SUPPLEMENTARY DATA

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Clinical Event Definitions

Excerpt from Clinical Events Classification Committee Charter, version 6.0

6.0 Endpoint Definitions

6.1 Stroke

Stroke is defined as the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown. Confirmed hemorrhagic strokes classified as subdural hematoma will be excluded from any analyses of adjudicated stroke events.

A. For the diagnosis of stroke, the following 4 criteria should be fulfilled:

1. Rapid onset* of a focal/global neurological deficit with at least one of the following:

- Change in level of consciousness
- Hemiplegia
- Hemiparesis
- Numbness or sensory loss affecting one side of the body
- Dysphasia/Aphasia
- Hemianopsia (loss of half of the field of vision of one or both eyes)
- Amaurosis fugax (transient complete/partial loss of vision of one eye)
- Other new neurological sign(s)/symptom(s) consistent with stroke

*If the mode of onset is uncertain, a diagnosis of stroke may be appropriate provided that there is no plausible non-stroke cause for the clinical presentation

2. Duration of a focal/global neurological deficit ≥ 24 hours

OR < 24 hours if

i. This is because of at least one of the following therapeutic interventions:

a. Pharmacologic (i.e., thrombolytic drug administration)

b. Non-pharmacologic (i.e.,neurointerventional procedure (e.g. intracranial angioplasty))

or

ii. Available brain imaging clearly documents a new hemorrhage or infarct

or

iii. The neurological deficit results in death

1. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, other metabolic abnormality, peripheral lesion, or drug side effect)

2. Confirmation of the diagnosis by at least one of the following:

a. Neurology or neurosurgical specialist

b. Brain imaging procedure (at least one of the following):

i. CT scan

ii. MRI scan

iii. Cerebral vessel angiography

c. Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

d. Other compelling evidence of stroke

B. If the acute focal signs represent a worsening of a previous deficit, these signs must have either

1. Persisted for more than one week, or
2. Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

C. Strokes may be sub-classified as follows:

1. Ischemic (Non-hemorrhagic): a stroke caused by an arterial obstruction due to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. Ischemic strokes which cannot clearly be attributed to either a thrombotic or embolic etiology should be designated as Uncertain.

2. Hemorrhagic: a stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma,* and primary subarachnoid hemorrhage.

***All subdural hematomas that develop during the clinical trial should be recorded and classified as either traumatic versus non-traumatic.**

3. Unknown: the stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

6.2 Myocardial Infarction

A. Criteria for Acute Myocardial Infarction

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the four following criteria meets the diagnosis for acute myocardial infarction.

1. Spontaneous MI

- Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL)* together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]**
  - Development of pathological Q waves ***
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the

99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK may be used in the absence of CK-MB.

**ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):

- ST elevation

New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

- ST depression and T-wave changes

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

***Definition of a pathological Q-wave

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)[a]

[a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

2. Percutaneous Coronary Intervention-Related Myocardial Infarction

For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL* within 48 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL* (Troponin or CK-MB > 3 x 99th percentile URL*) are consistent with PCI-related myocardial infarction. MB is the preferred biomarker.

If the cardiac biomarker is elevated prior to PCI, a ≥ 50% increase of the value in the second cardiac biomarker sample within 48 hours of the PCI (and Troponin or CK-MB > 3x 99th percentile URL*) and documentation that cardiac biomarker values were decreasing (two samples at least 3 hours apart) prior to the suspected recurrent MI is also consistent with PCI-related myocardial infarction.

Symptoms of cardiac ischemia are not required.

3. Coronary Artery Bypass Grafting-Related Myocardial Infarction

For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers greater than 5 x 99th percentile URL (Troponin or CK-MB > 5 x 99th percentile URL) plus

- Either new pathological Q waves in at least 2 contiguous leads that persist through 30 days or new persistent non-rate related LBBB

OR

- Angiographically documented new graft or native coronary artery occlusion or other complication in the operating room resulting in loss of myocardium

OR

- Imaging evidence of new loss of viable myocardium

is consistent with CABG-related myocardial infarction. MB is the preferred biomarker.

If the cardiac biomarker is elevated prior to CABG, a ≥ 50% increase of the value in the second cardiac biomarker sample within 72 hours of CABG (and Troponin or CK-MB > 5 x 99th percentile URL) and documentation that cardiac biomarker values were decreasing (two samples at least 3 hours apart) prior to the suspected recurrent MI plus any of the three bullets above is consistent with a peri-procedural myocardial infarction after CABG.

Symptoms of cardiac ischemia are not required.

