**Additional file 1.**

- **Discontinuance criteria**
- **Exploratory analysis**
- **Laboratory testing**
- **Outcome definitions for adverse events**

- **Discontinuance criteria**

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|---|---|
| Withdrawal criteria | 1) Inadequate glycemic control after administration of the study drug<br>2) Suspect of adverse side effects of the study drug<br>3) Frequent hypoglysemia<br>4) Onset of adverse cardiovascular event†<br>5) Declaration of withdrawal from the study by the participant<br>6) Turnig out of misunderstanding of all criteria for eligibility after enrollment<br>7) Pregnancy after enrollment<br>8) Lowere adherance for administration of the study drug (< 70%)<br>9) Assessment of inadequate for the study by the attending doctor |
| | |
| †Cardiovascular event | 1) Addition of heart failure treatment drugs as follows;<br>angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-blockers, diuretics, and aldosterone antagonists<br>2) Hospitalization of heart failure |

- **Exploratory analysis**

Further exploratory analysis in this study is planned for such parameters.

1) Blood glucose
2) Lipid metabolism [total cholesterol, high density lipoprotein, triglyceride, small dense low-density lipoprotein and Malondialdehyde-modified low density lipoprotein]
3) Blood pressure
4) High sensitive CRP
5) Adiponectin, microalbuminuria
6) Urinary 8-hydroxy-2' –deoxyguanosine
7) Estimated GFR

- **Laboratory testing**

- Brain natriuretic peptide, N-terminal brain natriuretic peptide, adiponectin, small dense low-density lipoprotein, malondialdehyde-modified low density lipoprotein, high-sensitive C-reactive protein, microalbuminuria, urinary 8-hydroxy-2' –deoxyguanosine

These parameters will be measured in a central laboratory (SRL, Inc. Hachioji, Tokyo, Japan).

- White blood cell, red blood cell, platelet, hemoglobin, hematocrit, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, blood urea nitrogen, serum creatinine, uric acid, serum sodium, serum potassium, serum chloride, total cholesterol, high density lipoprotein, triglyceride, total protein, albumin, blood sugar, glycohemoglobin

These parameters will be measured in each institusion.

- **Major adverse cardiovascular events (MACE)**

MACE include cardiovascular death, acute coronary syndrome, hospitalization of heart failure, and stroke.

- **Cardiovascular death**

The cause of death will be determined by the principal condition that caused the death, not the immediate mode of death. Clinical Events Committee (CEC) members will review all available information and use their clinical expertise to adjudicate the cause of death. All deaths not attributed to the categories of cardiovascular (CV) death and not attributed to a non-CV cause are presumed CV deaths and are part of the CV mortality outcome. Death certificates or summaries, if possible, including the date of death and other relevant details, will be provided for all patients who have died. However, if a death certificate is the only information available for review in addition to the patient data in the clinical trial database, the CEC may decide not to use this information as cause of death if another etiology appears more plausible. The following definitions will be used for the adjudication of fatal cases:

Sudden cardiac death. Death that occurs unexpectedly in a previously stable patient and includes the following:

- Witnessed and instantaneous death without new or worsening symptoms
- Witnessed death within 60 minutes of the onset of new or worsening cardiac symptoms
- Witnessed death attributed to an identified arrhythmia (e.g., captured by electrocardiogram or witnessed on a monitor by either a medic or paramedic)
- Subject unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest that dies within 24 hours without identification of a non-cardiac etiology

- Un-witnessed death with no conclusive evidence of another, non-CV, cause of death (i.e. presumed CV death).

Sudden death attributable to acute myocardial infarction (MI) (MI type 3). Sudden death occurring up to 14 days after a documented acute MI (verified either by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus) where there is no conclusive evidence of another cause of death. If death occurs before the biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death attributable to heart failure or cardiogenic shock. Death occurring in the context of clinically worsening symptoms and/or signs of congestive heart failure (CHF) without evidence of another cause of death.

New or worsening signs and/or symptoms of CHF include any of the following:

- 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
- Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration
- Confinement to bed predominantly because of heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- Cardiogenic shock not occurring in the context of an acute MI 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 mmHg for more than 1 hour, ack of response to fluid resuscitation and/or heart rate correction, and judged to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

1. Cool, clammy skin
2. Oliguria (urine output <30 mL/hour)
3. Altered sensorium
4. Cardiac index <2.2 L/min/$m^2$

Cardiogenic shock can also be defined in the presence of SBP ≥90 mmHg or for a time period <1 hour if the blood pressure measurement or time period is influenced by the presence of positive inotropic or vasopressor agents alone and/or with mechanical support <1 hour. The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study outcome. This category will include sudden death occurring during an admission for worsening heart failure

Death attributable to stroke or cerebrovascular event. Death occurring up to 30 days after a stroke that is either attributable to the stroke or caused by a complication of the stroke.

