For all parameters, there were no clinically significant changes over time.

	Saxa 2.5 mg + Gly N=248	Saxa 5 mg + Gly N=253	Placebo + Gly N=267
Sodium (mEq/L)	0.6±0.18 1.0 (0.23, 0.94)	0.7±0.18 1.0 (0.35, 1.07)	0.7±0.17 1.0 (0.4, 1.08)
Potassium (mEq/L)	0.02±0.027 0 (-0.035, 0.073)	-0.04±0.026 0 (-0.087, 0.017)	-0.01±0.033 0 (-0.078, 0.054)
Chloride (mEq/L)	0.3±0.21 0 (-0.14, 0.67)	0.8±0.19 1.0 (0.4, 1.16)	-0.1±0.20 0 (-0.47, 0.31)

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BUN (mg/dl)	0.3±0.29 0.4 (-0.24, 0.89)	0.1±0.25 0 (-0.44, 0.55)	0±0.28 0 (-0.58, 0.54)
Creatinine (mg/dL)	0.09±0.014 0 (0.058, 0.114)	0.09±0.013 0.02 (0.061, 0.113)	0.07±0.016 0 (0.042, 0.105)
Alkaline phosphatase (u/L)	-3.19±1.19 -4.0 (-6.22, -1.54)	-4.7±1.18 -3.0 (-6.98, -2.33)	-2.8±1.43 -3.0 (-5.59, 0.07)
Total Bilirubin (mg/dL)	-0.03±0.014 0 (-0.059, -0.004)	-0.03±0.013 0 (-0.052, 0)	-0.01±0.014 0 (-0.037, 0.02)

Source: Clinical Study Report, CV181040, Appendix 7.7

Add-on to TZD

Table 7.90 summarizes the changes from baseline to Week 24 for chemistry parameters for Study CV181013. Liver function tests and CPK have previously been addressed in Section 7. For all parameters, there were no clinically significant changes over time.

	Saxa 2.5 mg + TZD	Saxa 5 mg + TZD	Placebo + TZD
Sodium (mEq/L)	0.7±0.18 1.0 (0.37, 1.08)	0.4±0.21 0 (0.03, 0.85)	0.8±0.19 1.0 (0.39, 1.16)
Potassium (mEq/L)	-0.03±0.033 0 (-0.095, 0.034)	0±0.034 0 (-0.066, 0.069)	-0.06±0.034 -1.10 (-0.127, 0.01)
Chloride (mEq/L)	0.8±0.23 1.0 (0.36, 1.27)	0.6±0.28 1.0 (0.08, 1.19)	0.6±0.26 1.0 (0.13, 1.17)
BUN (mg/dl)	0.2±1.29 0.8 (-0.37, 0.76)	-0.1±0.28 0 (-0.67, 0.44)	-0.1±0.38 0 (-0.85, 0.67)
Creatinine (mg/dL)	0.01±0.009 0 (-0.002, 0.031)	0.01±0.011 0 (-0.011, 0.032)	0.02±0.013 0 (-0.011, 0.042)
Alkaline phosphatase (u/L)	-6.2±1.52 -5.0 (-9.25, -3.23)	-7.5±1.48 -6.0 (-10.4, -4.54)	-3.3±1.34 -1.0 (-5.91, -0.6)
Total Bilirubin (mg/dL)	-0.04±0.012 0 (-0.061, -0.012)	-0.05±0.016 0 (-0.079, -0.015)	-0.04±0.016 0 (-0.07, -0.086)

Source: Clinical Study Report, CV181013, Appendix 7.7

7.4.1.2.1.2.2 Urinalysis

See Section 7.4.2.3.3 for marked abnormalities in urinalysis.

7.4.1.2.1.3 Initial Combination with Metformin Study

7.4.1.2.1.3.1 Hematology

Table 7.91 summarizes the changes from baseline to Week 24 for hematology parameters for Study CV181039. Lymphocytes and platelets have previously been addressed in Section 7. For all parameters, there were no clinically significant changes over time.

Table 7.91. Change from Baseline to Week 24 According to Hematology Parameter and Treatment Group for Study CV181039				
	Saxa 2.5 mg + Met	Saxa 5 mg + Met	Saxa 10 mg + Met	Placebo + Met
	N=320	N=323	N=335	N=328
Basophils (10 ³ c/uL)	0±0.002 0 (0, 0.006)	0±0.002 0 (0.001, 0.007)	0±0.002 0 (0.001, 0.008)	0±0.002 0 (0.001, 0.007)
Eosinophils (10 ³ c/uL)	0.01±0.016 0.01 (-0.019, 0.043)	0.02±0.011 0.01 (-0.001, 0.041)	-0.01±0.009 0 (-0.029, 0.007)	0.03±0.014 0.02 (0.004, 0.058)
Hemoglobin (g/dL)	-0.49±0.064 -0.50 (-0.621, -0.368)	-0.49±0.051 -0.50 (-0.586, -0.386)	-0.14±0.060 -0.20 (-0.262, -0.023)	-0.41±0.056 -0.40 (-0.519, -0.298)
Hematocrit (%)	-1.2±1.21 -1.3 (-1.67, -0.83)	-1.2±0.17 -1.2 (-1.48, -0.83)	-0.4±0.18 -0.3 (-0.71, 0.01)	-0.8±0.20 -0.09 (-1.2, -0.43)
Monocytes (10 ³ c/uL)	0.02±0.011 0.03 (0.001, 0.043)	0.03±0.010 0.03 (0.013, 0.053)	0.02±0.010 0.02 (0.004, 0.044)	0.03±0.009 0.02 (0.016, 0.052)
Neutrophils (10 ³ c/uL)	0.25±0.092 0.30 (0.068, 0.43)	0.29±0.086 0.42 (0.118, 0.457)	0.10±0.076 0.20 (-0.048, 0.251)	0.26±0.083 0.22 (0.092, 0.421)

Source: Clinical Study Report, CV181039, Appendix 7.5

7.4.1.2.1.3.2 Chemistry

Table 7.92 summarizes the changes from baseline to Week 24 for chemistry parameters for Study CV181039. Liver function tests and CPK have previously been addressed in Section 7. For all parameters, there were no clinically significant changes over time.

Table 7.92. Change from Baseline to Week 24 According to Chemistry Parameter and Treatment Group for Study CV181039				
	Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	Metformin
	N=263	N=323	N=335	N=328

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Sodium (mEq/L)	1.5±0.22 2.0 (1.06, 1.91)	1.6±0.19 2.0 (1.23, 1.99)	0.5±0.22 0.5 (0.05, 0.91)	0.8±0.20 1.0 (0.37, 1.15)
Potassium (mEq/L)	0.09±0.033 0.10 (0.02, 0.151)	0.09±0.026 0.10 (0.042, 0.146)	0±0.030 0 (-0.063, 0.056)	0.10±0.027 0.10 (0.04, 0.151)
Chloride (mEq/L)	1.3±0.22 1.0 (0.87, 1.76)	1.5±0.19 2.0 (1.08, 1.84)	1.1±0.22 1.0 (0.69, 1.55)	0.8±0.21 1.0 (0.4, 1.24)
BUN (mg/dl)	0.7±0.30 1.0 (0.07, 1.24)	0.3±0.34 0.1 (-0.34, 1.03)	1.1±0.44 0 (0.26, 2.02)	0.2±0.46 0 (-0.74, 1.08)
Creatinine (mg/dL)	0.02±0.007 0 (0.004, 0.031)	0.02±0.009 0 (-0.002, 0.033)	0.03±0.007 0 (0.013, 0.039)	0.01±0.007 0 (-0.011, 0.028)
Alkaline phosphatase (u/L)	-17.8±1.26 15.0 (-20.26, -15.3)	-16.4±1.31 -14.0 (-18.97, -13.8)	-9.8±1.30 -10.0 (-12.37, -7.25)	-14.1±1.12 -13.0 (-16.28, -11.88)
Total Bilirubin (mg/dL)	-0.06±0.014 0 (-0.09, -0.037)	-0.09±0.014 -0.10 (-0.119, -0.064)	-0.03±0.016 0 (-0.062, 0.001)	-0.06±0.012 -0.10 (-0.085, -0.036)

Source: Clinical Study Report, CV181040, Appendix 7.7

		Week 24 Value--Number (%) of Subjects		
Hemoglobin				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg N=247	<LLN	2 (33.3)	4 (66.7)	0 (0)
	≥LLN to ≤ULN	8 (3.4)	222 (95.7)	2 (0.9)
	>ULN	0 (0)	2 (50.0)	2 (50.0)
Saxa 5 mg N=252	<LLN	4 (57.1)	3 (42.9)	0 (0)
	≥LLN to ≤ULN	4 (1.7)	227 (96.2)	5 (2.1)
	>ULN	0 (0)	4 (100.0)	0 (0)
Saxa 10 mg N=98	<LLN	3 (60.0)	2 (40.0)	0 (0)
	≥LLN to ≤ULN	1 (1.1)	85 (96.6)	2 (2.3)
	>ULN	0 (0)	1 (25.0)	3 (75.0)
All Saxa N=597	<LLN	9 (50.0)	9 (50.0)	0 (0)
	≥LLN to ≤ULN	13 (2.3)	534 (96.0)	9 (1.6)
	>ULN	0 (0)	7 (58.3)	5 (41.7)
Placebo N=169	<LLN	4 (50.0)	4 (50.0)	0 (0)
	≥LLN to ≤ULN	4 (2.6)	142 (92.8)	7 (4.6)
	>ULN	0 (0)	1 (33.3)	2 (66.7)

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Hematocrit				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg N=247	<LLN	1 (25.0)	3 (75.0)	0 (0)
	≥LLN to ≤ULN	11 (4.7)	217 (92.7)	6 (2.6)
	>ULN	0 (0)	3 (75.0)	1 (25.0)
Saxa 5 mg N=252	<LLN	5 (55.6)	4 (44.4)	0 (0)
	≥LLN to ≤ULN	4 (1.7)	212 (91.4)	16 (6.9)
	>ULN	0 (0)	2 (33.3)	4 (66.7)
Saxa 10 mg N=98	<LLN	1 (50.0)	1 (50.0)	0 (0)
	≥LLN to ≤ULN	2 (2.3)	84 (95.5)	2 (2.3)
	>ULN	0 (0)	2 (28.6)	5 (71.4)
All Saxa N=597	<LLN	7 (46.7)	8 (53.3)	0 (0)
	≥LLN to ≤ULN	17 (3.1)	513 (92.6)	24 (4.3)
	>ULN	0 (0)	7 (41.2)	10 (58.8)
Placebo N=169	<LLN	5 (71.4)	2 (28.6)	0 (0)
	≥LLN to ≤ULN	4 (2.7)	136 (91.3)	9 (6.0)
	>ULN	0 (0)	4 (50.0)	4 (50.0)
WBC Count				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg N=247	<LLN	3 (30.0)	7 (70.0)	0 (0)
	≥LLN to ≤ULN	4 (1.8)	218 (97.3)	2 (0.9)
	>ULN	0 (0)	4 (50.0)	4 (50.0)
Saxa 5 mg N=252	<LLN	4 (50.0)	4 (50.0)	0 (0)
	≥LLN to ≤ULN	4 (1.7)	222 (94.9)	8 (3.4)
	>ULN	0 (0)	4 (80.0)	1 (20.0)
Saxa 10 mg N=98	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	91 (95.8)	4 (4.2)
	>ULN	0 (0)	1 (50.0)	1 (50.0)
All Saxa N=597	<LLN	7 (38.9)	11 (61.1)	0 (0)
	≥LLN to ≤ULN	8 (1.4)	531 (96.0)	14 (2.5)
	>ULN	0 (0)	9 (60.0)	6 (40.0)
Placebo N=169	<LLN	0 (0)	5 (100.0)	0 (0)
	≥LLN to ≤ULN	5 (3.3)	145 (94.8)	3 (2.0)
	>ULN	0 (0)	4 (66.7)	2 (33.3)
Platelets (x 10⁹ c/L)				
	Baseline value (g/dL)	≤100	>100 - ≤600	>600
Saxa 2.5 mg N=247	≤100	0 (0)	0 (0)	0 (0)
	>100 - ≤600	0 (0)	240 (100.0)	0 (0)
	>600	0 (0)	1 (100.0)	0 (0)
Saxa 5 mg N=252	≤100	0 (0)	0 (0)	0 (0)
	>100 - ≤600	0 (0)	246 (100.0)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
Saxa 10 mg N=98	≤100	0 (0)	0 (0)	0 (0)
	>100 - ≤600	0 (0)	94 (100.0)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
All Saxa N=597	≤100	0 (0)	0 (0)	0 (0)
	>100 - ≤600	0 (0)	580 (100.0)	0 (0)
	>600	0 (0)	1 (100.0)	0 (0)

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Placebo	≤100	0 (0)	0 (0)	0 (0)
N=169	>100 - ≤600	0 (0)	164 (100.0)	0 (0)
	>600	0 (0)	0 (0)	0 (0)

Source: Response to FDA Question Received on 18-March-2009

7.4.1.2.1.3.3 Chemistry

Table 7.94 summarizes shifts from baseline to Week 24 for pertinent chemistry parameters for the pooled monotherapy group. No unusual shifts were observed.

