

Supplemental Appendices

Appendix A. Clinical Events List. Events from this list were collected systematically at each visit and have been tabulated for analysis. These prespecified events were not reported as adverse events.

I. Primary or Secondary Study Endpoints

- A. **Obvious study endpoints** (These events will prompt the investigator to complete an endpoint package which will then be adjudicated according to the Clinical Events Classification [CEC] charter)
- Death
 - Cardiovascular (CV) death (i.e., fatal myocardial infarction [MI]/cerebrovascular accident [CVA]/ congestive heart failure [CHF]/arrhythmia, cardiac arrest, death following CV intervention)
 - Non-CV death
 - Nonfatal MI
 - Unstable angina
 - Nonfatal CVA
 - CHF requiring hospitalization
- B. **Cardiovascular Events of Interest** (some of these events will result in prompts to answer additional questions in the eCRF – these questions will be designed to determine whether or not a primary or secondary outcome of interest has occurred)
- Atrial fibrillation/atrial flutter
 - Ventricular fibrillation/tachycardia requiring intervention
 - Deep vein thrombosis (DVT)
 - Pulmonary embolism
 - Percutaneous Coronary Intervention (PCI)
 - Coronary artery bypass graft (CABG)
 - Coronary catheterization
 - Stress test
 - Abdominal aortic aneurysm/repair
 - Carotid endarterectomy/carotid angioplasty and/or stenting
 - Any hospitalization due to cardiovascular events (i.e., whether or not the hospitalization was for an obvious study endpoint)
 - Shock/hypotension
 - Accelerated or malignant hypertension/hypertensive urgency
 - Transient ischemic attack (TIA)
 - Syncope
 - Renal artery angioplasty and/or stenting
 - Other arterial angioplasty and/or stenting

II. Expected Events and Diabetic Complications (subcategories indicate potential additional information to be captured, usually as an indication of severity)

- A. Peripheral vascular disease (PVD)
- Limb PCI
 - Vascular surgery
 - Amputation

- Surgical debridement of ulcer
- B. Gangrene
- C. Hypoglycemia/hyperglycemia /diabetic ketoacidosis /hyperosmolar hyperglycemic nonketotic coma
- D. Diabetic eye disease
- Photocoagulation or other laser therapy
 - Cataract extraction
 - Blindness
 - Enucleation
 - Steroid/bevacizumab injection
 - Scleral buckling or other retinal fixation procedure
- E. Diabetic neuropathy (including distal sensorimotor, focal/multifocal, or autonomic)
- Foot ulcer
- F. Diabetic nephropathy
- Microalbuminuria
 - Proteinuria
- G. Renal failure/peritoneal or hemodialysis/renal transplant (including creation of fistula or other vascular access for hemodialysis)
- H. Any hospitalization due to complications of DM
- I. Infections
- Osteomyelitis
 - IV antibiotic therapy vs. debridement
 - Cellulitis
 - Oral vs. IV antibiotic therapy
 - Mucormycosis
 - Pneumonia
 - Community acquired vs. hospital acquired
 - Oral vs. IV antibiotic therapy
 - Bacteremia
 - Sepsis
 - Infected joints
 - Prosthetic joint
 - Complicated or serious urinary tract infection (UTI)/pyelonephritis
 - Requiring hospitalization
 - Malignant external otitis
- J. Gastrointestinal (GI) conditions
- Abdominal pain
 - Nausea/vomiting
 - Diarrhea
 - Fatty liver disease/Nonalcoholic steatohepatitis (NASH)
 - Pancreatitis
 - Cholecystitis/cholelithiasis
- K. Metabolic conditions associated with diabetes
- Hyperlipidemia/dyslipidemia
 - Hypertension

- Gout

III. Terms Listed in the Sitagliptin Product Circular

A. Allergic reactions

- Hypersensitivity reactions
- Anaphylaxis
- Angioedema
- Urticaria
- Exfoliative skin reaction
- Stevens-Johnson syndrome
- Rash

B. For all other terms please refer to the current local product circular

Appendix B

Table S1. Characteristics of patient follow-up

	All participants		≥75 years old	
	≥ 75 years old (n=2004)	<75 years old (n=12,347)	Sitagliptin (n=970)	Placebo (n=1034)
Median (IQR) duration of follow-up, years	2.9 (2.2, 3.6)	3.0 (2.3, 3.8)	2.8 (2.2, 3.6)	2.9 (2.2, 3.6)
Completed study, n (%)	1,856 (92.6)	11,717 (94.9)	908 (93.6)	948 (91.7)
Lost to follow-up, n (%)	21 (1.0)	111 (0.9)	8 (0.8)	13 (1.3)
Withdrawn consent, n (%)	127 (6.3)	519 (4.2)	54 (5.6)	73 (7.1)
Median (IQR) study drug exposure, years	2.4 (1.7, 3.2)	2.7 (2.0, 3.5)	2.3 (1.7, 3.2)	2.4 (1.7, 3.3)

