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# The effect of luseogliflozin and alpha-glucosidase inhibitor on heart failure with preserved ejection fraction in diabetic patients: rationale and design of the MUSCAT-HF randomised controlled trial

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## Abstract

**Introduction:** Type 2 diabetes mellitus (T2DM) is a strong risk factor for coronary artery disease and heart failure, particularly heart failure with preserved ejection fraction (HFpEF). The aim of the ongoing MUSCAT-HF trial is to evaluate the efficacy of luseogliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, versus voglibose, an alpha-glucosidase inhibitor, using brain natriuretic peptide (BNP) as the index of therapeutic effect in T2DM patients with HFpEF.

**Methods and Analysis:** A total of 190 patients with T2DM and HFpEF (EF>45%) who are drug-naïve or taking any anti-diabetic agents will be randomised (1:1) to receive luseogliflozin 2.5 mg once daily or voglibose 0.2 mg three times daily. Patients will be stratified by age (<65 years, ≥65 years), baseline hemoglobin A1c (<8.0%, ≥8.0%), baseline BNP (<100 pg/ml, ≥100 pg/ml), baseline renal function (eGFR ≥60 ml/min/1.73 $m^2$, <60 ml/min/1.73 $m^2$), use of thiazolidine or not, and presence or absence of atrial fibrillation and flutter at screening. After randomisation, participants will receive the study drug for 12 weeks in addition to their background therapy. The primary endpoint is the percentage change in baseline BNP after 12 weeks of treatment. The key secondary endpoints are the change from baseline in the ratio of early mitral inflow velocity to mitral annular early diastolic velocity, body weight, and glycemic control after 12 weeks of treatment.

**Ethics and dissemination:** The study has been approved by the ethics committee and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals**.**

**Trial registration:** UMIN Clinical Trials Registry (UMIN-CTR), UMIN000018395.

**Keywords:** luseogliflozin; heart failure; voglibose; brain natriuretic peptide; sodium-glucose cotransporter 2 inhibitor; type 2 diabetes mellitus

**Strengths and limitations of this study**

- This study will be the first randomised controlled trial to evaluate the efficacy of an SGLT2 inhibitor in patients with T2DM and heart failure with preserved ejection fraction.
- This study is adequately powered to provide a clinically meaningful outcome.
- A 12-week intervention period may not be sufficient to see the full impact of treatment on long term outcome.

## Introduction

Type 2 diabetes mellitus (T2DM) is a strong risk factor for coronary artery disease and heart failure, particularly, heart failure with preserved ejection fraction (HFpEF) [1]. A previous cohort study showed that the risk of heart failure was increased in patients n with T2DM [2]. Therefore, the treatment of abnormal glucose metabolism is a promising strategy in the treatment of heart failure. However, large clinical trials have shown that intensive glucose-lowering treatment of hyperglycemia, compared with less-intensive control treatment, did not decrease hospitalization or mortality of heart failure [3]. However, Kim et al. reported that a α-glucosidase inhibitor regulated glucose metabolism and improved the pathophysiology of chronic heart failure in patients with T2DM [4]. The STOP-NIDDM trial showed that the treatment of impaired glucose tolerance with a α-glucosidase inhibitor resulted in a significant reduction in the risk of cardiovascular disease [5]. These data suggest that α-glucosidase inhibitors may be beneficial in the treatment of chronic heart failure.

Recently, the EMPA-REG OUTCOME [6, 7] and CANVAS [8, 9] randomised controlled trials showed that sodium glucose cotransporter 2 (SGLT2) inhibitors reduced all-cause mortality, cardiovascular mortality, and hospitalization of heart failure in T2DM compared with placebo. These results indicated that SGLT2 inhibitors may be effective in lowering glucose levels and reducing cardiovascular events, particularly in patients with heart failure. Given that these trials were not specifically designed to investigate the effect of SGLT2 inhibitors in heart failure patients, no detailed data on their effects in heart failure were obtained.

The MUSCAT-HF (Prospective coMpArison of luSeogliflozin and alpha-gluCosidAse on The management of diabetic patients with chronic Heart Failure and preserved left-ventricular ejection fraction) trial described here is designed to evaluate the efficacy of luseogliflozin, an

SGLT2 inhibitor, compared with voglibose, an alpha-glucosidase inhibitor, using brain natriuretic peptide (BNP) as the index of therapeutic effect in patients with T2DM and HFpEF. The results of this study will support a novel strategy for the treatment of heart failure using an SGLT2 inhibitor, independent of its glucose-lowering effects.

## Methods and analysis

### Study design

The MUSCAT-HF trial is an ongoing, multi-center, prospective, open-label, randomised controlled trial designed to assess the effect of luseogliflozin (2.5 mg once daily) compared with voglibose (0.2 mg three times daily) on left ventricular load in patients with T2DM and HFpEF. BNP level at 24 weeks after administration of the study drug will be used as a surrogate marker for heart failure.

### Study population

The planned sample size of this study is 95 patients per group (190 patients in total). The recruitment of study patients is planned to take place from September 2015 to September 2018. Patients aged ≥20 years with T2DM (hemoglobin A1c [HbA1C] ≤9.0%) and HFpEF (left ventricular ejection fraction ≥45%) needing additional treatment for T2DM despite the ongoing treatment are eligible for participation. The key inclusion and exclusion criteria are detailed in Table 1. Given that the definition of chronic heart failure according to European Society of Cardiology guidelines includes BNP ≥35 pg/ml [10], patients with BNP <35 pg/ml will be excluded from this study. Study candidates will be assessed for eligibility within 4 weeks prior to enrollment (Figure 1).

### Study outline and randomisation

Patients fulfilling all criteria who provide written informed consent to participate in this study will be enrolled and subsequently randomised (1:1) to receive luseogliflozin (2.5 mg once daily) or voglibose (0.2 mg three times daily) in addition to their background medication. Randomisation will be performed using a computer-generated random sequence web response system. Patients will be stratified by age (<65 years, ≥65 years), baseline HbA1c (<8.0%, ≥8.0%), baseline BNP (<100 pg/ml, ≥100 pg/ml), baseline renal function (eGFR ≥60 ml/min/1.73 $m^2$, <60 ml/min/1.73 $m^2$), use of thiazolidine or not, and presence or absence of atrial fibrillation (AF) and flutter (AFL) at screening.