		Week 24 Value--Number (%) of Subjects		
		<LLN	≥LLN to ≤ULN	>ULN
Sodium				
Saxa 2.5 mg N=247	Baseline value (g/dL)			
	<LLN	1 (16.7)	5 (83.3)	0 (0)
	≥LLN to ≤ULN	1 (0.4)	231 (99.1)	1 (0.4)
Saxa 5 mg N=252	>ULN	0 (0)	3 (100.0)	0 (0)
	<LLN	0 (0)	3 (100.0)	0 (0)
	≥LLN to ≤ULN	1 (0.4)	239 (98.4)	3 (1.2)
Saxa 10 mg N=98	>ULN	0 (0)	1 (100.0)	0 (0)
	<LLN	0 (0)	5 (100.0)	0 (0)
	≥LLN to ≤ULN	0 (0)	89 (96.7)	3 (3.3)
All Saxa N=597	>ULN	0 (0)	0 (0)	0 (0)
	<LLN	1 (7.1)	13 (92.9)	0 (0)
	≥LLN to ≤ULN	2 (0.4)	559 (98.4)	7 (1.2)
Placebo N=169	>ULN	0 (0)	4 (100.0)	0 (0)
	<LLN	0 (0)	6 (100.0)	0 (0)
	≥LLN to ≤ULN	2 (1.3)	153 (98.1)	1 (0.6)
	>ULN	0 (0)	3 (100.0)	1 (0.6)
Potassium				
Saxa 2.5 mg N=247	Baseline value (g/dL)			
	<LLN	1 (100)	0 (0)	0 (0)
	≥LLN to ≤ULN	3 (1.3)	232 (97.1)	4 (1.7)
Saxa 5 mg N=252	>ULN	0 (0)	2 (100.0)	0 (0)
	<LLN	0 (0)	2 (100.0)	0 (0)
	≥LLN to ≤ULN	2 (0.8)	235 (97.9)	3 (1.3)
Saxa 10 mg N=98	>ULN	0 (0)	5 (100.0)	0 (0)
	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	93 (97.9)	2 (2.1)
All Saxa N=597	>ULN	0 (0)	1 (50.0)	1 (50.0)
	<LLN	1 (33.3)	2 (66.7)	0 (0)
	≥LLN to ≤ULN	5 (0.9)	560 (97.6)	9 (1.6)
	>ULN	0 (0)	8 (88.9)	1 (11.1)

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Placebo N=169	<LLN	0 (0)	2 (100.0)	0 (0)
	≥LLN to ≤ULN	1 (0.6)	152 (95.0)	7 (4.4)
	>ULN	0 (0)	3 (100.0)	0 (0)
Creatinine				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg N=247	<LLN	3 (42.9)	4 (57.1)	0 (0)
	≥LLN to ≤ULN	1 (0.4)	225 (97.4)	5 (2.2)
	>ULN	0 (0)	3 (75.0)	1 (25.0)
Saxa 5 mg N=252	<LLN	2 (33.3)	4 (66.7)	0 (0)
	≥LLN to ≤ULN	1 (0.4)	225 (97.4)	5 (2.2)
	>ULN	0 (0)	5 (50.0)	5 (50.0)
Saxa 10 mg N=98	<LLN	1 (25.0)	3 (75.0)	0 (0)
	≥LLN to ≤ULN	1 (1.1)	87 (97.8)	1 (1.1)
	>ULN	0 (0)	2 (50.0)	2 (50.0)
All Saxa N=597	<LLN	6 (35.3)	11 (64.7)	0 (0)
	≥LLN to ≤ULN	3 (0.5)	537 (97.5)	11 (2.0)
	>ULN	0 (0)	10 (55.6)	8 (44.4)
Placebo N=169	<LLN	6 (60.0)	4 (40.0)	0 (0)
	≥LLN to ≤ULN	1 (0.7)	146 (98.0)	2 (1.3)
	>ULN	0 (0)	3 (50.0)	3 (50.0)

Source: Response to FDA Question Received on 18-March-2009

7.4.1.2.1.3.4 Urinalysis

See Section 7.4.2.3.3 for marked abnormalities in urinalysis.

7.4.1.2.1.4 Add-on Combination Studies

7.4.1.2.1.4.1 Hematology

Add-on to Metformin

Table 7.95 summarizes shifts from baseline to Week 24 for pertinent hematology parameters for Study CV181014. No unusual shifts were observed.

Table 7.95. Shift from Baseline to Week 24 (LOCF) for Hematology Parameters for Study CV181014		Week 24 Value--Number (%) of Subjects		
Hemoglobin	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + Met N=192	<LLN	3 (33.3)	6 (66.7)	0 (0)
	≥LLN to ≤ULN	8 (4.6)	166 (94.9)	1 (0.6)
	>ULN	0 (0)	3 (75.0)	1 (25.0)
Saxa 5 mg + Met	<LLN	7 (87.5)	1 (12.5)	0 (0)

N=191	≥LLN to ≤ULN	14 (7.9)	163 (92.1)	0 (0)
	>ULN	0 (0)	4 (80.0)	1 (20.0)
Saxa 10 mg + Met	<LLN	6 (50.0)	6 (50.0)	0 (0)
N=181	≥LLN to ≤ULN	6 (3.7)	156 (95.1)	2 (1.2)
	>ULN	0 (0)	3 (60.0)	2 (40.0)
All Saxa	<LLN	16 (55.2)	13 (44.8)	0 (0)
N=564	≥LLN to ≤ULN	28 (5.4)	485 (94.0)	3 (0.6)
	>ULN	0 (0)	10 (71.4)	4 (28.6)
Placebo + Metformin	<LLN	8 (50.0)	8 (50.0)	0 (0)
N=179	≥LLN to ≤ULN	12 (7.6)	145 (91.8)	1 (0.6)
	>ULN	0 (0)	2 (66.7)	1 (33.3)
Hematocrit				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + Met	<LLN	1 (20.0)	4 (80.0)	0 (0)
N=192	≥LLN to ≤ULN	5 (2.8)	173 (96.1)	2 (1.1)
	>ULN	0 (0)	0 (0)	3 (100.0)
Saxa 5 mg + Met	<LLN	4 (66.7)	2 (33.3)	0 (0)
N=191	≥LLN to ≤ULN	8 (4.4)	170 (94.4)	2 (1.1)
	>ULN	0 (0)	3 (75.0)	1 (25.0)
Saxa 10 mg + Met	<LLN	2 (25.0)	6 (75.0)	0 (0)
N=181	≥LLN to ≤ULN	8 (4.8)	158 (94.6)	1 (0.6)
	>ULN	0 (0)	4 (66.7)	2 (33.3)
All Saxa	<LLN	7 (36.8)	12 (63.2)	0 (0)
N=564	≥LLN to ≤ULN	21 (4.0)	501 (95.1)	5 (0.9)
	>ULN	0 (0)	7 (53.8)	6 (46.2)
Placebo + Metformin	<LLN	4 (44.4)	5 (55.6)	0 (0)
N=179	≥LLN to ≤ULN	5 (3.0)	156 (94.5)	4 (2.4)
	>ULN	0 (0)	2 (66.7)	1 (33.3)
WBC Count				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + Met	<LLN	0 (0)	1 (100.0)	0 (0)
N=192	≥LLN to ≤ULN	0 (0)	169 (97.1)	5 (2.9)
	>ULN	0 (0)	6 (46.2)	7 (53.8)
Saxa 5 mg + Met	<LLN	1 (50.0)	1 (50.0)	0 (0)
N=191	≥LLN to ≤ULN	0 (0)	162 (94.7)	9 (5.3)
	>ULN	0 (0)	10 (58.8)	7 (41.2)
Saxa 10 mg + Met	<LLN	0 (0)	0 (0)	0 (0)
N=181	≥LLN to ≤ULN	1 (0.6)	161 (94.7)	8 (4.7)
	>ULN	0 (0)	3 (27.3)	8 (72.7)
All Saxa	<LLN	1 (33.3)	2 (66.7)	0 (0)
N=564	≥LLN to ≤ULN	1 (0.2)	492 (95.5)	22 (4.3)
	>ULN	0 (0)	19 (46.3)	22 (53.7)
Placebo + Metformin	<LLN	0 (0)	1 (100.0)	0 (0)
N=179	≥LLN to ≤ULN	0 (0)	162 (95.9)	7 (4.1)
	>ULN	0 (0)	3 (42.9)	4 (57.1)
Platelets (x 10⁹ c/L)				
	Baseline value (g/dL)	≤100	>100 - ≤600	>600
Saxa 2.5 mg + Met	≤100	0 (0)	1 (100.0)	0 (0)

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N=192	>100 - ≤600	0 (0)	187 (100.0)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
Saxa 5 mg + Met	≤100	0 (0)	0 (0)	0 (0)
N=191	>100 - ≤600	0 (0)	187 (100.0)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
Saxa 10 mg + Met	≤100	0 (0)	0 (0)	0 (0)
N=181	>100 - ≤600	0 (0)	181 (100.0)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
Placebo + Metformin	≤100	0 (0)	0 (0)	0 (0)
N=179	>100 - ≤600	1 (0.6)	175 (99.4)	176 (100)
	>600	0 (0)	0 (0)	0 (0)

Source: Response to FDA Question Received on 18-March-2009

Add-on to Sulfonylurea

Table 7.96 summarizes shifts from baseline to Week 24 for pertinent hematology parameters for Study CV181040. No unusual shifts were observed.

Hemoglobin	Baseline value (g/dL)	Week 24 Value--Number (%) of Subjects		
		<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + Gly N=248	<LLN	4 (40.0)	6 (60.0)	0 (0)
	≥LLN to ≤ULN	7 (3.0)	224 (96.6)	1 (0.4)
	>ULN	0 (0)	4 (80.0)	1 (20.0)
Saxa 5 mg + Gly N=253	<LLN	2 (22.2)	7 (77.8)	0 (0)
	≥LLN to ≤ULN	7 (2.9)	235 (97.1)	0 (0)
	>ULN	0 (0)	2 (100.0)	0 (0)
All Saxa N=501	<LLN	6 (31.6)	13 (68.4)	0 (0)
	≥LLN to ≤ULN	14 (3.0)	459 (96.8)	1 (0.2)
	>ULN	0 (0)	6 (85.7)	1 (14.3)
Placebo + Glyburide N=267	<LLN	6 (46.2)	7 (53.8)	0 (0)
	≥LLN to ≤ULN	9 (3.6)	236 (94.8)	4 (1.6)
	>ULN	0 (0)	2 (66.7)	1 (33.3)
Hematocrit				
Saxa 2.5 mg + Gly N=248	<LLN	8 (53.3)	7 (46.7)	0 (0)
	≥LLN to ≤ULN	8 (3.7)	207 (95.0)	3 (1.4)
	>ULN	0 (0)	8 (61.5)	5 (38.5)
Saxa 5 mg + Gly N=253	<LLN	5 (55.6)	4 (44.4)	0 (0)
	≥LLN to ≤ULN	7 (2.9)	230 (96.6)	1 (0.4)
	>ULN	0 (0)	6 (100.0)	0 (0)
All Saxa N=501	<LLN	13 (54.2)	11 (45.8)	0 (0)
	≥LLN to ≤ULN	15 (3.3)	437 (95.8)	4 (0.9)
	>ULN	0 (0)	14 (73.7)	5 (26.3)
Placebo + Glyburide N=267	<LLN	10 (58.8)	7 (41.2)	0 (0)
	≥LLN to ≤ULN	6 (2.5)	224 (94.5)	7 (3.0)

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	>ULN	0 (0)	8 (72.7)	3 (27.3)
WBC Count				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + Gly N=248	<LLN	4 (57.1)	3 (42.9)	0 (0)
	≥LLN to ≤ULN	0 (0)	238 (100.0)	0 (0)
	>ULN	0 (0)	2 (100.0)	0 (0)
Saxa 5 mg + Gly N=253	<LLN	2 (20.0)	8 (80.0)	0 (0)
	≥LLN to ≤ULN	2 (0.8)	237 (98.3)	2 (0.8)
	>ULN	0 (0)	2 (100.0)	0 (0)
All Saxa N=501	<LLN	6 (35.3)	11 (64.7)	0 (0)
	≥LLN to ≤ULN	2 (0.4)	475 (99.2)	2 (0.4)
	>ULN	0 (0)	4 (100.0)	0 (0)
Placebo + Glyburide N=267	<LLN	1 (16.7)	5 (83.3)	0 (0)
	≥LLN to ≤ULN	5 (2.0)	246 (96.5)	4 (1.6)
	>ULN	0 (0)	4 (100.0)	0 (0)
Platelets (x 10⁹ c/L)				
	Baseline value (g/dL)	≤100	>100 - ≤600	>600
Saxa 2.5 mg + Gly N=248	≤100	0 (0)	0 (0)	0 (0)
	>100 - ≤600	0 (0)	246 (100.0)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
Saxa 5 mg + Gly N=253	≤100	0 (0)	246 (100.0)	0 (0)
	>100 - ≤600	0 (0)	0 (0)	0 (0)
	>600	0 (0)	253 (100.0)	0 (0)
All Saxa N=501	≤100	0 (0)	0 (0)	0 (0)
	>100 - ≤600	0 (0)	253 (100.0)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
Placebo + Glyburide N=267	≤100	0 (0)	265 (100.0)	0 (0)
	>100 - ≤600	0 (0)	0 (0)	0 (0)
	>600	0 (0)	265 (100.0)	0 (0)

Source: Response to FDA Question Received on 18-March-2009

Add-on to TZD

Table 7.97 summarizes shifts from baseline to Week 24 for pertinent hematology parameters for Study CV181013. No unusual shifts were observed.