4. Pathological findings of an acute myocardial infarction

B. Criteria for Prior Myocardial Infarction

No evidence of acute myocardial infarction

AND any one of the following criteria:

- Appearance of new pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a healed or healing myocardial infarction

ECG Changes associated with prior myocardial infarction:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)[a]
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

[a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

C. Criteria for Reinfarction

In patients where recurrent myocardial infarction is suspected from clinical signs or symptoms following the initial infarction, recurrent infarction should be diagnosed if there is a ≥ 20% increase of the value between a measurement (cardiac biomarker) made at the time of the initial presentation and a further sample taken 3-6 hours later. This value should also exceed the 99th percentile URL.*

If cardiac biomarkers are elevated prior to the suspected new MI, there must be decreasing cardiac biomarker values on two samples at least 3 hours apart prior to the suspected new MI in combination with other criteria for re-infarction (ECG, imaging).

If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.

Clinical Classification of Different Types of Myocardial Infarction

- **Type 1**

Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

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- **Type 2**

Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

- **Type 3**

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

- **Type 4a**

Myocardial infarction associated with PCI

- **Type 4b**

Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

- **Type 5**

Myocardial infarction associated with CABG

For each myocardial infarction (MI) identified by the CEC, the type of MI may also be described as:

- ST-Elevation MI (STEMI) Also categorize as:
  - Q-wave
  - Non-Q-wave
  - Unknown (no ECG or ECG not interpretable)
- Non-ST-Elevation MI (NSTEMI) Also categorize as:
  - Q-wave
  - Non-Q-wave
  - Unknown (no ECG or ECG not interpretable)
- Unknown (no ECG or ECG not interpretable)

6.3 Unstable Angina Requiring Hospitalization

Unstable angina requiring hospitalization is defined as:

1. Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (does not include chest pain observation units) within 24 hours of the most recent symptoms

AND

3. At least one of the following:

- New or worsening ST or T wave changes on resting ECG

<u>ST elevation</u>

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New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

ST depression and T-wave changes

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

- Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs
- Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs
- Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criteria would be fulfilled if the admission for myocardial ischemia led to transfer to another institution for the revascularization procedure without interceding home discharge

AND

4. No evidence of acute myocardial infarction

6.4 Death

All deaths will be considered cardiovascular unless an unequivocal non-cardiovascular cause of death can be established.

A. Cardiovascular death includes:

Sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Sudden Cardiac Death:** refers to death that occurs unexpectedly and includes the following deaths:
   - Witnessed and instantaneous without new or worsening symptoms
   - Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
   - Witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
   - Subjects unsuccessfully resuscitated from cardiac arrest
   - Subjects successfully resuscitated from cardiac arrest but who die without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)
   - Unwitnessed death or other causes of death (information regarding the patient's clinical status preceding death should be provided, if available)
2. **Death due to Acute Myocardial Infarction:** refers to an acute myocardial infarction (MI) leading inexorably to death, generally within 30 days. Death due to known sequelae of MI including mechanical complications, arrhythmia, and/or pump failure, as well as death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should be considered death due to acute MI. The acute myocardial infarction should be verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy

findings showing recent myocardial infarction or recent coronary thrombus, and there should be no conclusive evidence of another cause of death.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be classified as death due to other cardiovascular cause.

3. **Death due to Heart Failure or Cardiogenic Shock:** refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure (See CHF definition) without evidence of another cause of death.

Death due to heart failure or cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
b. Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
c. Confinement to bed predominantly due to heart failure symptoms
d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
e. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin *or*
- Oliguria (urine output < 30 mL/hour) *or*
- Altered sensorium *or*
- Cardiac index < 2.2 L/min/m^2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

4. **Death due to Cerebrovascular Event:** (intracranial hemorrhage or non-hemorrhagic stroke): refers to a cerebrovascular event or a complication of a cerebrovascular event that leads inexorably to death, generally within 30 days after the suspected event. These deaths may be based on clinical signs and symptoms as well as neuroimaging and/or autopsy. There should be no conclusive evidence of another cause of death.
5. **Death due to Other Cardiovascular Causes:** refers to death due to a cardiovascular cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of

cardiac surgery or non-surgical revascularization, even if "non-cardiovascular" in nature, should be classified as cardiovascular deaths.

B. Non-cardiovascular death:

Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death. Categories include:

- Pulmonary causes
- Renal causes
- Gastrointestinal causes
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Malignancy (i.e., new malignancy, worsening of prior malignancy)
- Accidental/Trauma
- Hemorrhage, not intracranial
- Suicide
- Non-cardiovascular system organ failure (e.g., hepatic failure)
- Non-cardiovascular surgery
- Other non-cardiovascular

C. Undetermined Cause of Death:

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause.