Assessments during the study period are listed in Fig 2. Laboratory data, electrocardiogram, echocardiography and patients' vital signs, body weight, and waist circumference, will be evaluated at 4 ± 2 weeks (visit 29 ± 14 days) and 12 weeks (visit 85 ± 28 days) after initiation of study treatment. Safety and tolerability will be assessed during the treatment period. The primary outcome of change in BNP compared with baseline will be evaluated at 12 weeks (visit 85 ± 28 days) and patient will be followed up for an additional 12 weeks (visit 169 ± 28 days) after the end of treatment. If a patient's glycemic control worsens after 4 ± 2 weeks, the investigator can increase the dose of allocated treatment (to luseogliflozin 5 mg once daily or voglibose 0.3 mg three times daily) and other specific T2DM drugs, except for sulfonylureas. Investigators will also be encouraged to treat all other cardiovascular risk factors according to local standard of care. Under the following circumstances, the investigator must evaluate the data and patient's vital sign: 1) discontinuation of study treatment; 2) dose increase of specific treatment for heart failure; 3) initiation of new treatment for heart failure; 4) withdrawal from the study. The permitted medications for the treatment of heart failure include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics,

and mineralocorticoid/aldosterone receptor antagonists.

**Outcomes**

***Primary outcome***

The primary outcome of this study is the difference in BNP after 12 weeks (visit 85 ± 28 days) of treatment between the luseogliflozin and the voglibose groups, defined as the difference in logarithmic BNP change calculated as follows:

(*) BNP change rate = BNP [at follow-up]/BNP [at baseline];

(†) logarithmic BNP change = logarithmic BNP [at follow-up] – logarithmic BNP [at baseline];

(‡) the ratio of BNP change rate [the luseogliflozin group to the voglibose group] = (*) [in the luseogliflozin group]/(*) [in the voglibose group];

(§) the difference of logarithmic BNP change = (†) [in the luseogliflozin group] – (†) [in the voglibose group].

***Secondary outcomes***

The key secondary outcomes of this study are the differences in the following parameters between the luseogliflozin and the voglibose groups:

1) Ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e')

2) Body weight

3) HbA1c

The difference in E/e' and HbA1c between the groups is defined as the difference in logarithmic E/e' and HbA1c using the same calculation as for BNP. Difference in body weight is defined as the difference between body weight at follow-up and at baseline.

***Safety outcomes: including, but not limited to:***

- clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), physical

examination, and the use of rescue medication

- Adverse events including major adverse cardiovascular events (MACE), hypoglycemic adverse events (requiring any intervention), and urinary tract infection.

Safety will be assessed based on adverse events reported throughout the study, clinical laboratory tests, vital signs, 12-lead electrocardiogram, physical examination, and the use of rescue medication. Prespecified adverse events include MACE, hypoglycemic adverse events (requiring any intervention), and urinary tract infection (details listed in Additional file 1).

**Study oversight and organization**

Members of the Steering Committee also designed the study and are responsible for its conduction (details listed in Additional file 2). Significant adverse events (SAEs) occurring within 30 days after final administration of the study drug or after 30 days with a suspicion of association with the study drug, as well as all pregnancies, will be immediately reported to the Steering Committee and the sponsor by the investigator, in accordance with GCP.

**Statistical analysis**

***Sample size and power calculation***

The primary hypothesis of this study is that the SGLT2 inhibitor luseogliflozin can reduce cardiac load in patients with T2DM and HFpEF. Therefore, the primary outcome was the difference in change in BNP from baseline to 12 weeks between patients receiving luseogliflozin or voglibose. As of the start of recruitment in September 2015, no interventional study of the effect of SGLT2 inhibitors on heart failure in patients with T2DM has been reported. Therefore, we estimated that BNP change rate in the luseogliflozin group will be 30% lower as compared with that in the globose group according to previous studies of the effect of renin-angiotensin-aldosterone system inhibitors on heart failure [11-13]. The standard deviation of the natural logarithmic

transformation of BNP was estimated at 0.83, in reference to the PARAMOUNT study [13]. A minimum of 172 patients (86 patients per group) is required to provide 80% power with a two-sided α level of 0.05 by Student's t-test on the ratio of BNP change rate between the luseogliflozin and voglibose groups. With 10% of patients estimated to withdraw from participation during the study period, the final enrollment target was set at 190 patients (95 patients per group).

***Analysis plan***

In the efficacy analysis, the primary population comprises the Full Analysis Set (FAS), defined as all randomised patients who receive one dose of study drug and are followed up at least once. Patients with no BNP data and patients who withdraw or discontinue treatment will be excluded from the FAS. Missing values at 4, 12, and 24 weeks will be replaced by the last observed value for that variable (last observation carried forward). In the primary outcome analysis, baseline observation carried forward analysis will be also performed. Efficacy analysis will be performed according to the treatment to which patients are randomly assigned, based on the intention-to-treat analysis. The primary outcome analysis will be based on an analysis of covariance (ANCOVA) ($\alpha = 0.05$, level of significance) for the ratio of BNP change rate in the FAS. Adjusted covariates will include the assigned treatment (luseogliflozin, voglibose), baseline age (<65 or ≥65 years), baseline HbA1c (<8.0 or ≥8.0%), baseline BNP (<100 or ≥100 pg/ml), baseline renal function (eGFR ≥60 or <60 ml/min/1.73 $m^2$), use of thiazolidine or not at baseline, and presence or absence of AF and AFL at baseline as stratified factors of randomisation. Furthermore, BNP change rate, ratio of BNP change rate, and 95% confidence intervals will be calculated. The same ANCOVA analysis as for the primary outcome will be performed for the ratio of BNP change rate at 4 weeks and 24 weeks between the two groups.