Table S2. Baseline characteristics for the intention to treat population

Characteristic	All participants		≥75 years old	
	≥75 years old (n=2004)	<75 years old (n=12,347)	Sitagliptin (n=970)	Placebo (n=1034)
Male gender	1356 (67.7%)	8847 (71.7%)	682 (70.3%)	674 (65.2%)
Age, years	78.3 ± 3.1	63.4 ± 6.4	78.3 ± 3.0	78.4 ± 3.2
Race*				
White	1530 (76.3%)	8107 (65.7%)	755 (78%)	775 (75%)
Black	37 (1.8%)	410 (3.3%)	12 (1%)	25 (2%)
Asian	270 (13.5%)	2995 (24.3%)	131 (14%)	139 (13%)
Other	167 (8.3%)	835 (6.8%)	72 (7%)	95 (9%)
BMI, kg/m ² *	28.9 ± 4.8	30.3 ± 5.7	29.0 ± 4.9	28.9 ± 4.8
SBP, mmHg*	137 ± 18	134 ± 17	137 ± 18	137 ± 18
DBP, mmHg*	74 ± 11	78 ± 10	74 ± 11	74 ± 11
HbA1c, %*	7.18 ± 0.46	7.24 ± 0.48	7.19 ± 0.46	7.17 ± 0.46
HbA1c, mmol/mol*	55.0 ± 5.1	55.7 ± 5.2	55.1 ± 5.1	54.8 ± 5.0
eGFR, mL/min/1.73 m ² *				
≥90	205/1983 (10.3%)	3026/12,226 (24.8%)	95/960 (9.9%)	110/1023 (10.8%)
60-89	963/1983 (48.6%)	6761/12,226 (55.3%)	474/960 (49.4%)	489/1023 (47.8%)
30-59	814/1983 (41.0%)	2437/12,226 (19.9%)	390/960 (40.6%)	424/1023 (41.4%)
<30	1/1983 (0.1%)	2/12,226 (<0.1%)	1/960 (<1.0%)	0
Total cholesterol, mmol/L*	4.1 ± 1.0	4.3 ± 1.2	4.1 ± 1.0	4.1 ± 1.1
LDL, mmol/L*	2.3 ± 2.6	2.4 ± 1.2	2.4 ± 3.7	2.2 ± 0.9
HDL, mmol/L*	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
Triglycerides, mmol/L*	1.6 ± 0.9	1.9 ± 1.1	1.7 ± 1.0	1.6 ± 0.8
Median duration of diabetes, years (IQR)*	12 (7, 21)	9 (5, 15)	13 (7, 21)	12 (7, 21)
Prior cardiovascular disease				
≥50% stenosis in a coronary artery	1036 (51.7%)	6470 (52.4%)	493 (50.8%)	543 (52.5%)
Myocardial infarction	823 (41.1%)	5275 (42.7%)	402 (41.4%)	421 (40.7%)
Prior PCI	743/1969 (37.7%)	4852/12,184 (39.8%)	355/956 (37.1%)	388/1013 (38.3%)
CABG*	579 (28.9%)	3012 (24.4%)	298 (30.7%)	281 (27.2%)
Stroke	376 (18.8%)	2092 (16.9%)	172 (17.7%)	204 (19.7%)
TIA*	119 (5.9%)	430 (3.5%)	64 (6.6%)	55 (5.3%)
≥50% stenosis in a carotid artery*	180 (9.0%)	665 (5.4%)	84 (8.7%)	96 (9.3%)
Peripheral arterial disease	352 (17.6%)	2040 (16.5%)	178 (18.4%)	174 (16.8%)

Characteristic	All participants		≥75 years old	
	≥75 years old (n=2004)	<75 years old (n=12,347)	Sitagliptin (n=970)	Placebo (n=1034)
Prior congestive heart failure*	422 (21.1%)	1970 (16.0%)	190 (19.6%)	232 (22.4%)
Medication use				
<i>Antidiabetic</i>				
Metformin*	1449 (72.3%)	10,265 (83.1%)	711 (73.3%)	738 (71.4%)
Sulfonylurea	946 (47.2%)	5,569 (45.1%)	442 (45.6%)	504 (48.7%)
Thiazolidinedione	57 (2.8%)	319 (2.6%)	24 (2.5%)	33 (3.2%)
Insulin	501 (25.0%)	2844 (23.0%)	255/717 (35.6%)	246/728 (33.8%)
Median daily dose, units (IQR)	51.0 (34.0, 80.0)	44.0 (28.0, 67.5)	44.0 (28.0, 72.0)	42.0 (28.5, 64.0)
Monotherapy*	1066 (53.2%)	5755 (46.6%)	514 (53.0%)	552 (53.4%)
Dual combination therapy*	913 (45.6%)	6477 (52.5%)	446 (46.0%)	467 (45.2%)
<i>Antihypertensive</i>				
Beta blocker	1207 (60.2%)	7865 (63.7%)	585 (60.3%)	622 (60.2%)
ACE Inhibitor	1018 (50.8%)	6634 (53.7%)	506 (52.2%)	512 (49.5%)
Angiotensin receptor blocker	615 (30.7%)	3479 (28.2%)	293 (30.2%)	322 (31.1%)
Calcium channel blocker*	818 (40.8%)	4036 (32.7%)	395 (40.7%)	423 (40.9%)
Diuretic*	967 (48.3%)	4912 (39.8%)	453 (46.7%)	514 (49.7%)
<i>Antiplatelet</i>				
Aspirin*	1473 (73.5%)	9829 (79.6%)	702 (72.4%)	771 (74.6%)
Clopidogrel/Ticlopidine	383 (19.1%)	2745 (22.2%)	195 (20.1%)	188 (18.2%)
Vitamin K antagonist*	255 (12.7%)	717 (5.8%)	134 (13.8%)	121 (11.7%)
Any antiplatelet*	1591 (79.4%)	10,443 (84.6%)	771 (79.5%)	820 (79.3%)
<i>Lipid Lowering</i>				
Statin	1582 (78.9%)	9998 (81.0%)	761 (78.5%)	821 (79.4%)
Fibrate	99 (4.9%)	840 (6.8%)	54 (5.6%)	45 (4.4%)
Niacin	50 (2.5%)	237 (1.9%)	27 (2.8%)	23 (2.2%)
Ezetimibe	94 (4.7%)	667 (5.4%)	45 (4.6%)	49 (4.7%)
Any lipid lowering	1641 (81.9%)	10,340 (83.7%)	797 (82.2%)	844 (81.6%)