Hemoglobin	Baseline value (g/dL)	Week 24 Value--Number (%) of Subjects		
		<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + TZD N=195	<LLN	11 (52.4)	10 (47.6)	0 (0)
	≥LLN to ≤ULN	4 (2.3)	167 (97.7)	0 (0)
	>ULN	0 (0)	1 (100.0)	0 (0)
Saxa 5 mg + TZD N=186	<LLN	14 (63.6)	8 (36.4)	0 (0)
	≥LLN to ≤ULN	15 (9.2)	148 (90.8)	0 (0)
	>ULN	0 (0)	0 (0)	0 (0)
All Saxa	<LLN	25 (58.1)	18 (41.9)	0 (0)

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N=381	≥LLN to ≤ULN	19 (5.7)	315 (94.3)	0 (0)
	>ULN	0 (0)	1 (100.0)	0 (0)
Placebo + TZD	<LLN	14 (73.7)	5 (26.3)	0 (0)
N=184	≥LLN to ≤ULN	14 (8.6)	148 (91.4)	0 (0)
	>ULN	0 (0)	0 (0)	0 (0)
Hematocrit				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + TZD	<LLN	19 (79.2)	5 (20.8)	0 (0)
N=195	≥LLN to ≤ULN	11 (6.5)	157 (93.5)	0 (0)
	>ULN	0 (0)	1 (100.0)	0 (0)
Saxa 5 mg + TZD	<LLN	16 (64.0)	9 (36.0)	0 (0)
N=186	≥LLN to ≤ULN	20 (12.7)	137 (87.3)	0 (0)
	>ULN	0 (0)	1 (33.3)	2 (66.7)
All Saxa	<LLN	35 (71.4)	14 (28.6)	0 (0)
N=381	≥LLN to ≤ULN	31 (9.5)	294 (90.5)	0 (0)
	>ULN	0 (0)	2 (50.0)	2 (50.0)
Placebo + TZD	<LLN	13 (76.5)	4 (23.5)	0 (0)
N=184	≥LLN to ≤ULN	18 (11.0)	146 (89.0)	0 (0)
	>ULN	0 (0)	0 (0)	1 (100.0)
WBC Count				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + TZD	<LLN	4 (30.8)	9 (69.2)	0 (0)
N=195	≥LLN to ≤ULN	5 (2.8)	173 (96.6)	1 (0.6)
	>ULN	0 (0)	1 (100.0)	0 (0)
Saxa 5 mg + TZD	<LLN	8 (72.7)	3 (27.3)	0 (0)
N=186	≥LLN to ≤ULN	6 (3.4)	167 (96.0)	1 (0.6)
	>ULN	0 (0)	0 (0)	0 (0)
All Saxa	<LLN	12 (50.0)	12 (50.0)	0 (0)
N=381	≥LLN to ≤ULN	11 (3.1)	340 (96.3)	2 (0.6)
	>ULN	0 (0)	1 (100.0)	0 (0)
Placebo + TZD	<LLN	2 (100.0)	0 (0)	0 (0)
N=184	≥LLN to ≤ULN	8 (4.5)	170 (95.0)	1 (0.6)
	>ULN	0 (0)	1 (100.0)	0 (0)
Platelets (x 10⁹ c/L)				
	Baseline value (g/dL)	≤100	>100 - ≤600	>600
Saxa 2.5 mg + TZD	≤100	0 (0)	0 (0)	0 (0)
N=195	>100 - ≤600	0 (0)	169 (100.0)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
Saxa 5 mg + TZD	≤100	0 (0)	0 (0)	0 (0)
N=186	>100 - ≤600	1 (0.7)	147 (99.3)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
Placebo + TZD	≤100	0 (0)	0 (0)	0 (0)
N=184	>100 - ≤600	0 (0)	139 (99.3)	1 (0.7)
	>600	0 (0)	0 (0)	0 (0)
<i>Source: Response to FDA Question Received on 18-March-2009</i>				

7.4.1.2.1.4.2 Chemistry

Add-on to Metformin

Table 7.98 summarizes shifts from baseline to Week 24 for pertinent chemistry parameters for Study CV181014. No unusual shifts were observed.

Sodium		Week 24 Value--Number (%) of Subjects		
		<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + Met N=192	Baseline value (g/dL)			
	<LLN	1 (12.5)	7 (87.5)	0 (0)
	≥LLN to ≤ULN	6 (3.4)	171 (96.1)	1 (0.6)
Saxa 5 mg + Met N=191	>ULN	0 (0)	3 (100.0)	0 (0)
	<LLN	0 (0)	4 (100.0)	0 (0)
	≥LLN to ≤ULN	0 (0)	185 (100.0)	0 (0)
Saxa 10 mg + Met N=181	>ULN	0 (0)	1 (100.0)	0 (0)
	<LLN	0 (0)	6 (100.0)	0 (0)
	≥LLN to ≤ULN	2 (1.2)	170 (98.3)	1 (0.6)
All Saxa N=564	>ULN	0 (0)	2 (100.0)	0 (0)
	<LLN	1 (5.6)	17 (94.4)	0 (0)
	≥LLN to ≤ULN	8 (1.5)	526 (98.2)	2 (0.4)
Placebo + Met N=179	>ULN	0 (0)	6 (100.0)	0 (0)
	<LLN	1 (9.1)	10 (90.9)	0 (0)
	≥LLN to ≤ULN	4 (2.5)	158 (97.5)	0 (0)
	>ULN	0 (0)	4 (100.0)	0 (0)
Potassium		<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + Met N=192	Baseline value (g/dL)			
	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	1 (0.6)	167 (94.4)	9 (5.1)
Saxa 5 mg + Met N=191	>ULN	0 (0)	7 (58.3)	4 (41.7)
	<LLN	0 (0)	3 (100.0)	0 (0)
	≥LLN to ≤ULN	2 (1.1)	166 (92.7)	11 (6.1)
Saxa 10 mg + Met N=181	>ULN	0 (0)	7 (87.5)	1 (12.5)
	<LLN	0 (0)	1 (100.0)	0 (0)
	≥LLN to ≤ULN	2 (1.1)	165 (93.8)	9 (5.1)
All Saxa N=564	>ULN	0 (0)	4 (100.0)	0 (0)
	<LLN	0 (0)	4 (100.0)	0 (0)
	≥LLN to ≤ULN	5 (0.9)	498 (93.6)	29 (5.5)
Placebo + Met N=179	>ULN	0 (0)	18 (75.0)	6 (25.0)
	<LLN	0 (0)	2 (100.0)	0 (0)
	≥LLN to ≤ULN	0 (0)	159 (93.5)	11 (6.5)
	>ULN	0 (0)	4 (80.0)	1 (20.0)
Creatinine		<LLN	≥LLN to ≤ULN	>ULN
Saxa 2.5 mg + Met N=192	Baseline value (g/dL)			
	<LLN	10 (58.8)	7 (41.2)	0 (0)
	≥LLN to ≤ULN	5 (3.0)	153 (92.7)	7 (4.2)

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Saxa 5 mg + Met N=191	>ULN	0 (0)	4 (57.1)	3 (42.9)
	<LLN	11 (61.1)	7 (38.9)	0 (0)
	≥LLN to ≤ULN	10 (6.1)	151 (91.5)	4 (2.4)
Saxa 10 mg + Met N=181	>ULN	0 (0)	7 (100.0)	0 (0)
	<LLN	8 (57.1)	6 (42.9)	0 (0)
	≥LLN to ≤ULN	9 (5.5)	153 (93.9)	1 (0.6)
All Saxa N=564	>ULN	0 (0)	3 (75.0)	1 (25.0)
	<LLN	29 (59.2)	20 (40.8)	0 (0)
	≥LLN to ≤ULN	24 (4.9)	457 (92.7)	12 (2.4)
Placebo + Met N=179	>ULN	0 (0)	14 (77.8)	4 (22.2)
	<LLN	9 (47.4)	10 (52.6)	0 (0)
	≥LLN to ≤ULN	8 (5.3)	139 (92.7)	3 (2.0)
	>ULN	0 (0)	6 (75.0)	2 (25.0)

Source: Response to FDA Question Received on 18-March-2009

Add-on to Sulfonylurea

Table 7.99 summarizes shifts from baseline to Week 24 for pertinent chemistry parameters for Study CV181040. No unusual shifts were observed.

Table 7.99. Shift from Baseline to Week 24 (LOCF) for Chemistry Parameters for Study CV181040		Week 24 Value--Number (%) of Subjects		
Sodium				
Saxa 2.5 mg + Gly N=248	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
	<LLN	0 (0)	1 (100.0)	0 (0)
	≥LLN to ≤ULN	1 (0.4)	243 (99.2)	1 (0.4)
Saxa 5 mg + Gly N=253	>ULN	0 (0)	1 (100.0)	0 (0)
	<LLN	1 (25.0)	3 (75.0)	0 (0)
	≥LLN to ≤ULN	1 (0.4)	248 (99.6)	0 (0)
All Saxa N=501	>ULN	0 (0)	0 (0)	0 (0)
	<LLN	1 (20.0)	4 (80.0)	0 (0)
	≥LLN to ≤ULN	2 (0.4)	491 (99.4)	1 (0.2)
Placebo + Glyburide N=267	>ULN	0 (0)	1 (100.0)	0 (0)
	<LLN	0 (0)	4 (100.0)	0 (0)
	≥LLN to ≤ULN	2 (0.8)	259 (99.2)	0 (0)
	>ULN	0 (0)	0 (0)	0 (0)
Potassium				
Saxa 2.5 mg + Gly N=248	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
	<LLN	0 (0)	2 (100.0)	0 (0)
	≥LLN to ≤ULN	1 (0.4)	243 (99.2)	1 (0.4)
Saxa 5 mg + Gly N=253	>ULN	0 (0)	0 (0)	0 (0)
	<LLN	1 (25.0)	3 (75.0)	0 (0)
	≥LLN to ≤ULN	2 (0.8)	244 (98.4)	2 (0.8)
All Saxa N=501	>ULN	0 (0)	1 (100.0)	0 (0)
	<LLN	1 (16.7)	5 (83.3)	0 (0)
	≥LLN to ≤ULN	3 (0.6)	487 (98.8)	3 (0.6)

Table 7.99. Shift from Baseline to Week 24 (LOCF) for Chemistry Parameters for Study CV181040

Placebo + Glyburide N=267	>ULN	0 (0)	1 (100.0)	0 (0)
	<LLN	0 (0)	2 (100.0)	0 (0)
	≥LLN to ≤ULN	2 (0.8)	254 (97.7)	4 (1.5)
	>ULN	0 (0)	2 (66.7)	1 (33.3)
Creatinine				
Saxa 2.5 mg + Gly N=248	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
	<LLN	0 (0)	2 (100.0)	0 (0)
	≥LLN to ≤ULN	1 (0.4)	229 (96.2)	8 (3.4)
Saxa 5 mg + Gly N=253	>ULN	0 (0)	2 (28.6)	5 (71.4)
	<LLN	0 (0)	1 (100.0)	0 (0)
	≥LLN to ≤ULN	0 (0)	238 (95.6)	11 (4.4)
All Saxa N=501	>ULN	0 (0)	1 (33.3)	2 (66.7)
	<LLN	0 (0)	3 (100.0)	0 (0)
	≥LLN to ≤ULN	1 (0.2)	467 (95.9)	19 (3.9)
Placebo + Glyburide N=267	>ULN	0 (0)	3 (30.0)	7 (70.0)
	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	1 (0.4)	253 (96.9)	7 (2.7)
	>ULN	0 (0)	1 (25.0)	3 (75.0)

Source: Response to FDA Question Received on 18-March-2009

Add-on to TZD

Table 7.100 summarizes shifts from baseline to Week 24 for pertinent chemistry parameters for Study CV181013. No unusual shifts were observed.

Table 7.100. Shift from Baseline to Week 24 (LOCF) for Chemistry Parameters for Study CV181013

	Baseline value (g/dL)	Week 24 Value--Number (%) of Subjects		
		<LLN	≥LLN to ≤ULN	>ULN
Sodium				
Saxa 2.5 mg + TZD N=195	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	1 (0.5)	192 (99.5)	0 (0)
	>ULN	0 (0)	0 (0)	0 (0)
Saxa 5 mg + TZD N=186	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	184 (99.5)	1 (0.5)
	>ULN	0 (0)	0 (0)	0 (0)
All Saxa N=381	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	1 (0.3)	376 (99.5)	1 (0.3)
	>ULN	0 (0)	0 (0)	0 (0)
Placebo + TZD N=184	<LLN	0 (0)	1 (100.0)	0 (0)
	≥LLN to ≤ULN	1 (0.6)	180 (99.4)	0 (0)
	>ULN	0 (0)	0 (0)	0 (0)
Potassium				
Saxa 2.5 mg + TZD N=195	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
	<LLN	0 (0)	1 (100.0)	0 (0)
	≥LLN to ≤ULN	1 (0.5)	189 (98.4)	2 (1.0)
	>ULN	0 (0)	0 (0)	0 (0)

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Saxa 5 mg + TZD N=186	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	2 (1.1)	180 (97.8)	2 (1.1)
	>ULN	0 (0)	1 (100.0)	0 (0)
All Saxa N=381	<LLN	0 (0)	1 (100.0)	0 (0)
	≥LLN to ≤ULN	3 (0.8)	369 (98.1)	4 (1.1)
	>ULN	0 (0)	1 (100.0)	0 (0)
Placebo + TZD N=184	<LLN	1 (50.0)	1 (50.0)	0 (0)
	≥LLN to ≤ULN	1 (0.6)	178 (99.4)	0 (0)
	>ULN	0 (0)	1 (100.0)	0 (0)
Creatinine				
Saxa 2.5 mg + TZD N=195	Baseline value (g/dL) <LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	186 (100.0)	0 (0)
	>ULN	0 (0)	2 (28.6)	5 (71.4)
Saxa 5 mg + TZD N=186	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	176 (97.8)	4 (2.2)
	>ULN	0 (0)	1 (20.0)	4 (80.0)
All Saxa N=381	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	362 (98.9)	4 (1.1)
	>ULN	0 (0)	3 (25.0)	9 (75.0)
Placebo + TZD N=184	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	169 (96.6)	6 (3.4)
	>ULN	0 (0)	4 (57.1)	3 (42.9)

Source: Response to FDA Question Received on 18-March-2009

7.4.1.2.1.4.3 Urinalysis

See Section 7.4.2.3.3 for marked abnormalities in urinalysis.

7.4.1.2.1.5 Initial Combination with Metformin Study

7.4.1.2.1.5.1 Hematology

Table 7.101 summarizes shifts from baseline to Week 24 for pertinent hematology parameters for Study CV181039. No unusual shifts were observed.