6.5 Congestive Heart Failure Requiring Hospitalization

Congestive heart failure requiring hospitalization is defined as an event that meets **ALL** of the following criteria (1-5):

1. The patient is admitted to the hospital with a primary diagnosis of heart failure (HF)
2. The patient's length of stay in the hospital extends for at least 24 hours or a change in calendar date if the hospital admission and discharge times are unavailable.
3. The patient exhibits documented new or worsening symptoms due to HF on presentation, including **at least ONE** of the following:

a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough in supine position, tachypnea)

b. Decreased exercise tolerance

c. Fatigue

d. Worsened end-organ perfusion (worsening cerebral, renal, liver, abdominal or gastrointestinal, peripheral circulatory function as manifested by symptoms such as dizziness, lightheadedness, syncope, confusion, altered mental status, restlessness, decline in cognitive state, nausea, vomiting, abdominal pain, abdominal fullness, abdominal discomfort or abdominal tenderness, cold clammy extremities, discoloration of extremities or lips, jaundice, pain in extremities, reduced urine output, darkening of urine color, chest pain, palpitations)

e. Volume overload (swelling of lower extremities, swelling or indentation of pressure marks in areas of fluid accumulation such as legs, ankles, lower back; increase in abdominal girth, right-sided

abdominal fullness, discomfort or tenderness, increase in body weight, oozing and development of skin breakdown in lower extremities)

4. The patient exhibits objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR ONE** physical examination finding and **at least ONE** laboratory criterion.

Physical examination findings considered to be due to HF, include new or worsened:

a. Peripheral edema (swelling or pitting indentation when pressed in feet, ankles, legs, thighs, upper extremities, scrotal, pre-sacral area, or abdominal wall)
b. Increasing abdominal distention or ascites (in the absence of primary hepatic disease.
c. Pulmonary rales/crackles/crepitations
d. Increased jugular venous pressure and/or hepatojugular reflux
e. S3 gallop
f. Clinically significant or rapid weight gain thought to be related to fluid retention (usually more than 3-4 lbs in 3-4 days)

Laboratory Evidence of HF: Laboratory evidence of new or worsening HF should be obtained within 24 hours of presentation. Laboratory criteria include new or worsened:

a. Increased B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) concentrations.
b. Radiological evidence of pulmonary congestion.
c. Non-invasive diagnostic evidence of HF (echocardiography, cardiac MRI, Cardiac PET scan, nuclear imaging).
d. Invasive diagnostic evidence of HF.

5. Initiation or intensification of HF treatment, including at least **ONE** of the following:

a. Augmentation in oral diuretic therapy
b. Intravenous diuretic, or intravenous vasoactive therapy
c. Mechanical or surgical intervention, including mechanical circulatory support or mechanical fluid removal.

6.6 Ventricular Tachycardia/Ventricular Fibrillation requiring Intervention

Ventricular Tachycardia/Ventricular Fibrillation requiring intervention is defined as:

Sustained Ventricular Tachycardia (VT)

Sustained Ventricular Tachycardia (VT) is defined as a wide complex tachycardia of ventricular origin:

Lasting > 30 seconds and requiring intervention such as a new medication or medication change directed to VT

OR

Requiring external cardioversion or ICD/AICD therapy (anti-tachycardic pacing or electrical cardioversion)

OR

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Resulting in significant hemodynamic compromise

OR

Requiring hospitalization

Ventricular Fibrillation (VF)

Ventricular Fibrillation (VF) is defined as irregular undulations of varying contour and amplitude on ECG with absence of distinct QRS complexes and requiring intervention such as a new medication or medication change directed to VF or associated with external cardioversion or ICD/AICD therapy (anti-tachycardic pacing or electrical cardioversion) or hemodynamic compromise.

6.7 Pancreatitis

Pancreatitis is defined as:

Symptoms of abdominal pain **OR** vomiting

AND

Objective evidence of pancreatic inflammation:

Elevated pancreatic enzymes, defined by:

- Amylase OR Lipase > 3x the upper limit normal.
- Amylase OR Lipase > 2x the upper limit normal. (In patients with chronic pancreatitis)

OR

Evidence of pancreatitis documented by imaging:

Abdominal CT, MRI or ultrasound showing focal, diffuse and inhomogeneous gland enlargement

Confirmed acute pancreatitis will be graded as *mild or severe*.