Data are n (%) or mean ± SD, except where indicated. Denominators are indicated where they differ from that provided in the column header. Characteristics with p-values <0.0001 comparing older to younger cohorts are indicated by *. P values comparing sitagliptin and placebo groups were not calculated.

Table S3. Treatment-emergent serious adverse events according to system organ class (SOC) in the older and younger cohorts

System Organ Class Preferred Term Subjects with one or more:	Age ≥ 75 years old (N=1979)	Age < 75 years old (N=12,246)	Difference in proportion with an event (95% CI)
Neoplasms benign, malignant and unspecified (inclu. cysts and polyps)	174 (8.8%)	527 (4.3%)	4.49 (3.26, 5.86)
Basal cell carcinoma	35 (1.8%)	61 (0.5%)	1.27 (0.76, 1.96)
Squamous cell carcinoma	22 (1.1%)	42 (0.3%)	0.77 (0.37, 1.34)
Squamous cell carcinoma of skin	17 (0.9%)	15 (0.1%)	0.74 (0.41, 1.25)
Colon cancer	7 (0.4%)	17 (0.1%)	0.21 (0.02, 0.59)
Malignant melanoma	5 (0.3%)	11 (0.1%)	0.16 (0.00, 0.50)
Lung adenocarcinoma	5 (0.3%)	5 (0.0%)	0.21 (0.06, 0.55)
Plasma cell myeloma	3 (0.2%)	4 (0.0%)	0.12 (0.01, 0.41)
Injury, poisoning and procedural complications	63 (3.2%)	212 (1.7%)	1.45 (0.72, 2.35)
Fall	7 (0.4%)	11 (0.1%)	0.26 (0.07, 0.64)
Femur fracture	7 (0.4%)	10 (0.1%)	0.27 (0.08, 0.65)
Hip fracture	4 (0.2%)	7 (0.1%)	0.14 (0.01, 0.46)
Spinal compression fracture	4 (0.2%)	5 (0.0%)	0.16 (0.03, 0.48)
Head injury	3 (0.2%)	4 (0.0%)	0.12 (0.01, 0.41)
Gastrointestinal disorders	46 (2.3%)	183 (1.5%)	0.83 (0.21, 1.62)
Gastroesophageal reflux disease	4 (0.2%)	5 (0.0%)	0.16 (0.03, 0.48)
Musculoskeletal and connective tissue disorders	29 (1.5%)	179 (1.5%)	0.00 (-0.50, 0.66)
Lumbar spinal stenosis	6 (0.3%)	12 (0.1%)	0.21 (0.03, 0.56)
Respiratory, thoracic and mediastinal disorders	27 (1.4%)	116 (0.9%)	0.42 (-0.05, 1.05)

System Organ Class Preferred Term Subjects with one or more:	Age ≥ 75 years old (N=1979)	Age < 75 years old (N=12,246)	Difference in proportion with an event (95% CI)
Pneumothorax	3 (0.2%)	4 (0.0%)	0.12 (0.01, 0.41)
Renal and urinary disorders	15 (0.8%)	68 (0.6%)	0.20 (-0.13, 0.70)
Urinary retention	5 (0.3%)	5 (0.0%)	0.21 (0.06, 0.55)
Metabolism and nutrition disorders	14 (0.7%)	51 (0.4%)	0.29 (-0.02, 0.78)
Hyponatraemia	8 (0.4%)	21 (0.2%)	0.23 (0.01, 0.63)
Dehydration	5 (0.3%)	8 (0.1%)	0.19 (0.03, 0.53)

Analysis cohort is all patients as treated. This table includes 1) SOC's exceeding 1% or where the 95% CI excludes 0; 2) within the SOC's that exceed 1%, any preferred term that exceeds 1%; and 3) any individual preferred term where the 95% CI excludes 0.