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Rationale and design of the EMPA-ELDERLY trial: a randomised, double-blind, placebo-controlled, 52-week clinical trial of the efficacy and safety of the sodium–glucose cotransporter-2 inhibitor empagliflozin in elderly Japanese patients with type 2 diabetes

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ABSTRACT

Introduction Elderly people (≥65 years) with type 2 diabetes mellitus (T2DM) are becoming increasingly prevalent, notably in Japan. As cardiovascular (CV) risk increases with age and sodium–glucose cotransporter-2 (SGLT2) inhibitors reduce CV risk, elderly patients with T2DM are increasingly likely to be prescribed these glucose-lowering drugs. There is controversy surrounding the effects of SGLT2 inhibitors on muscle mass, particularly in elderly patients for whom loss of muscle is especially undesirable; however, robust evidence on this important issue is lacking. Consequently, we have designed a clinical trial of the SGLT2 inhibitor empagliflozin in elderly Japanese patients with T2DM (Empagliflozin in Elderly T2DM Patients (EMPA-ELDERLY)) to assess its effects on body composition as well as glycaemic control. EMPA-ELDERLY will be the first randomised clinical trial of an SGLT2 inhibitor in elderly patients with T2DM to evaluate effects on skeletal muscle mass, muscle strength and physical performance concurrently.

Methods and analysis EMPA-ELDERLY is a randomised, double-blind, placebo-controlled, parallel-group clinical trial to be conducted in Japan. Patients with T2DM aged ≥65 years are eligible if they are Japanese with a body mass index of ≥22 kg/m^2 and glycated haemoglobin (HbA1c) levels from ≥7.0% to ≤10.0% from either diet and exercise alone or treatment with oral glucose-lowering drugs. Approximately 128 participants will be randomised 1:1 to once per day, oral, double-blind treatment with empagliflozin 10 mg or matching placebo for 52 weeks. The primary endpoint is the change in HbA1c level from baseline at week 52. Secondary endpoints include changes from baseline to 52 weeks in body composition, including muscle mass and body fat, measured by bioelectrical impedance analysis, as well as skeletal muscle index, grip strength and time in the five-time chair stand test. Other endpoints include changes in patient-reported outcomes (including quality of life), cognitive function and safety.

Strengths and limitations of this study

► This is the first randomised clinical trial designed to evaluate the effects of a sodium–glucose cotransporter-2 inhibitor on muscle mass, strength and physical performance in elderly patients with type 2 diabetes.

► The robust methodology employed in the trial includes the use of multiple study sites, central randomisation, a placebo control arm and double-blinding.

► The results may be limited to elderly patients who are physically similar to Japanese patients, such as East Asian patients.

Ethics and dissemination We will submit the trial results to conferences and peer-reviewed journals.
Trial registration number NCT04531462.

INTRODUCTION

The global prevalence of diabetes mellitus has grown substantially over recent decades, and its prevalence also increases with age.[1] An estimated 135.6 million people with diabetes worldwide were aged at least 65 years in 2019 (comprising 29.3% of the 463 million patients in total), and this prevalence is predicted to increase across all regions to total 195.2 million by 2030 and 276.2 million by 2045.[1] Therefore, management of diabetes in elderly patients is assuming greater significance globally. In Japan, which is one of the super-ageing countries, approximately 20 million people suffer from either diabetes mellitus or

pre-diabetes,[2] and it is estimated that approximately 71% of hospitalised patients and outpatients with type 2 diabetes mellitus (T2DM) are ≥65 years old and over half are ≥75 years old.[3]

There are some important considerations for the management of T2DM in elderly patients. According to guidelines from the Japan Diabetes Society,[4] the International Diabetes Federation[5] and the American Diabetes Association,[6] older patients with T2DM have higher rates of comorbidities such as chronic kidney disease, vascular disease and heart failure, compared with younger patients, as well as geriatric syndromes such as sarcopenia, frailty and cognitive impairment/dementia. Elderly patients with T2DM also have a higher risk of hypoglycaemia for several reasons, including the reduced excretion of glucose-lowering drugs that results from declining kidney function.[4 6] As hypoglycaemia is associated with adverse outcomes, clinical guidelines for treatment of elderly patients with T2DM emphasise the importance of avoiding hypoglycaemia.[4–11]

Sodium–glucose cotransporter-2 (SGLT2) inhibitors are a class of oral glucose-lowering drugs that reduce hyperglycaemia by inhibiting SGLT2 in the proximal tubule of the kidney, which is responsible for reabsorbing filtered glucose, thus leading to glucosuria.[12 13] Despite improving glycaemic control by eliciting glucose loss in the urine, SGLT2 inhibitors have a low risk of hypoglycaemia,[12] likely because decreases in plasma glucose levels are partially offset by increases in glucagon levels and hepatic glucose production.[14]