Prespecified subgroup analyses will be performed on the primary outcome using ANCOVA (covariates: assigned treatment and BNP at screening) in the following subgroups: baseline age (<65 or ≥65 years), baseline HbA1c (<8.0 or ≥8.0%), baseline BNP (<100 or ≥100 pg/ml), baseline renal function (eGFR ≥60 or <60 ml/min/1.73 $m^2$), use of thiazolidine or not at baseline, baseline body weight (<60 kg, ≥60 kg), and presence or absence of AF and AFL at baseline. Furthermore, exploratory analysis on the primary outcome will be performed in subgroups based on blood pressure, heart rate, waist circumference, cardiovascular risk factors (hypertension, T2DM, hyperuricemia, family history, and smoking), alcohol consumption, regular medication, and serum lipid levels (details listed in Additional file 3).

The key secondary outcomes, difference in E/e', body weight, and HbA1C at 12 weeks between the luseogliflozin and voglibose groups, will be analyzed using the same ANCOVA as for the primary outcome. Subgroup analysis for the key secondary outcomes will be performed in the same subgroups as for the primary outcome analysis. The following secondary outcomes will be also analyzed using the same analysis plan: E/e', body weight, and HbA1C at 4 and 24 weeks; and exploratory parameters at 4, 12, and 24 weeks.

For the safety analysis, the primary population is the Safety Analysis Set (SAFETY), defined as all patients who receive at least one dose of study drug. Although patients who withdraw without receiving study drug will be excluded from SAFETY, other patients who withdraw for any other reason will be included. The safety analysis will be performed according to the treatment administered to patients in practice, based on the as-treated analysis. Analysis of SAEs (MACE, hypoglycemia, and urinary tract infection) will be performed using the Cochran–Mantel–Haenszel test with stratification factors of age (<65 or ≥65 years), baseline HbA1c (<8.0 or ≥8.0%), baseline BNP (<100 or ≥100 pg/ml), baseline renal function (eGFR ≥60 or <60

ml/min/1.73 $m^2$), use of thiazolidine or not, and presence or absence of AF and AFL at screening.

All comparisons are planned, and the analyses will be two sided With P values <0.05 considered statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). The statistical analysis plan will be developed by the principal investigator and a biostatistician prior to the completion of patient recruitment and database lock.

**Ethics and dissemination**

***Ethics approval and consent to participate***

This study was approved by the Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences and the Okayama University Hospital Ethics Committee, as well as the ethics committee of each participating center. This trial will be conducted in compliance with the Declaration of Helsinki. Trial registration: UMIN Clinical Trials Registry (UMIN-CTR), UMIN000018395.

***Consent for publication***

All participants will provide written informed consent prior to participation.

***Dissemination policy***

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise the research to clinicians and commissioners.

## Discussion

The MUSCAT-HF trial is an ongoing, multi-center, randomised controlled trial designed to investigate the clinical efficacy of luseogliflozin on HFpEF in patients with T2DM. Eligible participants will be randomised to receive luseogliflozin or voglibose in addition to their

background medication for 24 weeks. The primary endpoint is the percentage change from baseline in BNP level after 12 weeks of treatment. This trial has the potential to provide novel clinical evidence regarding the treatment of HFpEF in patients with T2DM.

The EMPA-REG OUTCOME and CANVAS trials showed that the treatment of empagliflozin and canagliflozin, respectively, significantly reduced cardiovascular events in T2DM patients with higher cardiovascular risk [6, 8]. Specifically, a 35% and 33% relative risk reduction in hospitalization for heart failure was observed in the EMPA-REG OUTCOME and CANVAS trials, respectively. Although a significant reduction in hospitalization for heart failure was clearly documented, the proportion of patients with heart failure and reduced or preserved ejection fraction was not reported precisely in either trials. Therefore, the therapeutic effect of SGLT2 inhibitors specifically in patients with heart failure has yet to be established. At present, HFpEF prognosis cannot be improved with the use of conventional drugs such as an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, or mineralocorticoid receptor blocker [14-17]. SGLT2 inhibitors therefore represent a promising strategy for the prevention of HFpEF and improvement of HFpEF outcome by improving left ventricular diastolic function in patients with T2DM. A recent small prospective cohort study in 37 patients showed that canagliflozin improved left ventricular diastolic function within 3 months, although the data in terms of prognosis were limited [18]. Taken together, the use of SGLT2 inhibitors in patients with T2DM and HFpEF is of significant interest in the clinical management of this population.

In summary, emerging evidence suggests that SGLT2 inhibitors exert protective effects against cardiovascular events beyond their glucose-lowering capabilities, although further investigation of the mechanisms underlying these effects is warranted. The MUSCAT-HF trial,

the results of which are expected to be published in 2019, will provide novel clinical insights into the treatment of patients with T2DM and HFpEF.

**Funding**

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**Contributions**

KE, TM, and HI contributed to the study design. KE, TM, KN, SS, MM, SN, AT, and HI contributed to data interpretation and the drafting of the manuscript. All authors read and approved the final manuscript.

**Competing interests**

KE, SS, MM, SN, and AT have no competing interests to declare. TM and KN has received honorarium from Novartis Pharmaceuticals (Basel, Switzerland). HI has received research funding and honorarium from Novartis Pharmaceuticals (Basel, Switzerland).

**Data statement**

All data are available upon request.

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## Figure Legends

Figure 1. Study design.

ECG, electrocardiogram

Figure 2. Assessments during the study period

Table 1. Detailed inclusion and exclusion criteria

| **Inclusion criteria** |
|---|
| 1) Diagnosis of T2DM and left ventricular ejection fraction >45% with current or previous symptoms of heart failure (dyspnea on effort, orthopnea, or leg edema) |
| 2) Inadequately controlled T2DM in patients who have received diet and exercise therapy, a lifestyle modification program, and hypoglycemic medications based on standard guidelines of the Japan Diabetes Society |
| 3) Age >20 years |
| 4) Provision of written informed consent prior to participation |
| **Exclusion criteria** |
| 1) BNP <35 pg/ml |
| 2) Use of alpha-glucosidase inhibitors, SGLT2 inhibitors, glinides, or high-dose sulfonylurea |
| 3) Renal insufficiency (eGFR <30 ml/min/1.73m$^2$) |
| 4) Left ventricular ejection fraction <45% |
| 5) History of severe ketoacidosis or diabetic coma within 6 months prior to participation |
| 6) Serious infection or severe trauma, or perioperative patients |
| 7) Type 1 diabetes mellitus |
| 8) Poorly controlled T2DM (HbA1c >9.0%) |
| 9) Uncontrolled hypertension (systolic blood pressure >160 mmHg) |
| 10) History of stroke, myocardial infarction, or severe cardiovascular disease with hospitalization within 6 months prior to participation |
| 11) Women who are pregnant or breastfeeding |
| 12) Allergy to either investigation product |