To confirm severe pancreatitis, the following criteria must be present:

1. Evidence of organ failure (at least one of the following)
    a. Shock: systolic BP < 90 mm Hg
    b. Pulmonary insufficiency: Pa02 < 60 mm Hg
    c. Renal failure: serum creatinine > 2 mg/dl after rehydration
    d. Gastrointestinal bleeding: > 500 ml/24 hours

OR

2. Local complications demonstrated on abdominal CT, MRI, or ultrasound (at least one of the following)
    a. Pancreatic necrosis (note: hemorrhagic pancreatitis is a pathologic term often used synonymously with pancreatic necrosis)
    b. Pancreatic abscess
    c. (Acute) Pancreatic pseudocyst

Confirmed cases of acute pancreatitis not meeting criteria for severe pancreatitis will be classified as mild pancreatitis.

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6.8 Neoplasms

The following definitions will be utilized by the CEC for purposes of adjudication neoplasms:

Has a malignancy occurred? The CEC will answer yes to this question if the subject has either evidence of a new malignancy or the first recurrence (during the study period) of a previous cancer.

New malignancies:

1. New primary cancer in patients with or without pre-existing cancer, or
2. New metastatic cancer in patients without previous diagnosis of cancer, or
3. New metastatic cancer of a clearly distinct histology from any pre-existing cancer

Recurrence of previous cancer:

1. Evidence of first recurrence of a pre-existing cancer during the study period (histological, imaging, or clinical)

AND

2. History of this pre-existing cancer at the time of randomization (i.e. diagnosis of original cancer predates randomization)

AND

3. No evidence to indicate based on histological type or clinical picture that this is a different cancer.

Non-malignant neoplasms which are reported should be classified as benign neoplasms.

Progression of prior malignancy - does not meet EXSCEL definition of malignancy

Date of Initial Detections: This will be the date of initial detection by a treating physician, when the patient demonstrated either clinical symptoms or diagnostic testing results (for example, imaging, laboratory) with evidence of neoplasm that allows for a probable clinical diagnosis. Whichever date can be confirmed to occur first will be used.

Date of histological diagnosis: This will be the date that the diagnosis of Neoplasm was documented by histological and/or cytological evidence.

Status of Disease:

1. No evidence of disease: A patient who after treatment has normal tumor markers and no evidence of disease on physical exam or imaging studies.
2. Active disease: A patient who has evidence of disease and has either had a new and/or change in treatment since their previous evaluation or could be eligible for a new and/or change in treatment but either refused or did not receive the therapy for another clinical reason (e.g. terminal disease for which alteration in treatment would not be expected to meaningfully prolong life expectancy).
3. Stable/Inactive disease: A patient that has evidence of disease, but is not progressing, and has had no new and/or change in treatment since their previous evaluation
4. Cannot be determined: Is used to describe cases for which there is not enough information to indicate a classification.

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Supplementary Table 1. Change in A1c from baseline to 6 months*

	Intent to Treat Population		
	Exenatide N=6116	**Placebo N=6079**	**All Subjects N=12195**
Tertiles of ΔA1c			
Tertile 1 (ΔA1c > -0.07%)	1257 (20.6%)	2814 (46.3%)	4071 (33.4%)
Tertile 2 (-0.9% < ΔA1c ≤ -0.07%)	1919 (31.4%)	1988 (32.7%)	3907 (32.0%)
Tertile 3 (ΔA1c ≤ -0.9%)	2940 (48.1%)	1277 (21.0%)	4217 (34.6%)
Drop in A1c >2%	827 (13.5%)	267 (4.4%)	1094 (9.0%)

*A1c lab value closest to 180 days after baseline was selected to calculate ΔA1c. Subjects with no follow-up A1c labs in the first year are excluded.

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Supplementary Table 2. Impact of treatment on macrovascular and renal composite outcomes according to baseline CKD stage