Hemoglobin	Baseline value (g/dL)	Week 24 Value--Number (%) of Subjects		
		<LLN	≥LLN to ≤ULN	>ULN
Saxa 5 mg + Met N=320	<LLN	5 (50.0)	5 (50.0)	0 (0)
	≥LLN to ≤ULN	14 (4.7)	281 (94.3)	3 (1.0)
	>ULN	0 (0)	6 (85.7)	1 (14.3)
Saxa 10 mg + Met N=323	<LLN	6 (85.7)	1 (14.3)	0 (0)
	≥LLN to ≤ULN	15 (4.9)	291 (95.1)	0 (0)

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Table 7.101 Shift from Baseline to Week 24 (LOCF) for Hematology Parameters for Study CV181039				
	>ULN	0 (0)	4 (100.0)	0 (0)
Saxa 10 mg	<LLN	7 (70.0)	3 (30.0)	0 (0)
N=335	≥LLN to ≤ULN	14 (4.5)	293 (94.2)	4 (1.3)
	>ULN	0 (0)	1 (33.3)	2 (66.7)
All Saxa	<LLN	18 (66.7)	9 (33.3)	0 (0)
N=978	≥LLN to ≤ULN	43 (4.7)	965 (94.5)	7 (0.8)
	>ULN	0 (0)	11 (78.6)	3 (21.4)
Metformin	<LLN	5 (38.5)	8 (61.5)	0 (0)
N=328	≥LLN to ≤ULN	10 (3.4)	284 (95.9)	2 (0.7)
	>ULN	0 (0)	7 (87.5)	1 (12.5)
Hematocrit				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 5 mg + Met	<LLN	6 (50.0)	6 (50.0)	0 (0)
N=320	≥LLN to ≤ULN	18 (6.2)	268 (92.4)	4 (1.4)
	>ULN	0 (0)	9 (81.8)	2 (18.2)
Saxa 10 mg + Met	<LLN	8 (72.7)	3 (27.3)	0 (0)
N=323	≥LLN to ≤ULN	15 (5.1)	275 (93.2)	5 (1.7)
	>ULN	0 (0)	6 (60.0)	4 (40.0)
Saxa 10 mg	<LLN	5 (45.5)	6 (54.5)	0 (0)
N=335	≥LLN to ≤ULN	14 (4.6)	287 (94.1)	4 (1.3)
	>ULN	0 (0)	4 (50.0)	4 (50.0)
All Saxa	<LLN	19 (55.9)	14 (44.1)	0 (0)
N=978	≥LLN to ≤ULN	47 (5.3)	830 (93.3)	13 (1.5)
	>ULN	0 (0)	19 (65.5)	10 (34.5)
Metformin	<LLN	6 (50.0)	6 (50.0)	0 (0)
N=328	≥LLN to ≤ULN	20 (6.8)	269 (91.5)	5 (1.7)
	>ULN	0 (0)	7 (63.6)	4 (36.4)
WBC Count				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 5 mg + Met	<LLN	5 (45.5)	6 (54.5)	0 (0)
N=320	≥LLN to ≤ULN	0 (0)	299 (99.0)	3 (1.0)
	>ULN	0 (0)	1 (50.0)	1 (50.0)
Saxa 10 mg + Met	<LLN	4 (50.0)	4 (50.0)	0 (0)
N=323	≥LLN to ≤ULN	4 (1.3)	298 (97.4)	4 (1.3)
	>ULN	0 (0)	2 (66.7)	1 (33.3)
Saxa 10 mg	<LLN	3 (30.0)	7 (70.0)	0 (0)
N=335	≥LLN to ≤ULN	2 (0.6)	309 (99.0)	1 (0.3)
	>ULN	0 (0)	0 (0)	2 (100.0)
All Saxa	<LLN	12 (41.4)	17 (58.6)	0 (0)
N=978	≥LLN to ≤ULN	6 (0.7)	906 (98.5)	8 (0.9)
	>ULN	0 (0)	3 (42.9)	4 (57.1)
Metformin	<LLN	1 (16.7)	5 (83.3)	0 (0)
N=328	≥LLN to ≤ULN	3 (1.0)	300 (97.4)	5 (1.6)
	>ULN	0 (0)	2 (66.7)	1 (33.3)
Platelets (x 10⁹ c/L)				
	Baseline value (g/dL)	≤100	>100 - ≤600	>600

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Saxa 5 mg + Met N=320	≤100	0 (0)	1 (100.0)	0 (0)
	>100 - ≤600	2 (0.6)	312 (99.4)	0 (0)
	>600	0 (0)	0 (0)	0 (0)
Saxa 10 mg + Met N=323	≤100	0 (0)	1 (100.0)	0 (0)
	>100 - ≤600	2 (0.6)	311 (99.4)	0 (0)
	>600	0 (0)	1 (100.0)	0 (0)
Saxa 10 mg N=335	≤100	0 (0)	0 (0)	0 (0)
	>100 - ≤600	1 (0.3)	322 (99.7)	1 (0.7)
	>600	0 (0)	0 (0)	0 (0)
Metformin N=328	≤100	0 (0)	1 (100.0)	0 (0)
	>100 - ≤600	1 (0.3)	315 (99.7)	0 (0)
	>600	0 (0)	0 (0)	0 (0)

Source: Response to FDA Question Received on 18-March-2009

7.4.1.2.1.5.2 Chemistry

Table 7.102 summarizes shifts from baseline to Week 24 for pertinent chemistry parameters for Study CV181039. No unusual shifts were observed.

		Week 24 Value--Number (%) of Subjects		
Sodium				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 5 mg + Met N=320	<LLN	0 (0)	1 (100.0)	0 (0)
	≥LLN to ≤ULN	0 (0)	309 (99.4)	2 (0.6)
	>ULN	0 (0)	2 (100.0)	0 (0)
Saxa 10 mg + Met N=323	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	1 (0.3)	312 (98.4)	4 (1.3)
	>ULN	0 (0)	0 (0)	0 (0)
Saxa 10 mg N=335	<LLN	0 (0)	1 (100.0)	0 (0)
	≥LLN to ≤ULN	2 (0.6)	317 (98.4)	3 (0.9)
	>ULN	0 (0)	1 (100.0)	0 (0)
All Saxa N=978	<LLN	0 (0)	2 (100.0)	0 (0)
	≥LLN to ≤ULN	3 (0.3)	938 (98.7)	9 (0.9)
	>ULN	0 (0)	3 (100.0)	0 (0)
Metformin N=328	<LLN	1 (33.3)	2 (66.7)	0 (0)
	≥LLN to ≤ULN	1 (0.3)	312 (99.7)	0 (0)
	>ULN	0 (0)	2 (100.0)	0 (0)
Potassium				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 5 mg + Met N=320	<LLN	0 (0)	3 (100.0)	0 (0)
	≥LLN to ≤ULN	3 (1.0)	302 (97.4)	5 (1.6)
	>ULN	0 (0)	1 (100.0)	0 (0)

Table 7.102. Shift from Baseline to Week 24 (LOCF) for Chemistry Parameters for Study CV181039				
Saxa 10 mg + Met N=323	<LLN	1 (33.3)	2 (66.7)	0 (0)
	≥LLN to ≤ULN	1 (0.3)	308 (98.7)	3 (1.0)
	>ULN	0 (0)	2 (100.0)	0 (0)
Saxa 10 mg N=335	<LLN	0 (0)	4 (100.0)	0 (0)
	≥LLN to ≤ULN	2 (0.6)	315 (99.1)	1 (0.3)
	>ULN	0 (0)	2 (100.0)	0 (0)
All Saxa N=978	<LLN	1 (10.0)	9 (90.0)	0 (0)
	≥LLN to ≤ULN	6 (0.6)	925 (98.4)	9 (1.0)
	>ULN	0 (0)	5 (100.0)	0 (0)
Metformin N=328	<LLN	1 (12.5)	7 (87.5)	0 (0)
	≥LLN to ≤ULN	0 (0)	304 (98.7)	4 (1.3)
	>ULN	0 (0)	2 (100.0)	0 (0)
Creatinine				
	Baseline value (g/dL)	<LLN	≥LLN to ≤ULN	>ULN
Saxa 5 mg + Met N=320	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	306 (99.0)	3 (1.0)
	>ULN	0 (0)	2 (40.0)	3 (60.0)
Saxa 10 mg + Met N=323	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	314 (99.4)	2 (0.6)
	>ULN	0 (0)	1 (100.0)	0 (0)
Saxa 10 mg N=335	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	317 (99.4)	2 (0.6)
	>ULN	0 (0)	1 (20.0)	4 (80.0)
All Saxa N=978	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	937 (99.3)	7 (0.7)
	>ULN	0 (0)	4 (36.4)	7 (63.6)
Metformin N=328	<LLN	0 (0)	0 (0)	0 (0)
	≥LLN to ≤ULN	0 (0)	312 (98.7)	4 (1.3)
	>ULN	0 (0)	0 (0)	2 (100.0)
<i>Source: Response to FDA Question Received on 18-March-2009</i>				

7.4.1.2.1.5.3 Urinalysis

See Section 7.4.2.3.3 for marked abnormalities in urinalysis.

7.4.1.2.2 Marked outliers and dropouts for laboratory abnormalities

7.4.1.2.2.1 Monotherapy Safety Population

7.4.1.2.2.1.1 Hematology

Table 7.103 summarizes the proportion of subjects with marked abnormalities (MAs) in hematology parameters for the pooled monotherapy studies. Lymphocyte abnormalities have already been discussed in detail and are not included here. Although overall rates of hematological MAs were low, the proportion of saxagliptin-treated subjects with hypereosinophilia (as defined by the Sponsor) was twice that of placebo-treated subjects. At least one-third of these saxagliptin-treated subjects had isolated increases. The saxagliptin 5 mg group had the highest overall frequency (4.9%) of hypereosinophilia.

Table 7.103. Marked Hematologic Abnormalities--Summary During ST + LT Treatment Period for Monotherapy Studies

Parameter	n/No. (%)				
	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
Hemoglobin < 8 g/dL	0 (0)	1/247 (0.4)	0 (0)	1/586 (0.2)	0 (0)
Hematocrit <0.75X pre-Rx	1/242 (0.4)	2/247 (0.4)	1/97 (1)	4/586 (0.7)	1/164 (0.6)
Platelets<50x10 ⁹ c/L	0 (0)	1/246 (0.4)	0 (0)	1/581 (0.2)	0 (0)
Platelets>1.5x ULN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leukocytes<2 x1000c/uL	0 (0)	1/247 (0.4)	0 (0)	1/586 (0.2)	0 (0)
Neutrophils+Bands<1X1000 c/uL	0 (0)	3/247 (1.2)	1/97 (1)	4/585 (0.7)	1/164 (0.6)
Eosinophils > 0.9 x1000 c/uL	6 /241 (2.5)	12/247 (4.9)	3/97 (3.1)	21/585 (3.6)	3/164 (1.8)

Source: *Integrated Summary of Safety, Appendix 8.3.1.2*

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

7.4.1.2.2.1.2 Chemistry

Abnormalities related to liver tests are discussed in detail in Section 7.3.5 and are not included here. Table 7.104 summarizes proportion of subjects with marked abnormalities (MAs) in chemistry parameters for the pooled monotherapy studies. Abnormalities were generally low among saxagliptin-treated subjects.

Table 7.104. Marked Chemistry Abnormalities--Summary During ST + LT Treatment Period for Monotherapy Studies

Parameter	n/No. (%)				
	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
Blood Urea Nitrogen>2X pre-RX and >ULN	1/195 (0.5)	1/200 (0.5)	1/97 (1)	3/492 (0.6)	0 (0)
Creatinine> 2.5 mg/dL	1/242 (0.4)	0 (0)	0 (0)	1/586 (0.2)	0 (0)

Sodium<0.9X pre-Rx and ≤130mEq/L	0 (0)	0 (0)	0 (0)	0 (0)	1/165 (0.6)
Sodium>1.1X pre-Rx and ≥150mEq/L	1/242 (0.4)	0 (0)	1/97 (1)	2/586 (0.3)	0 (0)
Potassium≤0.8 pre-Rx and ≤3.2mEq/L	0 (0)	1/247 (0.4)	0 (0)	1/586 (0.2)	0 (0)
Potassium≥1.2X pre-Rx and ≥6.0mEq/L	9/242 (3.7)	7/247 (2.8)	1/97 (1)	17/586 (2.9)	6/165 (3.6)
Chloride<90 mEq/L	2/242 (0.8)	1/247 (0.4)	0 (0)	3/586 (0.5)	1/165 (0.6)
Chloride>120mEq/L	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Albumin<0.9LLN or if pre-Rx<LLN use<0.75X pre-Rx	0 (0)	1/247 (0.4)	0 (0)	1/586 (0.2)	0 (0)
Creatine Kinase>5X ULN	3/242 (1.2)	3/247 (1.2)	1/97 (1)	7/586 (1.2)	6/165 (3.6)

Source: Integrated Summary of Safety, Appendix 8.3.1.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

7.4.1.2.2.1.3 Urinalysis

Table 7.105 summarizes proportion of subjects with marked abnormalities (MAs) in urinalysis parameters for the pooled monotherapy studies. Elevated WBCs in urine were observed much more frequently in saxagliptin-treated subjects versus placebo. As noted in Section 8.1.1, the frequency of UTI was slightly elevated in the all saxagliptin group versus placebo.

Table 7.105. Marked Urinalysis Abnormalities--Summary During ST + LT Treatment Period for Monotherapy Studies

Parameter	n/No. (%)				
	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
Protein Urine	7/237 (3)	7/242 (2.9)	2/94 (2.1)	16/573 (2.8)	4/160 (2.5)
Blood Urine	12/237 (5.1)	19/242 (7.9)	7/94 (7.4)	38/573 (6.6)	16/160 (10)
RBC Urine	7/129 (5.4)	12/129 (9.3)	7/89 (7.9)	26/347 (7.5)	11/99 (11.1)
WBC Urine	26/142 (18.3)	31/136 (22.8)	10/89 (11.2)	67/367 (18.3)	8/108 (7.4)

Source: Integrated Summary of Safety, Appendix 8.3.1.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

7.4.1.2.2.2 Add-on Combination Studies

7.4.1.2.2.2.1 Hematology

Add-on to Metformin

Table 7.106 summarizes the proportion of subjects with marked abnormalities (MAs) in hematology parameters for the add-on to metformin study. MAs for eosinophils were reported in 7.2% of subjects in the saxagliptin 10 mg + metformin versus 4.5% in the metformin + placebo group.