13) Other medical reason at the investigator's discretion

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T2DM, type 2 diabetes mellitus; BNP, brain natriuretic peptide; SGLT2, sodium/glucose cotransporter 2; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C

Figure 1

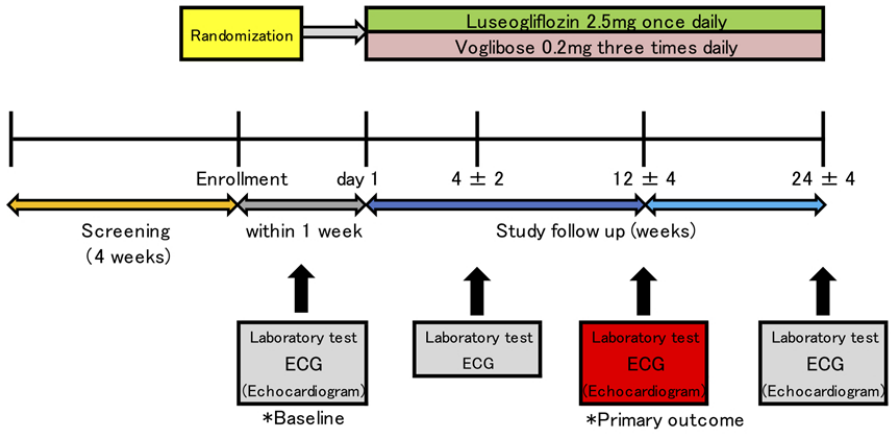


Figure 1

254x190mm (96 x 96 DPI)

Figure 2

| Assessment | Enrollment | Treatment period | | |
|---|---|---|---|---|
| | | 4 ± 2 weeks (visit 29 ± 14 days) | 12 weeks (visit 85 ± 28 days) | 24 weeks (visit 169 ± 28 days) |
| Medical examination | X | X | X | X |
| Written informed consent | X | | | |
| Clinical symptoms | X | X | X | X |
| Adverse events | | X | X | X |
| Treatment discontinuation | | X | X | X |
| Vital signs | X | X | X | X |
| Body weight | X | X | X | X |
| Waist circumference | X | | X | X |
| Laboratory tests | X | X | X | X |
| Electrocardiogram | X | X | X | X |
| Echocardiography | X | | X (if possible) | X (if possible) |

Figure 2

254x190mm (96 x 96 DPI)

**Additional file 1.** Outcome definitions for adverse events

**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).

**Additional file 2.** Study organization

Steering Committee

Hiroshi Ito (Chair), Kazufumi Nakamura, Toru Miyoshi, Kentaro Ejiri, Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences, Okayama, Japan; Satoru Sakuragi, Iwakuni Clinical Center, Yamaguchi, Japan; Mitsuru Munemasa, Okayama Medical Center, Okayama, Japan; Seiji Nanba, Okayama Rosai Hospital, Okayama, Japan; Tomosato Suezawa, Takamatsu Red Cross Hospital, Kagawa, Japan; Atsushi Takaishi, Mitoyo General Hospital, Kagawa, Japan.

Statistical consulting

Tetsutaro Hamano, P4 Statistics Co. Ltd., Tokyo, Japan.

Clinical Event Committee

Masayuki Doi, Kagawa Prefectural Central Hospital, Kagawa, Japan; Takefumi Oka, Tsuyama Central Hospital, Okayama, Japan.

Data Monitoring

Given that invasive intervention will not be performed in this study, data monitoring is not planned.

**Additional file 3**. Selected and exploratory subgroups

| | Variables | Category |
|---|---|---|
| Prespecified subgroup analyses | • Age (years) | <65<br>≥65 |
| | • HbA1c (%) | <8.0<br>≥8.0 |
| | • BNP (pg/nL) | <100<br>≥100 |
| | • eGFR (mL/min/1.73m$^2$) | <60<br>≥60 |
| | • Thiazolidine use | Yes<br>No |
| | • Body weight (kg) | <60<br>≥60 |
| | • AF/AFL | Yes<br>No |
| Exploratory analyses | • Blood pressure (mmHg) | |

BMJ Open

# The effect of luseogliflozin and alpha-glucosidase inhibitor on heart failure with preserved ejection fraction in diabetic patients: rationale and design of the MUSCAT-HF randomised controlled trial



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| | |

# The effect of luseogliflozin and alpha-glucosidase inhibitor on heart failure with preserved ejection fraction in diabetic patients: rationale and design of the MUSCAT-HF randomised controlled trial

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## Abstract

**Introduction:** Type 2 diabetes mellitus (T2DM) is a strong risk factor for coronary artery disease and heart failure, particularly heart failure with preserved ejection fraction (HFpEF). The aim of the ongoing MUSCAT-HF trial is to evaluate the efficacy of luseogliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, versus voglibose, an alpha-glucosidase inhibitor, using brain natriuretic peptide (BNP) as the index of therapeutic effect in T2DM patients with HFpEF.

**Methods and Analysis:** A total of 190 patients with T2DM and HFpEF (EF>45%) who are drug-naïve or taking any anti-diabetic agents will be randomised (1:1) to receive luseogliflozin 2.5 mg once daily or voglibose 0.2 mg three times daily. Patients will be stratified by age (<65 years, ≥65 years), baseline haemoglobin A1c (<8.0%, ≥8.0%), baseline BNP (<100 pg/ml, ≥100 pg/ml), baseline renal function (eGFR ≥60 ml/min/1.73 $m^2$, <60 ml/min/1.73 $m^2$), use of thiazolidine or not, and presence or absence of atrial fibrillation and flutter at screening. After randomisation, participants will receive the study drug for 12 weeks in addition to their background therapy. The primary endpoint is the percentage change in baseline BNP after 12 weeks of treatment. The key secondary endpoints are the change from baseline in the ratio of early mitral inflow velocity to mitral annular early diastolic velocity, body weight, and glycaemic control after 12 weeks of treatment.

