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

Table 7.70. ST + LT Treatment Period

SOC (%)	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Comparator
PT (%)	N=937	N=1269	N=1000	N=3356	N=1251
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

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

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