Death attributable to other CV causes. Death must be caused by a fully documented CV event not included in the above categories (e.g. dysrhythmia, pulmonary embolism, or CV intervention). Death attributable to an MI that occurs as a direct consequence of a CV investigation/procedure/operation will be classified as death due to another CV cause.

Non-CV death

Non-CV death is defined as any death not covered by cardiac death or vascular death. The CEC will be asked to determine the most likely cause of non-CV death. Examples of non-CV death are pulmonary causes, renal causes, gastrointestinal causes, infection (including sepsis), non-infectious causes (e.g., systemic inflammatory response syndrome), malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage (not intracranial), accidental/trauma, suicide, non-CV organ failure (e.g., hepatic failure) or non-CV surgery.

- **Acute coronary syndrome**

ACS includes MI and unstable angina.

MI (non-fatal)

The term 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 following criteria (A to C) meets the diagnosis for myocardial infarction.

A. Spontaneous MI (type 1)

To identify a type 1 MI, patients should demonstrate spontaneous symptoms of myocardial ischemia unprovoked by supply/demand inequity, together with ≥1 of the following criteria:

- Cardiac biomarker elevation: Troponin is the preferred marker for adjudicating the presence of acute MI. At least one value should show a rise and/or fall from the lowest cut-point providing 10% imprecision (typically the upper reference limit for the troponin run per standard of clinical care). Creatine kinase-MB is a secondary choice of marker to troponin; a rise in CK-MB

above the local upper reference limit would be consistent with myocardial injury.

• ECG changes consistent with new ischemic changes

– ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]) or ECG manifestations of acute myocardial ischemia (in the absence of left ventricular hypertrophy [LVH] and LBBB):

– Development of pathological Q waves in the ECG

1. Any Q-wave in leads V2–V3 ≥0.02 seconds or QS complex in leads V2 and V3
2. 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)

– ST elevation: New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men 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 T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1

• Imaging evidence of new non-viable myocardium or new wall motion abnormality

B. “Demand”-related (type 2) MI

Patients with type 2 MI should be considered under similar diagnostic criteria as a type 1 MI; however, type 2 MI should be considered present when myocardial ischemia and infarction are consequent to supply/demand inequity, rather than a spontaneous plaque rupture and coronary thrombosis.

C. Percutaneous coronary intervention (PCI)-related MI (type 4a/4b)

For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above

the 99th percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers >3 × 99th percentile URL (troponin or CK-MB >3 × 99th percentile URL) are consistent with PCI-related MI.

Where the cardiac biomarker is elevated prior to PCI, a ≥20% increase in the value of the second cardiac biomarker sample within 24 hours of PCI and documentation that cardiac biomarker values were decreasing (two samples ≥6 hours apart) prior to the suspected recurrent MI are consistent with PCI-related MI.

Symptoms of cardiac ischemia are not required.

D. Coronary artery bypass grafting (CABG)-related MI (type 5)

For 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 >5 × 99th percentile URL (troponin or CK-MB >5 × 99th percentile URL) plus at least one of the following is consistent with CABG-related MI:

- New pathological Q waves in at least two contiguous leads on the ECG that persist for 30 days, or new LBBB
- Angiographically documented new graft or native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium

If the cardiac biomarker is elevated prior to CABG, a ≥20% increase in the value of the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac biomarker values were decreasing (two samples ≥6 hours apart) prior to the suspected recurrent MI plus new pathological Q-waves in ≥2 contiguous leads on the electrocardiogram; or new LBBB,

angiographically documented new graft, or native coronary artery occlusion; or imaging evidence of new loss of viable myocardium are consistent with a periprocedural MI after CABG. Symptoms of cardiac ischemia are not required.