**Ethics and dissemination:** The study has been approved by the ethics committee and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals**.**

**Trial registration:** UMIN Clinical Trials Registry (UMIN-CTR), UMIN000018395.

**Keywords:** luseogliflozin; heart failure; voglibose; brain natriuretic peptide; sodium-glucose cotransporter 2 inhibitor; type 2 diabetes mellitus

**Strengths and limitations of this study**

- This study will be the first randomised controlled trial to evaluate the efficacy of an SGLT2 inhibitor in patients with T2DM and heart failure with preserved ejection fraction.
- This study is adequately powered to provide a clinically meaningful outcome.
- A 12-week intervention period may not be sufficient to see the full impact of treatment on long term outcome.

## Introduction

Type 2 diabetes mellitus (T2DM) is a strong risk factor for coronary artery disease and heart failure, particularly, heart failure with preserved ejection fraction (HFpEF) [1]. A previous cohort study showed that the risk of heart failure was increased in patients n with T2DM [2]. Therefore, the treatment of abnormal glucose metabolism is a promising strategy in the treatment of heart failure. However, large clinical trials have shown that intensive glucose-lowering treatment of hyperglycaemia, compared with less-intensive control treatment, did not decrease hospitalization or mortality of heart failure [3]. However, Kim et al. reported that a α-glucosidase inhibitor regulated glucose metabolism and improved the pathophysiology of chronic heart failure in patients with T2DM [4]. The STOP-NIDDM trial showed that the treatment of impaired glucose tolerance with a α-glucosidase inhibitor resulted in a significant reduction in the risk of cardiovascular disease [5]. These data suggest that α-glucosidase inhibitors may be beneficial in the treatment of chronic heart failure.

Recently, the EMPA-REG OUTCOME [6 7] and CANVAS [8 9] randomised controlled trials showed that sodium glucose cotransporter 2 (SGLT2) inhibitors reduced all-cause mortality, cardiovascular mortality, and hospitalization of heart failure in T2DM compared with placebo. These results indicated that SGLT2 inhibitors may be effective in lowering glucose levels and reducing cardiovascular events, particularly in patients with heart failure. Given that these trials were not specifically designed to investigate the effect of SGLT2 inhibitors in heart failure patients, no detailed data on their effects in heart failure were obtained.

The MUSCAT-HF (Prospective coMpArison of luSeogliflozin and alpha-gluCosidAse on The management of diabetic patients with chronic Heart Failure and preserved left-ventricular ejection fraction) trial described here is designed to evaluate the efficacy of luseogliflozin, an

SGLT2 inhibitor, compared with voglibose, an alpha-glucosidase inhibitor, using brain natriuretic peptide (BNP) as the index of therapeutic effect in patients with T2DM and HFpEF. The results of this study will support a novel strategy for the treatment of heart failure using an SGLT2 inhibitor, independent of its glucose-lowering effects.

## Methods and analysis

### Study design

The MUSCAT-HF trial is an ongoing, multi-centre, prospective, open-label, randomised controlled trial designed to assess the effect of luseogliflozin (2.5 mg once daily) compared with voglibose (0.2 mg three times daily) on left ventricular load in patients with T2DM and HFpEF. BNP level at 24 weeks after administration of the study drug will be used as a surrogate marker for heart failure.

### Study population

The planned sample size of this study is 95 patients per group (190 patients in total). The recruitment of study patients is planned to take place from September 2015 to September 2018. Patients aged ≥20 years with T2DM (haemoglobin A1c [HbA1C] ≤9.0%) and HFpEF (left ventricular ejection fraction ≥45%) needing additional treatment for T2DM despite the ongoing treatment are eligible for participation. The key inclusion and exclusion criteria are detailed in Table 1. Given that the definition of chronic heart failure according to European Society of Cardiology guidelines includes BNP ≥35 pg/ml [10], patients with BNP <35 pg/ml will be excluded from this study. Study candidates will be assessed for eligibility within 4 weeks prior to enrolment (Figure 1).

### Study outline and randomisation

Patients fulfilling all criteria who provide written informed consent to participate in this study will be enrolled and subsequently randomised (1:1) to receive luseogliflozin (2.5 mg once daily) or voglibose (0.2 mg three times daily) in addition to their background medication. Randomization will be performed using a computer-generated random sequence web response system. Patients will be stratified by age (<65 years, ≥65 years), baseline HbA1c (<8.0%, ≥8.0%), baseline BNP (<100 pg/ml, ≥100 pg/ml), baseline renal function (eGFR ≥60 ml/min/1.73 $m^2$, <60 ml/min/1.73 $m^2$), use of thiazolidine or not, and presence or absence of atrial fibrillation (AF) and flutter (AFL) at screening.

Assessments during the study period are listed in Fig 2. Laboratory data, electrocardiogram, echocardiography and patients' vital signs, body weight, and waist circumference, will be evaluated at 4 ± 2 weeks (visit 29 ± 14 days) and 12 weeks (visit 85 ± 28 days) after initiation of study treatment. Safety and tolerability will be assessed during the treatment period. The primary outcome of change in BNP compared with baseline will be evaluated at 12 weeks (visit 85 ± 28 days) and patient will be followed up for an additional 12 weeks (visit 169 ± 28 days) after the end of treatment. If a patient's glycaemic control worsens after 4 ± 2 weeks, the investigator can increase the dose of allocated treatment (to luseogliflozin 5 mg once daily or voglibose 0.3 mg three times daily) and other specific T2DM drugs, except for sulfonylureas. Investigators will also be encouraged to treat all other cardiovascular risk factors according to local standard of care. Under the following circumstances, the investigator must evaluate the data and patient's vital sign: 1) discontinuation of study treatment; 2) dose increase of specific treatment for heart failure; 3) initiation of new treatment for heart failure; 4) withdrawal from the study. The permitted medications for the treatment of heart failure include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics,

and mineralocorticoid/aldosterone receptor antagonists.