Table 7.106. Marked Hematology Abnormalities--Summary During ST+LT Treatment Period for Study CV181014

Parameter	n/No. (%)			
	Saxa 2.5 mg + Met N=192	Saxa 5 mg + Met N=191	Saxa 10 mg + Met N=181	Placebo + Met N=179
Hemoglobin < 8 g/dL	0 (0)	1/190 (0.5)	1/181 (0.6)	0 (0)
Hematocrit <0.75X pre-Rx	1/189 (0.5)	3/190 (1.6)	4/181 (2.2)	2/179 (1.1)
Platelets<50x10 ⁹ c/L	0 (0)	0 (0)	0 (0)	0 (0)
Platelets>1.5x ULN	0 (0)	0 (0)	3/181 (1.7)	1/178 (0.6)
Leukocytes<2 x1000c/uL	0 (0)	0 (0)	0 (0)	0 (0)
Neutrophils+Bands<1X1000 c/uL	1/189 (0.5)	0 (0)	0 (0)	1/179 (0.6)
Eosinophils > 0.9 x1000 c/uL	10/189 (5.3)	9/190 (4.7)	13/181 (7.2)	8/179 (4.5)

Source: Clinical Study Report, CV181014, Table 8.7.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with base value and at least one value during ST+LT Treatment Period; N=number of treated subjects

Add-on to Sulfonylurea

Table 7.107 summarizes the proportion of subjects with marked abnormalities (MAs) in hematology parameters for Study CV181040. MAs for eosinophils were seen more frequently in both saxagliptin groups compared to placebo.

Table 7.107. Marked Hematology Abnormalities--Summary During ST+LT Treatment Period for Study CV181040

Parameter	n/No. (%)		
	Saxa 2.5 mg + Gly N=248	Saxa 5 mg +Gly N=253	Placebo + Gly N=267
Hemoglobin < 8 g/dL	0 (0)	0 (0)	0 (0)
Hematocrit <0.75X pre-Rx	1/246 (0.4)	0 (0)	1/265 (0.4)
Platelets<50x10 ⁹ c/L	0 (0)	1/253 (0.4)	0 (0)
Platelets>1.5x ULN	0 (0)	0 (0)	1/265 (0.4)
Leukocytes<2 x1000c/uL	0 (0)	0 (0)	0 (0)
Neurophils+Bands<1X1000 c/uL	4/247 (1.6)	2/253 (0.8)	4/265 (1.5)
Eosinophils > 0.9 x1000 c/uL	20/247 (8.1)	18/253 (7.1)	12/265 (4.5)

Source: Clinical Study Report, CV181040, Table 8.7.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

Add-on to TZD

Table 7.108 summarizes the proportion of subjects with marked abnormalities (MAs) in hematology parameters for Study CV181013. MAs for eosinophils were seen across all treatment groups, including placebo.

Parameter	n/No. (%)		
	Saxa 2.5 mg + TZD	Saxa 5 mg + TZD	Placebo + TZD
	N=195	N=186	N=184
Hemoglobin < 8 g/dL	0 (0)	0 (0)	0 (0)
Hematocrit <0.75X pre-Rx	1/193 (0.5)	1/185 (0.5)	1/182 (0.5)
Platelets<50x10 ⁹ c/L	0 (0)	1/185 (0.5)	0 (0)
Platelets>1.5x ULN	0 (0)	0 (0)	1/182 (0.5)
Leukocytes<2 x1000c/uL	1/193 (0.5)	0 (0)	0 (0)
Neutrophils+Bands<1X1000 c/uL	4/193 (2.1)	0 (0)	0 (0)
Eosinophils > 0.9 x1000 c/uL	6/193 (3.1)	9/185 (4.9)	9/182 (4.9)

Source: Clinical Study Report, CV181040, Table 8.7.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

7.4.1.2.2.2.2 Chemistry

Add-on to Metformin

Table 7.109 summarizes proportion of subjects with marked abnormalities (MAs) in chemistry parameters for the add-on combination to metformin study. The frequency of abnormalities was low among all treatment groups.

Parameter	n/No. (%)			
	Saxa 2.5 mg + Met	Saxa 5 mg + Met	Saxa 10 mg + Met	Placebo + Met
	N=192	N=191	N=181	N=179
Blood Urea Nitrogen>2X pre-RX and >ULN	11/190 (5.8)	7/190 (3.7)	2/181 (1.1)	9/179 (0.6)
Creatinine> 2.5 mg/dL	1/190 (0.5)	1/190 (0.5)	0 (0)	1/179 (0.6)

Sodium<0.9X pre-Rx and ≤130mEq/L	0 (0)	2/190 (1.1)	4/181 (2.2)	0 (0)
Sodium>1.1X pre-Rx and ≥150mEq/L	0 (0)	0 (0)	0 (0)	0 (0)
Potassium≤0.8 pre-Rx and ≤3.2mEq/L	0 (0)	1/190 (0.5)	1/181 (0.6)	1/179 (0.6)
Potassium≥1.2X pre-Rx and ≥6.0mEq/L	4/190 (2.1)	5/190 (2.6)	3/181 (1.7)	7/179 (3.9)
Chloride<90 mEq/L	0 (0)	3/190 (1.6)	3/181 (1.7)	0 (0)
Chloride>120mEq/L	1/190 (0.5)	0 (0)	0 (0)	0 (0)
Albumin<0.9LLN or if pre-Rx<LLN use<0.75X pre-Rx	1/190 (0.5)	0 (0)	0 (0)	0 (0)
Creatine Kinase>5X ULN	0 (0)	2/190 (1.1)	3/181 (1.7)	1/179 (0.6)

Source: Clinical Study Report, CV181014, Table 8.7.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

Add-on to Sulfonylurea

Table 7.110 summarizes proportion of subjects with marked abnormalities (MAs) in chemistry parameters for Study CV181040. CK MAs were seen most frequently observed in the saxagliptin 5mg group. There was one discontinuation due to a CK elevation> 10ULN in a subject with elevated CK at baseline, treated with saxagliptin 5 mg. The CK returned to baseline within 2 months of cessation of study drug.

Parameter	n/No. (%)		
	Saxa 2.5 mg + Gly N=248	Saxa 5 mg +Gly N=253	Placebo + Gly N=267
Blood Urea Nitrogen>2X pre-RX and >ULN	7/247 (2.8)	3/253 (1.2)	2/265 (0.8)
Creatinine> 2.5 mg/dL	0 (0)	0 (0)	0 (0)
Sodium<0.9X pre-Rx and ≤130mEq/L	0 (0)	0 (0)	0 (0)
Sodium>1.1X pre-Rx and ≥150mEq/L	1/247 (0.4)	0 (0)	1/265 (0.4)
Potassium≤0.8 pre-Rx and ≤3.2mEq/L	1/247 (0.4)	1/253 (0.4)	2/265 (0.8)
Potassium≥1.2X pre-Rx and ≥6.0mEq/L	5/247 (2)	3/253 (1.2)	6/265 (2.3)

Chloride<90 mEq/L	2/247 (0.8)	0 (0)	0 (0)
Chloride>120mEq/L	0 (0)	0 (0)	0 (0)
Albumin<0.9LLN or if pre-Rx<LLN use<0.75X pre-Rx	2/247 (0.8)	0 (0)	1/265 (0.4)
Creatine Kinase>5X ULN	3/247 (1.2)	5/253 (2)	1/265 (0.4)

Source: Interim Clinical Study Report, Table 8.7.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

Add-on to TZD

Table 7.111 summarizes proportion of subjects with marked abnormalities (MAs) in chemistry parameters for Study CV181013. Overall frequencies of MAs were low.

Parameter	n/No. (%)		
	Saxa 2.5 mg + TZD N=195	Saxa 5 mg + TZD N=186	Placebo + TZD N=184
Blood Urea Nitrogen>2X pre-RX and >ULN	3/183 (1.6)	1/178 (0.6)	5/172 (2.9)
Creatinine> 2.5 mg/dL	0 (0)	0 (0)	0 (0)
Sodium<0.9X pre-Rx and ≤130mEq/L	0 (0)	0 (0)	0 (0)
Sodium>1.1X pre-Rx and ≥150mEq/L	0 (0)	0 (0)	0 (0)
Potassium≤0.8 pre-Rx and ≤3.2mEq/L	1/193 (0.5)	1/185 (0.5)	1/182 (0.5)
Potassium≥1.2X pre-Rx and ≥6.0mEq/L	1/193 (0.5)	1/185 (0.5)	2/182 (1.1)
Chloride<90 mEq/L	1/193 (0.5)	0 (0)	3/182 (1.6)
Chloride>120mEq/L	0 (0)	0 (0)	0 (0)
Albumin<0.9LLN or if pre-Rx<LLN use<0.75X pre-Rx	0 (0)	0 (0)	1/182 (0.5)
Creatine Kinase>5X ULN	1/193 (1)	4/185 (2.2)	0 (0)

7.4.1.2.2.2.3 Urinalysis

Add-on to Metformin

Table 7.112 summarizes the proportion of subjects with marked abnormalities (MAs) in urinalysis parameters for Study CV181014. Elevated WBCs in urine were reported frequently in the saxagliptin 2.5 mg group.

Table 7.112. Marked Chemistry Abnormalities--Summary During ST+LT Treatment Period for Study CV181014				
Parameter	n/No. (%)			
	Saxa 2.5 mg + Met N=192	Saxa 5 mg + Met N=191	Saxa 10 mg + Met N=181	Placebo + Met N=179
Protein Urine	5/187 (2.7)	7/189 (3.7)	10/180 (5.6)	11/178 (6.2)
Blood Urine	12/187 (6.4)	18/189 (9.5)	17/180 (9.4)	12/178 (6.7)
RBC Urine	23/175 (13.1)	21/175 (12)	20/161 (12.4)	18/164 (11)
WBC Urine	36/174 (20.7)	29/175 (16.6)	20/161 (12.4)	24/164 (14.6)

Source: Clinical Study Report, CV181014, Table 8.7.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

Add-on to Sulfonylurea

Table 7.113 summarizes the proportion of subjects with marked abnormalities (MAs) in urinalysis parameters for Study CV181040. MAS of urine WBCs were seen frequently among all treatment groups.

Table 7.113. Marked Urinalysis Abnormalities--Summary During ST+LT Treatment Period for Study CV181040			
Parameter	n/No. (%)		
	Saxa 2.5 mg + Gly N=248	Saxa 5 mg +Gly N=253	Placebo + Gly N=267
Protein Urine	3/245 (1.2)	4/251 (1.6)	8/264 (3)
Blood Urine	17/245 (6.9)	18/251 (7.2)	18/264 (6.8)
RBC Urine	9/56 (16.1)	7/59 (11.9)	6/59 (10.2)
WBC Urine	22/84 (26.2)	26/101 (25.7)	30/96 (31.3)

Source: Interim Clinical Study Report, CV181040, Table 8.7.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment;
 No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

Add-on to TZD

Table 7.114 summarizes the proportion of subjects with marked abnormalities (MAs) in urinalysis parameters for Study CV181013. Blood and RBCs in the urine were more frequent MAs in the saxagliptin 5 mg group.

Table 7.114. Marked Urinalysis Abnormalities--Summary During ST+LT Treatment Period for Study CV181013			
Parameter	n/No. (%)		
	Saxa 2.5 mg + TZD N=195	Saxa 5 mg + TZD N=186	Placebo + TZD N=184
Protein Urine	2/193 (1)	5/183 (2.7)	2/181 (1.1)
Blood Urine	6/193 (3.1)	20/183 (10.9)	13/181 (7.2)
RBC Urine	3/37 (8.1)	10/55 (18.2)	6/43 (14)
WBC Urine	13/59 (22)	18/68 (26.5)	16/66 (24.2)

Source: Interim Clinical Study Report, CV181040, Table 8.7.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment;
 No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

7.4.1.2.2.3 Initial Combination with Metformin Study

7.4.1.2.2.3.1 Hematology

Table 7.115 summarizes the proportion of subjects with marked abnormalities (MAs) in hematology parameters for Study CV181039. There was a somewhat increased frequency of MAs for hematocrit in saxagliptin-treated subjects compared with metformin alone (1.2% versus 0.3%), particularly seen in the 2.5 mg group (2.2%). Overall, however, the numbers of subjects with this abnormality were small.

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Table 7.115. Marked Hematologic Abnormalities--Summary During ST + LT Treatment Period for CV181039

Parameter	n/No. (%)					
	Saxa 2.5 mg + Met N=320	Saxa 5 mg + Met N=323	Saxa 10 mg + Met N=335	All Saxa N=978	Metformin N=328	
Hemoglobin < 8 g/dL	0 (0)	1/317 (0.3)	1/324 (0.3)	2/956 (0.2)	0 (0)	
Hematocrit <0.75X pre-Rx	7/313 (2.2)	2/316 (0.6)	2/324 (0.6)	11/953 (1.2)	1/318 (0.3)	
Platelets <50x10 ⁹ c/L	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Platelets >1.5x ULN	0 (0)	1/315 (0.3)	2/323 (0.6)	3/953 (0.3)	0 (0)	
Leukocytes <2 x1000c/uL	0 (0)	0 (0)	0 (0)	0 (0)	1/318 (0.3)	
Neutrophils+Bands <1X1000 c/uL	2/315 (2.9)	1/317 (0.3)	0 (0)	3/956 (0.3)	2/318 (0.6)	
Eosinophils > 0.9 x1000 c/uL	9/315 (2.9)	10/317 (3.2)	10/324 (3.1)	29/956 (3)	25/317 (7.9)	

Source: *Integrated Summary of Safety, Appendix 8.3.4.2*

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

7.4.1.2.2.3.2 Chemistry

Table 7.116 summarizes proportion of subjects with marked abnormalities (MAs) in chemistry parameters for Study CV181039. Abnormalities were generally low among saxagliptin-treated subjects.