	CKD stage 1			CKD stage 2			CKD stage 3a			CKD stage 3b			
Outcomes	**EX N=2127**	**PL N=2141**	**HR (95% CI)**	**EX N=3642**	**PL N=3604**	**HR (95% CI)**	**EX N=1140**	**PL N=1148**	**HR (95% CI)**	**EX N=417**	**PL N=472**	**HR (95% CI)**	**Int. p-value**
MACE-3	181 (8.5%)	208 (9.7%)	0.87 (0.71, 1.06)	368 (10.1%)	412 (11.4%)	0.86 (0.75, 0.99)	181 (15.9%)	182 (15.9%)	0.97 (0.79, 1.20)	99 (23.7%)	100 (21.2%)	1.11 (0.84, 1.47)	0.366
Fatal or Non-fatal MI	97 (4.6%)	106 (5.0%)	0.92 (0.70, 1.21)	218 (6.0%)	212 (5.9%)	1.00 (0.82, 1.20)	104 (9.1%)	107 (9.3%)	0.95 (0.73, 1.25)	58 (13.9%)	65 (13.8%)	0.99 (0.69, 1.41)	0.969
Fatal or Non-fatal Stroke	42 (2.0%)	53 (2.5%)	0.79 (0.53, 1.19)	80 (2.2%)	109 (3.0%)	0.71 (0.53, 0.95)	45 (3.9%)	36 (3.1%)	1.23 (0.79, 1.90)	19 (4.6%)	20 (4.2%)	1.07 (0.57, 2.01)	0.180
Cardiovascular Death	65 (3.1%)	82 (3.8%)	0.80 (0.57, 1.10)	135 (3.7%)	173 (4.8%)	0.76 (0.61, 0.95)	84 (7.4%)	79 (6.9%)	1.05 (0.77, 1.43)	49 (11.8%)	47 (10.0%)	1.18 (0.79, 1.75)	0.155
All-Cause Death	88 (4.1%)	121 (5.7%)	0.73 (0.55, 0.96)	214 (5.9%)	261 (7.2%)	0.80 (0.67, 0.96)	126 (11.1%)	123 (10.7%)	1.01 (0.79, 1.30)	69 (16.5%)	77 (16.3%)	1.01 (0.73, 1.40)	0.206
Hospitalization for Heart Failure	30 (1.4%)	46 (2.1%)	0.65 (0.41, 1.03)	92 (2.5%)	96 (2.7%)	0.93 (0.70, 1.24)	49 (4.3%)	60 (5.2%)	0.80 (0.55, 1.16)	44 (10.6%)	28 (5.9%)	1.80 (1.12, 2.90)	0.014
Hospitalization for Acute Coronary Syndrome	118 (5.5%)	128 (6.0%)	0.92 (0.72, 1.19)	290 (8.0%)	248 (6.9%)	1.14 (0.96, 1.35)	126 (11.1%)	122 (10.6%)	1.02 (0.80, 1.31)	62 (14.9%)	69 (14.6%)	1.00 (0.71, 1.41)	0.562
Renal Composite Endpoint 1	112 (6.0%)	114 (6.1%)	0.97 (0.74, 1.25)	71 (2.2%)	92 (2.9%)	0.75 (0.55, 1.03)	41 (4.1%)	35 (3.5%)	1.12 (0.72, 1.76)	22 (6.1%)	32 (7.9%)	0.73 (0.42, 1.25)	0.386
Renal Composite Endpoint 2	144 (7.8%)	145 (7.9%)	0.97 (0.77, 1.22)	123 (4.0%)	161 (5.2%)	0.74 (0.59, 0.94)	63 (6.6%)	69 (7.3%)	0.88 (0.62, 1.23)	34 (10.2%)	32 (9.0%)	1.09 (0.67, 1.76)	0.336

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Supplementary Table 3. Impact of treatment on macrovascular outcomes according to baseline eGFR above or below 60 mL/min/m^2

	eGFR ≥60 mL/min/1.73m^2			**eGFR <60 mL/min/1.73m^2**			
Outcomes	**EX N=5769**	**PL N=5745**	**HR (95% CI)**	**EX N=1557**	**PL N=1620**	**HR (95% CI)**	**Int. p-value**
MACE-3	549 (9.5%)	620 (10.8%)	0.86 (0.77, 0.97)	280 (18.0%)	282 17.4%)	1.01 (0.86, 1.19)	0.132
Fatal or Non-fatal MI	315 (5.5%)	318 (5.5$)	0.97 (0.83, 1.14)	162 (10.4%)	172 (10.6%)	0.96 (0.77, 1.18)	0.907
Fatal or Non-fatal Stroke	122 (2.1%)	162 (2.8%)	0.74 (0.58, 0.93)	64 (4.1%)	56 (3.5%)	1.17 (0.82, 1.67)	0.035
Cardiovascular Death	200 (3.5%)	255 (8.8%)	0.77 (0.64, 0.93)	133 (8.5%)	126 (7.8%)	1.08 (0.85, 1.38)	0.031
All-Cause Death	302 (5.2%)	382 (6.6%)	0.78 (0.67, 0.91)	195 (12.5%)	200 (12.4%)	1.00 (0.82, 1.22)	0.050
Hospitalization for Heart Failure	122 (2.1%)	142 (2.5%)	0.84 (0.66, 1.07)	93 (6.0%)	88 (5.4%)	1.08 (0.81, 1.44)	0.197
Hospitalization for Acute Coronary Syndrome	408 (7.1%)	376 (6.5%)	1.07 (0.93, 1.23)	188 (12.1%)	191 (11.8%)	1.01 (0.82, 1.23)	0.620