Supplementary Material

Data S1: Endpoint Event Definitions

**Stroke/TIA**
Stroke is defined as a new, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily identifiable cause such as a tumor or seizure.

If an event matching this definition lasts less than 24 hours, it will be considered a TIA. The duration of symptoms for a TIA will be recorded as will the results of any imaging procedures. TIA events with documented cerebral infarction in the appropriate location to explain the clinical syndrome will be recorded.

All suspected strokes (including TIA) will be reviewed and adjudicated by the clinical events committee (CEC). Further, the CEC will consider all clinically relevant information and imaging studies to classify all strokes as:

- **Primary hemorrhagic**: stroke with focal collections of intraparenchymal blood. Events of subarachnoid, subdural, and epidural hemorrhage will be recorded, but these events will not be considered part of the primary efficacy endpoint.

- **Primary ischemic infarction**: stroke without focal collections of intracranial blood. The occurrence of hemorrhagic conversion of a primary ischemic infarction will be recorded, including whether it was symptomatic or asymptomatic. Stroke subtype will be assessed as cardioembolic, non-cardioembolic (e.g., atherothrombotic, lacunar, other known cause), and uncertain. Imaging is not required to adjudicate an event as a primary ischemic stroke. If the clinical presentation and neurological findings are in a vascular distribution consistent with ischemic stroke, then primary ischemic stroke can be diagnosed without imaging.

- **Uncertain**: no imaging or autopsy data available.

Subjects who die within 30 days of the onset of the stroke will be regarded as having had a fatal stroke. Subjects who have a stroke and then die more than 30 days after the onset of the stroke will be regarded as having non-stroke death.

**Myocardial Infarction**
The adjudication of myocardial infarction as a clinical endpoint will consider the occurrence relative to a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. In the absence of a PCI or CABG, myocardial infarction is defined as:

Clinical symptoms consistent with myocardial infarction and cardiac biomarker elevation (troponin I or T, creatine kinase-muscle brain subunit [CK-MB]) greater than the site’s upper limit of normal (ULN) or development of new pathological Q
waves in at least 2 contiguous leads on the electrocardiogram or autopsy confirmation.

For subjects having a PCI, a myocardial infarction will be defined as:

CK-MB (or CK in the absence of CK-MB) >3 x ULN for samples obtained within 24 hours of the procedure if the baseline values were normal or at least a 50% increase over elevated baseline values that were stable or decreasing, or development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram. Symptoms of cardiac ischemia are not required.

After CABG surgery, a myocardial infarction is defined as either:

CK-MB (or CK in the absence of CK-MB) >5 x ULN for samples obtained within 24 hours of the procedure with development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram.

OR

CK-MB (or CK in the absence of CK-MB) >10 x ULN for samples obtained within 24 hours of the procedure with or without development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram.

Death
All deaths will be reviewed and adjudicated by the CEC. Further, the CEC will consider all clinically relevant information to classify all deaths as:

Vascular death: any death that is not clearly non-vascular. For example, vascular death may include deaths due to spontaneous bleeding, myocardial infarction, stroke, heart failure, sudden death, and arrhythmias. Sudden death is defined as either witnessed or unwitnessed but seen within 24 hours of death and known to be well with no premonitory symptoms of heart failure, myocardial infarction, or other illness.

Non-vascular death: any death that is not vascular.

Unknown death: if there is not sufficient information to determine whether the death was due to vascular or non-vascular causes, the CEC will adjudicate the death as “Unknown” cause.