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Table 7.116. Marked Chemistry Abnormalities--Summary During ST + LT Treatment Period for CV181039

Parameter	n/No. (%)				
	Saxa 2.5 mg + Met N=320	Saxa 5 mg + Met N=323	Saxa 10 mg + Met N=335	All Saxa N=978	Metformin N=328
Blood Urea Nitrogen > 2X pre-Rx and > ULN	1/142 (0.7)	1/142 (0.7)	2/145 (1.4)	4/429 (0.9)	4/142 (2.8)
Creatinine > 2.5 mg/dL	0 (0)	0 (0)	1/324 (0.3)	1/955 (0.1)	0 (0)
Sodium < 0.9X pre-Rx and ≤ 130mEq/L	1/314 (0.3)	0 (0)	3/324 (0.9)	4/955 (0.4)	0 (0)
Sodium > 1.1X pre-Rx and ≥ 150mEq/L	2/314 (0.6)	0 (0)	0 (0)	2/955 (0.2)	0 (0)
Potassium ≤ 0.8 pre-Rx and ≤ 3.2mEq/L	1/314 (0.3)	0 (0)	3/324 (0.9)	4/955 (0.4)	0 (0)
Potassium ≥ 1.2X pre-Rx and ≥ 6.0mEq/L	8/314 (2.5)	7/317 (2.2)	10/324 (3.1)	25/955 (2.6)	9/319 (2.8)
Chloride < 90 mEq/L	2/314 (0.6)	0 (0)	7/324 (2.2)	9/955 (0.9)	3/319 (0.9)
Chloride > 120mEq/L	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Albumin < 0.9LLN or if pre-Rx < LLN use < 0.75X pre-Rx	0 (0)	1/317 (0.3)	1/324 (0.3)	2/955 (0.2)	0 (0)
Creatine Kinase > 5X ULN	0 (0)	2/317 (0.6)	3/324 (0.9)	5/956 (0.5)	2/319 (0.6)

Source: Integrated Summary of Safety, Appendix 8.3.4.2

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

7.4.1.2.2.3.3 Urinalysis

Table 7.117 summarizes proportion of subjects with marked abnormalities (MAs) in urinalysis parameters Study CV181039. The frequency of abnormalities was not generally increased in saxagliptin-treated subjects compared to metformin.

Table 7.117 Marked Chemistry Abnormalities--Summary During ST + LT Treatment Period for CV181039					
Parameter	n/No. (%)				
	Saxa 2.5 mg + Met N=320	Saxa 5 mg + Met N=323	Saxa 10 mg + Met N=335	All Saxa N=978	Metformin N=328
Protein					
Urine	7/308 (2.3)	7/315 (2.2)	5/321 (1.6)	19/944 (2)	9/314 (2.9)
Blood Urine	13/308 (4.2)	14/315 (4.4)	15/321 (4.7)	42/944 (4.4)	22/314 (7)
RBC Urine	3/52 (5.8)	6/61 (9.8)	8/56 (14.3)	17/169 (10.1)	5/59 (8.5)
WBC Urine	12/74 (16.2)	28/110 (25.5)	23/87 (26.4)	63/271 (23.2)	29/85 (34.1)

Source: *Integrated Summary of Safety, Appendix 8.3.4.*

n=number of treated subjects with all abnormality criteria during ST+LT treatment; No.=Number of treated subjects with baseline value and at least one value during ST+LT Treatment Period; N=number of treated subjects

7.4.2 Vital Signs

7.4.2.1 Overview of vital signs testing in the development program

Vital signs, including heart rate and blood pressure, and body weight were collected at every study visit.

7.4.2.2 Selection of studies and analyses for overall drug-control comparisons

The vital sign analyses were performed using datasets from the pooled monotherapy studies, the three individual add-on combination studies, and the initial combination with metformin study.

7.4.2.3 Standard analyses and explorations of vital signs data

7.4.2.3.1 Analyses focused on measures of central tendency

7.4.2.3.1.1 Pooled Monotherapy studies

Table 7.118 summarizes the change from baseline in vital signs for the Pooled Monotherapy population. Overall, there were minimal, if any, effects of saxagliptin on blood pressure and heart rate over time.

Table 7.118. Change from baseline in vital signs for ST Period for Pooled Monotherapy Studies					
	Saxa 2.5 mg N=247	Saxa 5 mg N=252	Saxa 10 mg N=98	All Saxa N=597	Placebo N=169
n (%)	176 (71)	176 (70)	66 (67%)	418 (70)	106 (63)
Change from baseline: systolic blood pressure (mmHg)					
Mean±SD	-2.8±1.0	-3.5±0.9	-6.4±1.6	-3.6±0.6±	-4.1±1.5
Median	-2.0	-1.7	-6.8	-3.3	-5.7
(min, max)	(-4.7, -0.9)	(-5.3, -1.7)	(-9.6, -3.2)	(-4.9, -2.4)	(7.1, -1.1)
Change from baseline: diastolic blood pressure (mmHg)					
Mean±SD	-0.6±0.6	-1.7±0.5	-2.4±1.0	-1.3±0.4	-2.0±0.8
Median	-1.7	-0.5	-2	-1	-1.7
(min, max)	(-1.8, 0.6)	(-2.8, -0.6)	(-4.5, -0.4)	(-2.1, -0.6)	(-3.6, -0.3)
Change from baseline: heart rate (bpm)					
Mean±SD	-0.9±0.7	0.6±0.7	-0.7±1.0	-0.7±0.5	-1.4±0.8
Median	-1.3	-1.3	0	-1.3	-1.7
(min, max)	(-2.3, 0.6)	(-2.1, 0.8)	(-2.7, 1.3)	(-1.7, 0.2)	(-3, 0.3)

Source: Integrated Summary of Safety, Appendix 10.1

7.4.2.3.1.2 Add-on combination studies

Tables 7.119-7.121 summarize the change from baseline in vital signs for the three add-on combination studies. In all 3 studies, there were few, if any, effects of saxagliptin on blood pressure and heart rate over time.

Table 7.119. Change from baseline in vital signs for ST period for Study CV181014				
	Saxa 2.5 mg + Met N=192	Saxa 5 mg + Met N=191	Saxa 10 mg + Met N=181	Placebo + Met N=179
n (%)	142 (74)	141 (74)	137 (76)	105 (59)
Change from baseline: systolic blood pressure (mmHg)				
Mean±SD	-5.1±1.3	-3.8±1.4	-4.3±1.3	-3.7±1.3
Median	-5.3	-3.7	-4.7	-2.7
(min, max)	(-7.7, -2.6)	(-6.5, -1.1)	(-6.9, -1.7)	(-6.3, -1.1)
Change from baseline: diastolic blood pressure (mmHg)				
Mean±SD	-1.7±0.8	-1.8±0.9	-3.0±0.7	-1.9±0.8
Median	-3.4	-1.7	-3.3	-1.7

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(min, max)	(-3/2, -0.1)	(-3.5, 0)	(-4.5, -1.6)	(-3.5, -0.3)
Change from baseline: heart rate (bpm)				
Mean±SD	-0.5±0.8	-0.1±0.8	-0.1±0.8	-0.9±0.8
Median	0	0	0.7	0
(min, max)	(-2, 1)	(-1.6, 1.3)	(-1.6, 1.5)	(-2.5, 0.8)

Source: Clinical Study Report, CV 181014, Appendix 7.12

Table 7.120. Change from baseline in vital signs for ST period for Study CV181040			
	Saxa 2.5 mg + Gly N=248	Saxa 5mg + Gly N=253	Placebo + Gly N=267
n (%)	189	193	175
Change from baseline: systolic blood pressure (mmHg)			
Mean±SD	-3.9±1.0	-3.2±1.0	-2.0±1.1
Median	-3.3	-2	-0.7
(min, max)	(-6, -1.9)	(-5.2, -1.2)	(-4.1, 0.1)
Change from baseline: diastolic blood pressure (mmHg)			
Mean±SD	-3.3±0.6	-1.8±0.6	-2.4±0.7
Median	-2.3	-1.3	-2
(min, max)	(-4.6, -2)	(-3, -0.6)	(-3.7, -1)
Change from baseline: heart rate (bpm)			
Mean±SD	-0.5±0.7	-1.3±0.6	-2.2±0.7
Median	0.7	0.6	0.7
(min, max)	(-1.9, 1)	(-2.5, 0)	(-3.6, -0.7)

Source: Clinical Study Report, CV181040

Table 7.121. Change from baseline in vital signs for ST period for Study CV181013			
	Saxa 2.5 mg + TZD N=195	Saxa 5 mg + TZD N=186	Placebo + TZD N=184
n (%)	154 (79)	139 (75)	134 (73)
Change from baseline: systolic blood pressure (mmHg)			
Mean±SD	-1.5±1.0	-0.5±1.0	-0.6±1.2
Median	-1.3	0	0
(min, max)	(-3.5, 0.5)	(-2.5, 1.5)	(-3.1, 1.8)
Change from baseline: diastolic blood pressure (mmHg)			
Mean±SD	-1.4±0.7	-1.1±0.6	-1.9±0.8
Median	-0.7	-0.3	-0.2
(min, max)	(-2.7, 0)	(-2.4, 0.2)	(-3.4, -0.3)

Change from baseline: heart rate (bpm)			
Mean±SD	-0.7±0.7	-1.4±0.8	-0.6±0.8
Median	-0.7	-1.3	-1.3
(min, max)	(-2.1, 0.7)	(-3.1, 0.2)	(-2.2, 1)

Source: Clinical Study Report, CV181013, Appendix 7.12

7.4.2.3.1.3 Initial combination with metformin study

Table 7.122 summarizes the change from baseline in vital signs for the initial combination with metformin study. There were few, if any, effects of saxagliptin on blood pressure and heart rate over time.

Table 7.122. Change from baseline in vital signs for ST period for Study CV181039				
	Saxa 5 mg + Met N=320	Saxa 10 mg + Met N=323	Saxa 10 mg N=335	Metformin N=328
n (%)	255 (80%)	250 (77%)	215 (64%)	233 (71%)
Change from baseline: systolic blood pressure (mmHg)				
Mean±SD	-5.1±0.8	-5.0±0.8	-5.0±0.9	-5.3±0.9
Median	-4	-3.3	-5	-4
(min, max)	(-6.6, -3.5)	(-6.6, -3.4)	(-6.8, -3.3)	(-7, -3.6)
Change from baseline: diastolic blood pressure (mmHg)				
Mean±SD	-3.0±0.5	-2.9±0.5	-3.1±0.6	-4.1±0.6
Median	-2	-2.5	-3.3	-2.7
(min, max)	(-4, -2)	(-3.9, -1.9)	(-4.3, -2)	(-5.2, -3)
Change from baseline: heart rate (bpm)				
Mean±SD	-0.6±0.6	-1.4±0.5	-2.1±0.6	-0.3±0.6
Median	0	-1.3	-2	0
(min, max)	(-1.7, 0.6)	(-2.4, -0.4)	(-3.2, -0.9)	(-1.4, 0.8)

Source: Clinical Study Report, CV 181014, Appendix 7.12

7.4.2.3.2 Marked outliers and dropouts for vital sign abnormalities

In the Core Phase 3 studies, there were no dropouts for vital sign abnormalities.

7.4.3 Electrocardiograms (ECGs)

The thorough QT study has already been discussed in Section 4.4.2. This study confirmed that saxagliptin and BMS-510849 have no effect on the QTc interval or heart rate following 40 mg daily doses of saxagliptin.

Electrocardiograms were collected during screening, at Week 12, and Week 24 in the Core phase 3 studies, including quantitative information for HR, PR, QRS, QT, and QTc. These were based on tracings from a 12-lead ECG and captured on a Case Report Form. The Sponsor then analyzed the data by Investigator Assessment (normal/abnormal) using shift tables. There were no pre-defined notable EKG criteria used for the Investigator's assessments. The Sponsor did not perform any further integrated or pooled analyses.

Overall, there did not appear to be significant differences in shifts observed in saxagliptin-treated versus placebo subjects. However, these data are limited because the electrocardiograms were not analyzed in a central facility by cardiologists.

7.4.4 Special Safety Studies

The Sponsor conducted several special safety studies that have already been reviewed in detail:

- a. Two studies using daily and/or interrupted doses of saxagliptin (up to 40 mg) plus ketoconazole to study the flu-like syndrome observed with saxagliptin 100 mg in Clinical Pharmacology Studies (Section 7.3.5, lymphocytes)
- b. Thorough QT study (Section 4.4.2)

7.4.5 Immunogenicity

This section does not apply, since saxagliptin is not a protein, and is therefore not expected to elicit an immune response.

7.5 Other Safety Explorations

Dose Dependency for Adverse Events

In this Review, I have incorporated analyses and discussion regarding potential dose-dependent adverse events. These can be found under specific topics throughout the Review and will not be restated in this Section.

7.5.1 Time Dependency for Adverse Events

Analyses and discussion regarding time dependency for adverse events have been incorporated in this Review. When presenting tables of adverse events, I reviewed the frequencies of AEs observed in both the ST and ST + LT periods to exclude any major discrepancies. Given that frequencies of AEs across dose groups were similar in these 2 distinct periods, generally only one of these time periods is presented in tabular fashion.

7.5.2 Drug-Demographic Interactions

Efficacy subgroup analyses have already been presented in Section 6.1.7. Safety subgroup analyses are presented here.