**Outcomes**

***Primary outcome***

The primary outcome of this study is the difference in BNP after 12 weeks (visit 85 ± 28 days) of treatment between the luseogliflozin and the voglibose groups, defined as the difference in logarithmic BNP change calculated as follows:

(*) BNP change rate = BNP [at follow-up]/BNP [at baseline];

(†) logarithmic BNP change = logarithmic BNP [at follow-up] – logarithmic BNP [at baseline];

(‡) the ratio of BNP change rate [the luseogliflozin group to the voglibose group] = (*) [in the luseogliflozin group]/(*) [in the voglibose group];

(§) the difference of logarithmic BNP change = (†) [in the luseogliflozin group] – (†) [in the voglibose group].

***Secondary outcomes***

The key secondary outcomes of this study are the differences in the following parameters between the luseogliflozin and the voglibose groups:

1) Ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e')

2) Left ventricular ejection fraction

3) Body weight

4) HbA1c

The difference in E/e' and HbA1c between the groups is defined as the difference in logarithmic E/e' and HbA1c using the same calculation as for BNP. Difference in body weight and left ventricular ejection fraction is defined as the difference between those parameters at follow-up and at baseline. Further exploratory analysis is listed in Additional file 1.

***Safety outcomes: including, but not limited to:***

- clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), physical examination, and the use of rescue medication
- Adverse events including major adverse cardiovascular events (MACE), hypoglycaemic adverse events (requiring any intervention), and urinary tract infection.

Safety will be assessed based on adverse events reported throughout the study, clinical laboratory tests, vital signs, 12-lead electrocardiogram, physical examination, and the use of rescue medication. Prespecified adverse events include MACE, hypoglycaemic adverse events (requiring any intervention), and urinary tract infection (details listed in Additional file 1).

**Study oversight and organization**

Members of the Steering Committee also designed the study and are responsible for its conduction (details listed in Additional file 2). Significant adverse events (SAEs) occurring within 30 days after final administration of the study drug or after 30 days with a suspicion of association with the study drug, as well as all pregnancies, will be immediately reported to the Steering Committee and the sponsor by the investigator, in accordance with GCP.

**Statistical analysis**

***Sample size and power calculation***

The primary hypothesis of this study is that the SGLT2 inhibitor luseogliflozin can reduce cardiac load in patients with T2DM and HFpEF. Therefore, the primary outcome was the difference in change in BNP from baseline to 12 weeks between patients receiving luseogliflozin or voglibose. As of the start of recruitment in September 2015, no interventional study of the effect of SGLT2 inhibitors on heart failure in patients with T2DM has been reported. Therefore, we estimated that BNP change rate in the luseogliflozin group will be 30% lower as compared

with that in the globose group according to previous studies of the effect of renin-angiotensin-aldosterone system inhibitors on heart failure [11-13]. The standard deviation of the natural logarithmic transformation of BNP was estimated at 0.83, in reference to the PARAMOUNT study [13]. A minimum of 172 patients (86 patients per group) is required to provide 80% power with a two-sided α level of 0.05 by Student's t-test on the ratio of BNP change rate between the luseogliflozin and voglibose groups. With 10% of patients estimated to withdraw from participation during the study period, the final enrolment target was set at 190 patients (95 patients per group).

***Analysis plan***

In the efficacy analysis, the primary population comprises the Full Analysis Set (FAS), defined as all randomised patients who receive one dose of study drug and are followed up at least once. Patients with no BNP data and patients who withdraw or discontinue treatment will be excluded from the FAS. Missing values at 4, 12, and 24 weeks will be replaced by the last observed value for that variable (last observation carried forward). In the primary outcome analysis, baseline observation carried forward analysis will be also performed. Efficacy analysis will be performed according to the treatment to which patients are randomly assigned, based on the intention-to-treat analysis. The primary outcome analysis will be based on an analysis of covariance (ANCOVA) ($\alpha = 0.05$, level of significance) for the ratio of BNP change rate in the FAS. Adjusted covariates will include the assigned treatment (luseogliflozin, voglibose), baseline age (<65 or ≥65 years), baseline HbA1c (<8.0 or ≥8.0%), baseline BNP (<100 or ≥100 pg/ml), baseline renal function (eGFR ≥60 or <60 ml/min/1.73 $m^2$), use of thiazolidine or not at baseline, and presence or absence of AF and AFL at baseline as stratified factors of randomisation. Furthermore, BNP change rate, ratio of BNP change rate, and 95% confidence intervals will be

calculated. The same ANCOVA analysis as for the primary outcome will be performed for the ratio of BNP change rate at 4 weeks and 24 weeks between the two groups.

Prespecified subgroup analyses will be performed on the primary outcome using ANCOVA (covariates: assigned treatment and BNP at screening) in the following subgroups: baseline age (<65 or ≥65 years), baseline HbA1c (<8.0 or ≥8.0%), baseline BNP (<100 or ≥100 pg/ml), baseline renal function (eGFR ≥60 or <60 ml/min/1.73 $m^2$), use of thiazolidine or not at baseline, baseline body weight (<60 kg, ≥60 kg), and presence or absence of AF and AFL at baseline. Furthermore, exploratory analysis on the primary outcome will be performed in subgroups based on blood pressure, heart rate, waist circumference, cardiovascular risk factors (hypertension, T2DM, hyperuricemia, family history, and smoking), alcohol consumption, regular medication, and serum lipid levels (details listed in Additional file 3).

The key secondary outcomes, difference in E/e', left ventricular ejection fraction, body weight, and HbA1C at 12 weeks between the luseogliflozin and voglibose groups, will be analysed using the same ANCOVA as for the primary outcome. Subgroup analysis for the key secondary outcomes will be performed in the same subgroups as for the primary outcome analysis. The following secondary outcomes will be also analysed using the same analysis plan: E/e', left ventricular ejection fraction, body weight, and HbA1C at 4 and 24 weeks; and exploratory parameters at 4, 12, and 24 weeks.

For the safety analysis, the primary population is the Safety Analysis Set (SAFETY), defined as all patients who receive at least one dose of study drug. Although patients who withdraw without receiving study drug will be excluded from SAFETY, other patients who withdraw for any other reason will be included. The safety analysis will be performed according to the treatment administered to patients in practice, based on the as-treated analysis. Analysis of

SAEs (MACE, hypoglycaemia, and urinary tract infection) will be performed using the Cochran–Mantel–Haenszel test with stratification factors of age (<65 or ≥65 years), baseline HbA1c (<8.0 or ≥8.0%), baseline BNP (<100 or ≥100 pg/ml), baseline renal function (eGFR ≥60 or <60 ml/min/1.73 $m^2$), use of thiazolidine or not, and presence or absence of AF and AFL at screening.