Clinical classification of acute MI. Every MI identified by the CEC will be classified into one of the following categories:

- Type 1: Spontaneous MI related to ischemia arising from a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2: MI secondary to ischemia attributable 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, new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, with death occurring before blood samples could be obtained or before the appearance of cardiac biomarkers in the blood
- Type 4a: MI associated with PCI
- Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy
- Type 5: MI associated with CABG

Hospitalization for unstable angina

The date of this event will be the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. Unstable angina requiring hospitalization is defined as all of the following:

- No elevation in cardiac biomarkers (cardiac biomarkers negative for myocardial necrosis) according to conventional assays or contemporary sensitive assays
- Clinical presentation: Cardiac symptoms lasting ≥10 minutes and considered to be myocardial ischemia upon final diagnosis with one of the following:
  - Rest angina
  - New-onset (<2 months) severe angina (Canadian Cardiovascular Society [CCS] Grading Scale, or CCS classification system, classification severity ≥III)
  - Increasing angina (in intensity, duration, and/or frequency) with an increase in severity of >1 CCS class to CCS class >III
- Angina requiring an unscheduled visit to a healthcare facility and overnight admission
- At least one of the following:
  - New or worsening ST or T-wave changes by ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of LVH and LBBB:
    1. ST elevation: New transient (known to be <20 minutes) ST elevation at the J-point in two contiguous leads with cut-off points of ≥0.2 mV in men or ≥0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads
    2. ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1
  - Evidence of ischemia on stress testing with cardiac imaging
  - Evidence of ischemia on stress testing with angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery or initiation/increased dosing of antianginal therapy
  - Angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery

- **Heart failure requiring hospitalization**

The date of this event will be the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. Heart failure requiring hospitalization is defined as an event that meets all of the following criteria:

• Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or a date change if the time of admission/discharge is not available)

• Clinical manifestations of heart failure (new or worsening), including at least one of the followings:

– Dyspnea

– Orthopnea

– Paroxysmal nocturnal dyspnea

– Edema

– Pulmonary basilar crackles

– Jugular venous distension

– Third heart sound or gallop rhythm

– Radiological evidence of worsening heart failure

• Additional/increased therapy: at least one of the followings:

– Initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy

– Up-titration of oral diuretic or intravenous therapy, if already on therapy

– Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation, or ventricular pacing to improve cardiac function); or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at the treatment of heart failure

Changes in a biomarker (e.g., brain natriuretic peptide) consistent with CHF will support this

diagnosis.

Transient ischemic attack (TIA)

A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

- **Stroke**

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.

Diagnosis of stroke. For the diagnosis of stroke, the following four criteria should be fulfilled:

- 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
  - Hemianopia (loss of half of the field of vision of one or both eyes)
  - Other new neurological sign(s)/symptom(s) consistent with stroke

Note: If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is

no plausible non-stroke cause for the clinical presentation

- Duration of a focal/global neurological deficit ≥24 hours OR <24 hours if attributable to at least one of the following therapeutic interventions:
  - Pharmacologic (i.e., thrombolytic drug administration)
  - Non-pharmacologic (i.e., neurointerventional procedure such as intracranial angioplasty)

or

  - Available brain imaging clearly documents a new hemorrhage or infarct

or

  - The neurological deficit results in death
- No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)
- Confirmation of the diagnosis by at least one of the following:*
  - Neurology or neurosurgical specialist
  - Brain imaging procedure (at least one of the followings):

1 CT scan

2 MRI scan

3 Cerebral vessel angiography

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

If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus will be mandatory.

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

- Persisted for more than one week

OR

- Persisted for more than 24 hours and accompanied by an appropriate new CT or MRI finding

Classification of stroke. Strokes are sub-classified as follows:

- Ischemic (non-hemorrhagic): A stroke caused by an arterial obstruction attributable to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. This category includes ischemic stroke with hemorrhagic transformation (i.e. no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan)
- Hemorrhagic: A stroke caused by a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes attributable to primary intracerebral hemorrhage (intraparenchymal or intraventricular), subdural hematoma and primary subarachnoid hemorrhage
- Not assessable: The stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

**Hypoglycemic adverse events (requiring any intervention)**

Hypoglycemic adverse events are defined as the requirement of high-sugar food, drinks, or glucose because of a very low level of blood glucose.

Representative symptoms of hypoglycemia may include:

– Irregular heart rhythm

– Fatigue

– Pale skin

- Shakiness
- Anxiety
- Sweating
- Hunger
- Irritability
- Tingling sensation around the mouth
- Crying out during sleep

**Urinary tract infection**

Urinary tract infection is defined as the requirement of antibiotics because of infectious episodes in any part of the urinary system (kidneys, ureters, bladder, or urethra).