The Sponsor analyzed differences in the AE profile for the following subgroups: age, gender, race, ethnicity, BMI, duration of diabetes, and renal function. The analysis of adverse events in subjects with renal impairment is discussed separately in this Section. Table 7.123 summarizes the adverse events in the remainder of these subgroups. This analysis is limited by small sample sizes of certain subgroups, including those over 75 years old, blacks, and Hispanic/Latinos. Overall, this analysis revealed few differences in the AE profile based on these subgroups.

Table 7.123. Adverse Events by Subgroups for Pooled Monotherapy (ST Period, Excluding Rescue) and Placebo-controlled Pooled Safety Analysis (Double-blind Period up to Week 24)				
Intrinsic Factor n (%)	Pooled Monotherapy		Placebo-controlled Pooled Safety	
	All Saxa	Placebo	All Saxa	Placebo
Overall Study Population	N=597	N=169	N=2043	N=799
Age (years)				
<65	333 (66.5)	78 (56.5)	1220 (71.3)	445 (67.2)
≥65	66 (68.8)	23 (74.2)	236 (71.3)	109 (79.6)
≥75	9 (100.0)	2 (66.7)	25 (83.3)	11 (84.6)
Females				
≤50 years	70 (68.0)	15 (53.6)	252 (76.4)	95 (72.0)
>50 years	133 (65.2)	31 (52.5)	527 (72.8)	200 (71.2)
Gender				
Male	196 (67.6)	55 (67.1)	667 (68.5)	259 (67.1)
Female	203 (66.1)	46 (52.9)	779 (73.9)	295 (71.4)
Race				
White	309 (66.7)	84 (63.6)	1009 (70.8)	369 (69.0)
Black	23 (63.9)	3 (30.0)	74 (77.1)	18 (58.1)
Asian	56 (67.5)	10 (50.0)	209 (65.3)	90 (65.2)
Other	11 (73.3)	4 (57.1)	164 (81.6)	77 (81.1)

Table 7.123. Adverse Events by Subgroups for Pooled Monotherapy (ST Period, Excluding Rescue) and Placebo-controlled Pooled Safety Analysis (Double-blind Period up to Week 24)

Ethnicity				
Hispanic/Latino	38 (65.5)	10 (55.6)	142 (67.3)	55 (63.2)
Non Hispanic/Latino	191 (71.8)	47 (68.1)	454 (73.2)	134 (66.3)
BMI (kg/m²)				
<30	161 (64.9)	37 (50.7)	698 (69.5)	280 (68.6)
≥30	238 (68.2)	64 (66.7)	758 (73.0)	274 (70.1)
Duration of Diabetes (years)				
≤1.5	234 (63.9)	59 (59.6)	417 (68.0)	137 (63.7)
≤3	282 (64.7)	69 (56.5)	593 (68.5)	214 (63.7)
>3 to <5	55 (76.4)	18 (69.2)	245 (74.5)	99 (76.2)
≥5	62 (69.7)	14 (66.7)	618 (72.9)	241 (72.4)
≥10	13 (68.4)	5 (100.0)	235 (75.3)	99 (73.3)

Source: Summary of Clinical Safety, Table 5.1.1

Evaluation of AEs in Subjects with Renal Impairment

Overall, the clinical development program studied limited numbers of subjects with renal impairment (Core phase 3 studies had exclusion criteria of serum creatinine ≥ 1.5 mg/dL for males and ≥ 1.4 mg/dL for females). The Sponsor is conducting an ongoing study (CV181062) to specifically evaluate the safety and efficacy of saxagliptin in subjects with renal impairment in the following cohorts:

- Moderate (CrCl ≥ 30 - < 50 ml/min)
- Severe (< 30 ml/min not receiving dialysis)
- End-stage (hemodialysis-dependent)

Given the exclusion of subjects with elevated serum creatinine, the Sponsor's analysis of AEs in subjects with renal impairment is limited by its broad categorization of subjects with estimated creatinine clearance (by Cockcroft-Gault) of ≤ 80 ml/min (Sponsor-defined renal impairment) versus those with > 80 ml/min. As a reference, accepted guidelines classify patients with a glomerular filtration rate of ≥ 90 ml/min as normal.⁴

In the placebo-controlled Pooled Safety analysis, the overall frequency of AEs was lower for saxagliptin- than placebo-treated subjects with renal impairment (67.4% vs 73%, data not shown). The only PT that was higher in saxagliptin- than placebo-treated subjects (among most common AEs) with renal impairment was gastroenteritis (3.1% vs 0.6%).

In the Pooled Monotherapy populations (data not shown), the number of subjects with renal impairment was low (102 saxagliptin-treated subjects vs 35 placebo), and therefore these analyses

⁴ Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines, National Kidney Foundation.

are of limited value. Nevertheless, there were 2 PTs that were higher in saxagliptin- than placebo-treated subjects with renal impairment (among most common AEs): URI (7.8% vs 5.7%) and influenza (6.9% vs 2.9%).

Finally, in the Initial Combination with Metformin study, number of subjects with renal impairment was also relatively low (154 saxagliptin-treated subjects vs 59 active comparator). The following PTs (of the most common) were higher in saxagliptin- than metformin alone-treated subjects with renal impairment: URI (5.8% vs 3.4%), headache (8.4% vs 5.1%), blood creatinine decreased (5.2% vs 0), and hypertension (5.8% vs 1.7%). Table 7.124 summarizes the most common AEs and more frequent AEs in subjects with renal impairment in Study CV181039.

SOC (Number and % of subjects)	Estimated Creatinine Clearance (Cockcroft-Gault)			
	≤80 ml/min		>80 ml/min	
	All Saxa N=154	Metformin N=59	All Saxa N=823	Metformin N=269
Total Subjects with AE	105 (68.2)	39 (66.1)	434 (52.7)	151 (56.1)
Infections and Infestations				
Influenza	9 (5.8)	5 (8.5)	21 (2.6)	7 (2.6)
URI	9 (5.8)	2 (3.4)	27 (3.3)	4 (1.5)
UTI	7 (4.5)	4 (6.8)	34 (4.1)	12 (4.5)
Nervous System Disorders				
Headache	13 (8.4)	3 (5.1)	109 (13.2)	32 (11.9)
Investigations				
Blood creatinine increased	8 (5.2)	0	1 (0.1)	0
Vascular Disorders				
Hypertension	9 (5.8)	1 (1.7)	38 (4.6)	11 (4.1)

Source: Summary of Clinical Safety, Table 5.1.2C

Of the 8 saxagliptin-treated subjects with renal impairment with blood creatinine increased, 4 were discontinued due to this AE. Seven of the 8 subjects had serum creatinine increases of ≤0.2 mg/dL. The eighth subject had an increase of 0.5 mg/dL (from baseline 1.1 mg/dL to 1.6 mg/dL on Day 29); repeat measurement of serum creatinine on Day 43 was 1.2 mg/dL.

Hypertension was also seen more frequently in saxagliptin-treated subjects with renal impairment than metformin-treated subjects with renal impairment. In the 9 saxagliptin-treated subjects with AEs (Table 7.124 above), there were a total of 14 AEs of hypertension, none of which resulted in study drug discontinuation. Eight of the nine subjects were receiving antihypertensive therapy at baseline. There were only 2 subjects with excursions in systolic blood pressure of more than

30mmHg between Day 1 and the time of the reported AE. Narratives for these 2 subjects are included here:

- **Subject CV181039-225-2435**, a 63 year old male in the saxagliptin 5 mg + metformin group, had no documented history of hypertension (although was on baseline enalapril) and a Day 1 BP of 110/70 mmHg, but a Day -6 BP of 150/100 mmHg. On Day86, nifedipine was added. BP on Day 100 was 127/90 mmHg.
- **Subject CV181039-151-642**, a 57 year old female in the saxagliptin 5 mg + metformin group, had no documented history of hypertension and was reported to have a BP of 153/90 mmHg on Day 127 (Day 1 BP 117/77 mmHg). Losartan was initiated on Day 127. Day 141 BP was 137/83 mmHg.

Concomitant Antihyperglycemic Therapy

As discussed in Section 7.3.5, the concomitant use of saxagliptin as add-on treatment to SU or TZD may increase the frequency of hypoglycemia (SU) and peripheral edema (TZD), respectively.

7.5.3 Drug-Disease Interactions

The analysis of adverse events in subjects with renal impairment was discussed in depth in Section 7.5.2. The analysis is limited by small numbers of subjects with renal impairment enrolled into the Phase 3 program.

7.5.4 Drug-Drug Interactions

Drug-drug interactions were studied with 11 drugs, including simvastatin. As discussed in detail in Section 4.4.3, the most significant changes in saxagliptin exposure occurred in the presence of metabolic modulators, such as ketoconazole. Therefore, it is recommended that the dose of saxagliptin be reduced to 2.5 mg when patients are prescribed CYP3A4/5 inhibitors.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Saxagliptin did not appear to be carcinogenic in the nonclinical program.

The clinical development program, with LT periods of approximately 12 months, is likely of insufficient duration to reliably assess the long-term risk of carcinogenicity. Nevertheless, I reviewed all PTs under the SOC Neoplasms Benign, Malignant, and Unspecified for the pooled monotherapy studies, the individual add-on combination studies, and the initial combination with metformin study. Within each of these populations, no individual neoplasm PT appeared more than once in a saxagliptin-treated subject. In addition, no unusual neoplasms were reported.

7.6.2 Human Reproduction and Pregnancy Data

Within the saxagliptin clinical development program, a total of 13 cases of pregnancy have been observed. Of these 13 cases, 10 subjects received saxagliptin (4 on monotherapy and 6 with concomitant metformin) and 3 subjects received placebo and metformin as add-on or background therapy. Of the 4 subjects on saxagliptin monotherapy, the following outcomes were observed: one normal newborn, one spontaneous abortion in the wife of a male subject, one spontaneous abortion at 4-weeks of pregnancy with an unspecified birth defect, and one stillbirth. Of the 6 subjects on saxagliptin and metformin, the following outcomes were observed: 4 normal newborns, 1 spontaneous abortion, and 1 induced abortion. Of the 3 subjects on metformin or placebo, the following outcomes were observed: 2 normal newborns and 1 spontaneous abortion. Narratives for the adverse outcomes in saxagliptin-treated subjects are included here:

Saxagliptin—treated subjects

- CV181008-31-122 was a 50 year old male whose 33-year-old wife became pregnant 5 weeks prior to her husband entering the study. She experienced a miscarriage at 11 weeks gestational age.
- CV181011-145-681 was a 33-year-old female (gravida 2, para 2) who had a positive pregnancy test 9 months after saxagliptin and 3 months after metformin were initiated. She was using double barrier method of contraception. Estimated gestational age was 8 weeks at the time of the positive pregnancy test. Fifteen days later, she experienced a spontaneous abortion. She remained in the study.
- CV181040-40-1548 was a 39-year-old female (gravida 4, para 2) had a positive pregnancy test 4 months after saxagliptin was started. Study therapy was stopped that day. One month later, she experienced an incomplete spontaneous abortion at 4 weeks gestational age. An unspecified birth defect was noted in the abortus. She was using condom barrier method for birth control.
- CV181040-100-1186 was a 28-year-old female (gravida 2, para 1) became pregnant during the LT period. She was using oral medroxyprogesterone for contraception. She discontinued the study on Day 316. She had inadequate glycemic control during the study. At 39 weeks gestation, she had a stillbirth. Results of autopsy were not provided.
- CVV181039-200-232 was a 43-year-old female (gravida 6, para 4) with a positive pregnancy test 13 months after saxagliptin and 4 months after metformin were initiated. Gestational age at the time was 2 weeks. Study therapy was discontinued. She underwent an induced abortion at 5 weeks gestation.

Reviewer comment: The majority of spontaneous abortions occurred in the first trimester, which is when most clinically apparent miscarriages occur. Clinical miscarriages are thought to occur in 8% of pregnancies.ⁱⁱⁱ Uncontrolled diabetes is known to increase the risk of miscarriage. Based on the narratives provided, there is no concerning safety signal regarding saxagliptin and increased miscarriage rate or teratogenicity.

7.6.3 Pediatrics and Effect on Growth

In the clinical development program, saxagliptin was studied in subjects 18 years and older. Type 2 diabetes is rare in patients younger than age 10. Therefore there is no clear unmet medical need for children less than 10 years of age. In order to comply with the Pediatric Research and Equity Act (PREA), the Division has planned to grant a pediatric waiver for children <10 years old and a deferral for children who are 10 years of age up to but not including 17 years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Once-daily saxagliptin had no clinically meaningful effect on QTc interval or heart rate at doses up to 400 mg daily for 2 weeks (80 times the recommended human dose). Saxagliptin and its major metabolite are removed by hemodialysis (23% of dose over 4 hours). Appropriate supportive measures are recommended in the event of an overdose. Because 400 mg is the equivalent of taking eight 5 mg tablets, and because 400 mg daily for 2 weeks did not result in serious safety issues, it is unlikely that a patient who overdoses on saxagliptin will have any concerning toxicities.

Drug Abuse Potential

The potential for drug abuse was not specifically studied. There is no evidence that suggests a risk for abuse or dependence potential.

Withdrawal and Rebound

These effects were not studied.

7.7 Additional Submissions

8 Postmarketing Experience

Saxagliptin is not currently marketed. Therefore, post-marketing data are not available.

9 Appendices

9.1 Literature Review/References

Protocol for Study CV181008

Phase 2b dose finding study (CV181008): A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 2 Trial to Evaluate the Safety and Efficacy of BMS-477118 as Monotherapy in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control

Primary objective: To evaluate the positive efficacy trend among doses of saxagliptin in subjects with type 2 diabetes mellitus by assessing the change from baseline in HbA1c following 12 weeks of double-blind treatment.

This was a multicenter, randomized, parallel-group, double-blind, placebo-controlled study. A total of 423 subjects were randomized (1:1:1:1:1) and treated in the following groups:

- Saxagliptin 2.5 mg
- Saxagliptin 5 mg
- Saxagliptin 10 mg
- Saxagliptin 20 mg
- Saxagliptin 40 mg
- Placebo

An amendment to the protocol added 2 new dose arms, saxagliptin 100 mg and placebo.