All comparisons are planned, and the analyses will be two sided With P values <0.05 considered statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). The statistical analysis plan will be developed by the principal investigator and a biostatistician prior to the completion of patient recruitment and database lock.

## Ethics and dissemination

### *Ethics approval and consent to participate*

This study was approved by the Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences and the Okayama University Hospital Ethics Committee, as well as the ethics committee of each participating centre. This trial will be conducted in compliance with the Declaration of Helsinki. Trial registration: UMIN Clinical Trials Registry (UMIN-CTR), UMIN000018395.

### *Consent for publication*

All participants will provide written informed consent prior to participation.

### *Dissemination policy*

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise the research to clinicians and commissioners.

## Patient and public involvement

There is no patient and public involvement in this study.

**Study status**

Study enrolment was terminated at September 2018 and data collection was completed by the end of December 2018.

## Discussion

The MUSCAT-HF trial is an ongoing, multi-centre, randomised controlled trial designed to investigate the drug efficacy of luseogliflozin to reduce BNP in T2DM patients with HFpEF. Eligible participants will be randomised to receive luseogliflozin or voglibose in addition to their background medication for 24 weeks. The primary endpoint is the percentage change from baseline in BNP level after 12 weeks of treatment. This trial has the potential to provide novel clinical evidence regarding the treatment of HFpEF in patients with T2DM.

The EMPA-REG OUTCOME and CANVAS trials showed that the treatment of empagliflozin and canagliflozin, respectively, significantly reduced cardiovascular events in T2DM patients with higher cardiovascular risk [6 8]. Specifically, a 35% and 33% relative risk reduction in hospitalization for heart failure was observed in the EMPA-REG OUTCOME and CANVAS trials, respectively. Although a significant reduction in hospitalization for heart failure was clearly documented, the proportion of patients with heart failure and reduced or preserved ejection fraction was not reported precisely in either trials. Therefore, the therapeutic effect of SGLT2 inhibitors specifically in patients with heart failure has yet to be established. At present, HFpEF prognosis cannot be improved with the use of conventional drugs such as an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, or mineralocorticoid receptor blocker [14-17]. SGLT2 inhibitors therefore represent a promising strategy for the prevention of HFpEF and improvement of HFpEF outcome by improving left ventricular

diastolic function in patients with T2DM. A recent small prospective cohort study in 37 patients showed that canagliflozin improved left ventricular diastolic function within 3 months, although the data in terms of prognosis were limited [18]. Further, several clinical trials to investigate the effect of SGLT2 inhibitors in cardiovascular clinical hard endpoints in HFpEF patients with T2DM are ongoing (EMPEROR-Preserved; ClinicalTrials.gov Identifier: NCT03057951 and DELIVER; ClinicalTrials.gov Identifier: NCT0361921). Although our study focused on BNP as surrogate endpoint for worsening of heart failure, the results will provide the evidence for the drug efficacy of SGLT2 inhibitor on pathophysiological aspects in those patients.

In summary, emerging evidence suggests that SGLT2 inhibitors exert protective effects against cardiovascular events beyond their glucose-lowering capabilities, although further investigation of the mechanisms underlying these effects is warranted. The MUSCAT-HF trial, the results of which are expected to be published in 2019, will provide novel clinical insights into the treatment of patients with T2DM and HFpEF.

**Funding**

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**Contributions**

KE, TM, and HI contributed to the study design. KE, TM, KN, SS, MM, SN, AT, and HI contributed to data interpretation and the drafting of the manuscript. All authors read and approved the final manuscript.

**Competing interests**

KE, SS, MM, SN, and AT have no competing interests to declare. TM and KN has received honorarium from Novartis Pharmaceuticals (Basel, Switzerland). HI has received research funding and honorarium from Novartis Pharmaceuticals (Basel, Switzerland).

**Data statement**

All data are available upon request.

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## Figure Legends

Figure 1. Study design.

Arrows illustrate patients' flow and the timing of follow-up. Patients with type 2 diabetes mellitus are screened whether with heart failure with preserved ejection fraction or without (screening period, yellow arrow). One of the study drugs was administered to patients met inclusion criteria after collection of baseline data within one week after randomization (grey arrow). After administration, mandatory follow-up period is for 12 weeks (study follow-up period, blue arrow). After 12 weeks, expanding follow-up are continued in patients agreed with (Arrow with dotted line). During expanding follow-up, the change of an allocated drug was not allowed.

ECG, electrocardiogram

Figure 2. Assessments during the study period

369 Table 1. Detailed inclusion and exclusion criteria

| **Inclusion criteria** |
|---|
| 1) Diagnosis of T2DM and left ventricular ejection fraction >45% with current or previous symptoms of heart failure (dyspnoea on effort, orthopnoea, or leg oedema)<br>2) Inadequately controlled T2DM in patients who have received diet and exercise therapy, a lifestyle modification program, and hypoglycaemic medications based on standard guidelines of the Japan Diabetes Society<br>3) Age >20 years<br>4) Provision of written informed consent prior to participation |
| **Exclusion criteria** |
| 1) BNP <35 pg/ml<br>2) Use of alpha-glucosidase inhibitors, SGLT2 inhibitors, glinides, or high-dose sulfonylurea<br>3) Renal insufficiency (eGFR <30 ml/min/1.73m$^2$)<br>4) Left ventricular ejection fraction <45%<br>5) History of severe ketoacidosis or diabetic coma within 6 months prior to participation<br>6) Serious infection or severe trauma, or perioperative patients<br>7) Type 1 diabetes mellitus<br>8) Poorly controlled T2DM (HbA1c >9.0%)<br>9) Uncontrolled hypertension (systolic blood pressure >160 mmHg)<br>10) History of stroke, myocardial infarction, or severe cardiovascular disease with hospitalization within 6 months prior to participation<br>11) Women who are pregnant or breastfeeding<br>12) Allergy to either investigation product |

| |
|---|
| 13) Other medical reason at the investigator's discretion |

T2DM, type 2 diabetes mellitus; BNP, brain natriuretic peptide; SGLT2, sodium/glucose cotransporter 2; eGFR, estimated glomerular filtration rate; HbA1C, haemoglobin A1C