Inclusion criteria included:

- 1) Men and non-nursing, non-pregnant women, 21 to 77 years of age.
- 2) Type 2 diabetes with inadequate glycemic control at screening ($\geq 6.8\%$ but $\leq 9.7\%$).
- 3) Drug-naïve (never received medical treatment for diabetes or had received medical treatment for diabetes less than 6 months since original diagnosis).
- 4) Fasting C-peptide ≥ 0.5 ng/mL.
- 5) BMI ≤ 37 kg/m².

Exclusion criteria were the same as those listed for Study CV181011 in Section 5.3.1.1.1.

Following screening, there was a single-blind placebo lead-in period of 2 weeks, during which subjects' compliance was assessed. This was followed by a 12-week or 6-week (for the 0, 100mg cohort) double-blind, placebo-controlled treatment period, in which subjects were randomized to one of six treatment arms (2.5mg, 5mg, 10mg, 20mg, 40mg, or placebo) and to 2 additional treatment arms (100mg or placebo). During this period, dose titration was not permitted, and subjects who met discontinuation criteria for hyperglycemia (Table 9.1) entered the follow-up period. A third period of 4 week follow-up was required to be completed by all subjects. Subjects who completed their double-blind study period were given single-blind placebo and monitored for

4 weeks. Subjects who met hyperglycemic discontinuation criteria received open-label metformin (500mg daily and titrated as clinically indicated).

	Visit	Fasting Serum glucose
0-40 mg Cohort	Week 4	>250mg/dL
	Week 6	>240mg/dL
	Week 8	>220mg/dL
	Week 10	>200mg/dL
0, 100 mg Cohort	Week 4	>250mg/dL
	Week 6	>240mg/dL

Source: Study Report, Study CV181011, Table 5.1A

Primary efficacy variable: Log linear trend in HbA1c reduction across the treatment groups at week 12.

Secondary efficacy variables: This study had numerous secondary endpoints, including:

1. Change from baseline in HbA1c at Weeks 6 and 12
2. Change from baseline in fasting serum glucose at Weeks 6 and 12

	FDA Broad SMQ MACE	FDA Custom MACE	Prior BMS MACE
Myocardial Infarction Terms			
Acute coronary syndrome	X		X
Acute myocardial infarction	X	X	X
Agonal rhythm			X
Blood creatine phosphokinase abnormal	X		
Blood creatine phosphokinase increased	X		
Blood creatine phosphokinase MB abnormal	X		
Blood creatine phosphokinase MB increased	X		
Cardiac arrest			X
Cardiac death			X
Cardiac enzymes increased	X		
Cardio-respiratory arrest			X
Coronary artery embolism	X		X
Coronary artery occlusion	X		
Coronary artery reocclusion	X		
Coronary artery thrombosis	X	X	X
Coronary bypass thrombosis	X		X
Electrocardiogram Q wave abnormal	X		

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Table 9.2. Listing of preferred terms queried for MACE analyses

	FDA Broad SMQ MACE	FDA Custom MACE	Prior BMS MACE
Electrocardiogram ST segment abnormal	X		
Electrocardiogram ST segment elevation	X		
Electrocardiogram ST-T segment elevation	X		
Electromechanical dissociation			X
Infarction	X		
Myocardial infarction	X	X	X
Myocardial reperfusion injury	X		X
Papillary muscle infarction	X	X	X
Postinfarction angina	X		
Postprocedural myocardial infarction	X	X	X
Scan myocardial perfusion abnormal	X		
Silent myocardial infarction	X	X	
Sudden cardiac death			X
Sudden death			X
Troponin I increased	X		
Troponin increased	X		
Troponin T increased	X		
Vascular graft occlusion	X		
Ventricular asystole			X
Stroke Terms			
Agnosia	X		
Amaurosis fugax	X		
Angiogram cerebral abnormal	X		
Aphasia	X		
Balint's syndrome	X		
Basal ganglia hemorrhage	X		X
Basilar artery occlusion	X		
Basilar artery stenosis	X		
Basilar artery thrombosis	X	X	X
Brain stem hemorrhage	X		X
Brain stem infarction	X	X	X
Brain stem ischemia	X		
Brain stem stroke	X	X	
Brain stem thrombosis	X	X	X
Capsular warning syndrome	X		
Carotid aneurysm rupture	X		
Carotid arterial embolus	X	X	X
Carotid arteriosclerosis	X		
Carotid artery aneurysm	X		
Carotid artery bypass	X		
Carotid artery disease	X		
Carotid artery dissection	X		
Carotid artery insufficiency	X		
Carotid artery occlusion	X		
Carotid artery stenosis	X		
Carotid artery stent insertion	X		
Carotid artery thrombosis	X	X	X
Carotid endarterectomy	X		

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Table 9.2. Listing of preferred terms queried for MACE analyses			
	FDA Broad SMQ MACE	FDA Custom MACE	Prior BMS MACE
Central pain syndrome	X		
Cerebellar artery occlusion	X		
Cerebellar artery thrombosis	X		X
Cerebellar embolism	X		X
Cerebellar hemorrhage	X		X
Cerebellar hematoma	X		
Cerebellar infarction	X	X	X
Cerebellar ischemia	X		
Cerebral aneurysm ruptured syphilitic	X		
Cerebral arteriosclerosis	X		
Cerebral arteriovenous malformation hemorrhagic	X		
Cerebral artery embolism	X	X	X
Cerebral artery occlusion	X		
Cerebral artery stenosis	X		
Cerebral artery thrombosis	X	X	X
Cerebral hematoma	X		
Cerebral hemorrhage	X		X
Cerebral hemorrhage fetal	X		
Cerebral hemorrhage neonatal	X		
Cerebral infarction	X	X	X
Cerebral infarction fetal	X		
Cerebral ischemia	X		
Cerebral thrombosis	X	X	X
Cerebral vasoconstriction	X		
Cerebral venous thrombosis	X		
Cerebrovascular accident	X	X	X
Cerebrovascular accident prophylaxis	X		
Cerebrovascular disorder	X		
Cerebrovascular insufficiency	X		
Cerebrovascular spasm	X		
Cerebrovascular stenosis	X		
Charcot-Bouchard microaneurysms	X		
Diplegia	X		
Dysarthria	X		
Embolic cerebral infarction	X	X	X
Embolic stroke	X	X	X
Hematomyelia	X		
Hemiparesis	X		
Hemiplegia	X		
Hemorrhage intracranial	X		
Hemorrhagic cerebral infarction	X	X	X
Hemorrhagic stroke	X	X	X
Hemorrhagic transformation stroke	X	X	X
Intracerebral aneurysm operation	X		
Intracerebral hematoma evacuation	X		
Intracranial aneurysm	X		
Intracranial hematoma	X		
Intraventricular hemorrhage	X		X

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Table 9.2. Listing of preferred terms queried for MACE analyses

	FDA Broad SMQ MACE	FDA Custom MACE	Prior BMS MACE
Intraventricular hemorrhage neonatal	X		
Ischemic cerebral infarction	X	X	X
Ischemic stroke	X	X	X
Lacunar infarction	X	X	X
Lateral medullary syndrome	X	X	X
Meningorrhagia	X		
Millard-Gubler syndrome	X		
Monoparesis	X		
Monoplegia	X		
Moyamoya disease	X	X	
Paralysis	X		
Paralysis flaccid	X		
Paraparesis	X		
Paraplegia	X		
Paresis	X		
Postprocedural stroke	X	X	X
Precerebral artery occlusion	X		X
Putamen hemorrhage	X		X
Quadriparesis	X		
Quadriplegia	X		
Red blood cells CSF positive	X		
Reversible ischemic neurologic deficit	X		
Ruptured cerebral aneurysm	X		
Spastic paralysis	X		
Spastic paraplegia	X		
Spinal artery embolism	X		
Spinal cord hemorrhage	X		
Spinal hematoma	X		
Stroke in evolution	X	X	X
Subarachnoid hemorrhage	X		
Subdural hemorrhage	X		
Subdural hemorrhage neonatal	X		
Thalamic infarction	X	X	X
Thalamus hemorrhage	X		X
Thromboembolic stroke			X
Thrombotic cerebral infarction	X	X	X
Thrombotic stroke	X	X	X
Transient ischemic attack	X		
Vascular encephalopathy	X		
Vertebral artery occlusion	X		
Vertebral artery stenosis	X		
Vertebral artery thrombosis	X		X
Vertebrobasilar insufficiency	X		
Visual midline shift syndrome	X		
Wallenberg syndrome	X	X	X

9.2 Labeling Recommendations

A summary and line-by-line labeling review will be added as an addendum to this Review.

9.3 Advisory Committee Meeting

The following are the points for discussion and voting questions (both bolded) which were posed to the committee. Each question is followed by a brief overview of the panel's discussion and conclusions (italicized), as summarized by the committee Chairman. Official transcripts of the meeting are available at:

<http://www.fda.gov/ohrms/dockets/ac/cder09.html#EndocrinologicMetabolic>

Points for Discussion

1. **Please discuss whether the low cardiovascular safety event rate in the saxagliptin clinical trials permits a reliable assessment of cardiovascular safety.**

The committee felt that the clinical trials only examined patients with low CV risk for a relatively short duration of time which may not be applicable to longer studies with higher risk patients. Cardiac events were not assessed prospectively and were assessed using a categorization system. However, given these caveats, the committee agreed that there was acceptable CV safety risk as assessed by post-hoc adjudication. There was a question whether this low risk would apply to larger studies with patients of higher risk and the majority of the committee agreed it may apply. The risk from a statistical standpoint of missing significant CV events is low.

2. **Under the recent Guidance regarding evaluation of cardiovascular risk for diabetes therapies, ongoing and future diabetes drug development programs will be required to conduct preplanned adjudication of cardiovascular events, and to collect all data necessary for such adjudication. However, the saxagliptin development program was already complete by the time the guidance was issued. For saxagliptin, neither preplanned nor post-hoc adjudication occurred and full data were not available to permit meaningful assessment of many cardiovascular events. The "SMQ MACE" and "Custom MACE" endpoints were defined post-hoc for a drug development program that was not designed to prospectively measure cardiovascular risk associated with saxagliptin. Please discuss whether these endpoints and the post-hoc analyses permit a reliable assessment of cardiovascular safety. Please offer suggestions for improvement to the endpoints and analyses that may be applied to other diabetes programs that have already completed or had ongoing Phase 3 programs at the time the Final Guidance was issued.**

The committee agreed that assessment of cardiovascular events using post-hoc adjudication is inherently fraught with difficulties. The committee understood that the sponsor was working in

the interim between the former and present regulations; both the FDA and sponsor are working together to formulate an integrated system to help determine if there is an increased CV risk.

3. **The saxagliptin clinical trials included a 24-week, short-term, double-blind period followed by a long-term, double-blind period. Patients entered the long-term period if they completed the short-term period or if they were discontinued from the short-term period due to inadequate glycemic control. Patients who entered the long-term period because of inadequate glycemic control during the short-term period were administered open-label rescue medication. Please discuss whether this trial design affects interpretation of cardiovascular results for the short-term period and long-term periods.**

There was general consensus that, given the issues discussed, this approach seems appropriate and does provide to the panel members significant information regarding the risk of CV and other events in this group. The committee further discussed whether there is a relationship between rescue and higher rate of events and there did not seem so to the committee. It appeared that the longer duration of time patients were studied, the greater the chance of risk over time.

4. **Multiple statistical methods were used to analyze cardiovascular outcomes. Please discuss the adequacy of these methods for measuring sensitivity of the results to analytical method.**

The committee agreed that the methods for measuring are relatively sensitive. There seems to be a low likelihood that these statistical methods would result in misleading result and that over the longer term, there would be higher rate of adverse events.

Voting Questions

1. **Based on the preceding discussion, has the applicant provided appropriate evidence of cardiovascular safety to conclude that saxagliptin rules out unacceptable excess cardiovascular risk relative to comparators including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?**
 - a. **If “No” to Question 1, what additional cardiovascular data are needed to address any limitations resulting from the completed clinical development program and to support approvability, including satisfying the 1.8 non-inferiority margin?**

(VOTE requested) YES: 10

NO: 2

ABSTAIN: 0

The two committee members who voted No felt that there should be some limit on how the product to be labeled and it may need to be restricted to a certain population given the number of events are too low to provide adequate data for assessment.

2. For the Custom MACE endpoint, the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios was less than 1.3. These data involved a total of 11 cardiovascular events in the 24-week, double-blind, short-term study periods and a total of 40 cardiovascular events in the combined short-term and long-term study period of median 62-week exposure. Are these data adequate to conclude that post-marketing cardiovascular safety trials(s) are unnecessary?

- a. If "No" to Question 2, please comment on the limitations of the completed NDA program that will require an additional post-marketing trial(s).

(VOTE requested) YES: 0 NO: 12 ABSTAIN: 0

The committee would like to see that detailed, focused post-marketing studies be conducted. The drug needs to be studied in higher risk population. The committee had to balance a fine line between preserving patient safety while moving drugs in this transition period into the market.

ⁱ Knop F et al. Reduced Incretin Effect in Type 2 Diabetes: Cause or Consequence of the Diabetic State? Diabetes 2007; 1951-1959.

ⁱⁱ Campbell KR. Rationale for Dipeptidyl Peptidase 4 Inhibitors: A New Class of Oral Agents for The Treatment of Type 2 Diabetes Mellitus. Annals of Pharmacotherapy 2007, Volume 41.

ⁱⁱⁱ Wang X et al. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Ferti Sterol 79 (3): 577-84.

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/s/

Naomi Lowy
7/6/2009 09:18:44 AM
MEDICAL OFFICER

Hylton Joffe
7/6/2009 07:35:07 PM
MEDICAL OFFICER
Please see CDTL memorandum.