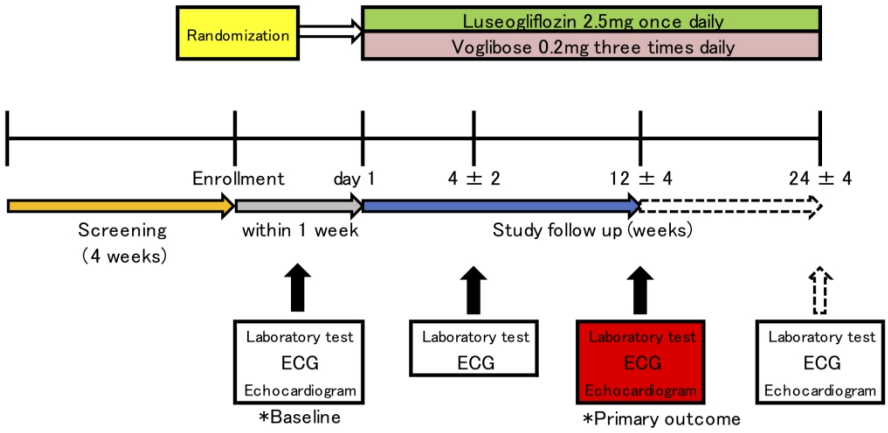


Fig1

190x100mm (300 x 300 DPI)

| Assessment | Enrollment | Study follow-up period | | Expanding follow-up (if possible) |
|---|---|---|---|---|
| | | 4 weeks (visit 29 ± 14 days) | 12 weeks (visit 85 ± 28 days) | 24 weeks (visit 169 ± 28 days) |
| Medical examination | X | X | X | X |
| Written informed consent | X | | | |
| Clinical symptoms | X | X | X | X |
| Adverse events | | X | X | X |
| Treatment discontinuation | | X | X | X |
| Vital signs | X | X | X | X |
| Body weight | X | X | X | X |
| Waist circumference | X | | X | X |
| Laboratory tests | X | X | X | X |
| Electrocardiogram | X | X | X | X |
| Echocardiography | X | | X | X |

Fig2

190x100mm (300 x 300 DPI)

**Additional file 1.**

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

- **Discontinuance criteria**

| | |
|---|---|
| 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).

**Additional file 2.** Study organization

Steering Committee

Hiroshi Ito (Chair), Kazufumi Nakamura, Toru Miyoshi, Kentaro Ejiri, Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences, Okayama, Japan; Satoru Sakuragi, Iwakuni Clinical Center, Yamaguchi, Japan; Mitsuru Munemasa, Okayama Medical Center, Okayama, Japan; Seiji Nanba, Okayama Rosai Hospital, Okayama, Japan; Tomosato Suezawa, Takamatsu Red Cross Hospital, Kagawa, Japan; Atsushi Takaishi, Mitoyo General Hospital, Kagawa, Japan.

Statistical consulting

Tetsutaro Hamano, P4 Statistics Co. Ltd., Tokyo, Japan.

Clinical Event Committee

Masayuki Doi, Kagawa Prefectural Central Hospital, Kagawa, Japan; Takefumi Oka, Tsuyama Central Hospital, Okayama, Japan.

Data Monitoring

Given that invasive intervention will not be performed in this study, data monitoring is not planned.

**Additional file 3**. Selected and exploratory subgroups

| | Variables | Category |
|---|---|---|
| Prespecified subgroup analyses | • Age (years) | <65<br>≥65 |
| | • HbA1c (%) | <8.0<br>≥8.0 |
| | • BNP (pg/nL) | <100<br>≥100 |
| | • eGFR (mL/min/1.73m$^2$) | <60<br>≥60 |
| | • Thiazolidine use | Yes<br>No |
| | • Body weight (kg) | <60<br>≥60 |
| | • AF/AFL | Yes<br>No |
| Exploratory analyses | • Blood pressure (mmHg)<br>• Heart rate (bpm)<br>• Waist circumference (cm)<br>• Coronary risk factors<br>• Other drugs<br>• Lipid profile<br>• Diabetes duration | |

HbA1C, hemoglobin A1C; BNP, brain natriuretic peptide, eGFR; estimated glomerular filtration rate; AF, atrial fibrillation; AFL, atrial flutter

1


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | ItemNo | Description | PageNo |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | N/A |
| Protocol version | 3 | Date and version identifier | N/A |
| Funding | 4 | Sources and types of financial, material, and other support | 15 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 15 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 15 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 15 |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5 |
| | 6b | Explanation for choice of comparators | 5 |

| | | | |
|---|---|---|---|
| Objectives | 7 | Specific objectives or hypotheses | 5 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5, 6 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 9 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 6, 7 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 7 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | N/A |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 8, 9 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 9 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8, 9 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | N/A |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 6, 7 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 6, 7 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | N/A |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | N/A |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 10 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 10, 11 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 10, 11 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 9 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | N/A |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 12 |

| | | | |
|---|---|---|---|
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 12 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 12 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | N/A |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 15 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 15 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | N/A |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | N/A |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | N/A |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N/A |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

# Correction: *The effect of luseogliflozin and alpha-glucosidase inhibitor on heart failure with preserved ejection fraction in diabetic patients: rationale and design of the MUSCAT-HF randomised controlled trial*

Ejiri K, Miyoshi T, Nakamura K, *et al*. The effect of luseogliflozin and alpha-glucosidase inhibitor on heart failure with preserved ejection fraction in diabetic patients: rationale and design of the MUSCAT-HF randomised controlled trial. *BMJ Open* 2019;9:e026590. doi: 10.1136/bmjopen-2018-026590.

This article was previously published with an error.

Under 'Finding' section, the authors have stated, "This study is funded by Novartis Pharmaceuticals (Basel, Switzerland)."

The correct sentence is as follows:

"This study is funded by Novartis Pharma K. K."



*BMJ Open* 2019;**9**:e026590corr1. doi:10.1136/bmjopen-2018-026590corr1