Partly because of calorie loss via glucosuria, SGLT2 inhibitors reduce body weight to a modest degree,[12 13] which is usually a desirable effect in T2DM. This body weight reduction appears to be primarily attributable to loss of adipose tissue but may also be accompanied by some loss of lean body mass, seemingly from skeletal muscle and water content, although heterogeneity is seen between studies.[15] Given the lower muscle mass in elderly patients compared with younger patients, a Japanese expert committee recommends to use SGLT2 inhibitors cautiously in elderly patients with T2DM aged over 65 years with geriatric syndromes such as sarcopenia and in those over 75 years.[16] It is estimated that approximately 15% of Japanese patients with T2DM aged ≥65 years have sarcopenia.[17]

Interim data from a large, ongoing, postmarketing, observational study that includes elderly Japanese patients with T2DM—2790 (36.6%) and 802 (10.5%) of whom were aged ≥65 and ≥75 years, respectively, at baseline—showed that empagliflozin, a highly selective SGLT2 inhibitor, improved glucose control without serious hypoglycaemia or sarcopenia in routine clinical practice.[18] However, there was no comparator in this study, and the effect of the drug on muscle mass and strength was not evaluated. The effect of other SGLT2 inhibitors on muscle mass in elderly patients prone to sarcopenia and frailty has not been specifically evaluated in randomised clinical trials anywhere in the world, to the best of our knowledge, despite the high prevalence of elderly patients with T2DM.

Given the importance of evaluating the efficacy and safety of SGLT2 inhibitors in elderly patients with T2DM, as well as their potential effects on skeletal muscle mass, muscle strength and physical performance, we have designed a randomised clinical trial of Empagliflozin in Elderly T2DM Patients (EMPA-ELDERLY), which is being conducted in Japan as East Asian patients may be particularly susceptible to muscle loss due to lower body mass index (BMI) than Western patients. We report here the study design and methodology of the EMPA-ELDERLY trial.

METHODS AND ANALYSIS
Study design
EMPA-ELDERLY is a randomised, double-blind, placebo-controlled, parallel-group, 52-week clinical trial to be conducted at approximately 20 sites in Japan. The trial is designed to investigate the long-term glycaemic efficacy and safety of empagliflozin in elderly Japanese patients with T2DM, as well as its potential effects on body composition, physical activity and quality of life. The trial is registered on ClinicalTrials.gov.

Patients
Japanese patients with T2DM aged ≥65 years are eligible for inclusion in the trial if they have a BMI of ≥22 kg/m^2 and insufficient glycaemic control (glycated haemoglobin (HbA1c) levels from ≥7.0% to ≤10.0%) from either diet and exercise alone or treatment with oral glucose-lowering drugs. If patients are already receiving glucose-lowering drugs with risk of severe hypoglycaemia (eg, sulfonylureas or glinides), HbA1c has to be ≥7.5% for those aged <75 years and ≥8.0% for those aged ≥75 years, based on recommendations in the Japanese Clinical Practice Guideline for Diabetes.[4]

Patients are excluded if they have any of the following characteristics: uncontrolled hyperglycaemia (fasting plasma glucose level>200 mg/dL); treatment with SGLT2 inhibitors, insulin or glucagon-like peptide-1 receptor agonists within 12 weeks prior to informed consent; impaired cognitive ability as supported by the Japanese Version of the Mini-Mental State Examination (MMSE-J) and verified by the investigator at screening; acute coronary syndrome, stroke or transient ischaemic attack within the 12 weeks prior to informed consent; impaired renal function, defined as estimated glomerular filtration rate of <45 mL/min/1.73 m^2; and history of diabetic ketoacidosis. In addition, in order to exclude individuals with possible sarcopenia, patients are not permitted to participate if they have low muscle strength, defined as handgrip strength of <28 kg for men and <18 kg for women. These criteria are based on the 2019 Consensus Update from the Asian Working Group for Sarcopenia.[19]

The full inclusion and exclusion criteria are shown in box 1.

Randomisation, investigational product administration and blinding
After screening, all eligible patients are assigned to placebo treatment for 2 weeks in order to assess their

Box 1   Inclusion and exclusion criteria for the EMPA-ELDERLY trial

Inclusion criteria

► Japanese* patients with T2DM diagnosis prior to informed consent.
► HbA1c ≥7.0% and ≤10.0% for patients at screening.
  – If the patient is on treatment with OADs potentially associated with severe hypoglycaemia (eg, sulfonylurea or glinide), the following HbA1c ranges apply:
  – HbA1c ≥7.5% and ≤10.0% for ages ≥65 and <75.
  – HbA1c ≥8.0% and ≤10.0% for age ≥75.
► Patients on diet and exercise regimen who are drug-naïve† or treated with any OAD except GLP-1 receptor agonists and SGLT2 inhibitors. Antidiabetic therapy has to be unchanged for 12 weeks prior to randomisation (any TZD therapy has to be unchanged for ≥18 weeks prior to informed consent).
► Age ≥65 years with informed consent.
► BMI ≥22 kg/m^2 at screening.
► Male or postmenopausal female patients.
► Patient signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

Exclusion criteria

► Uncontrolled hyperglycaemia with a fasting glucose level of >200 mg/dL (>11.1 mmol/L) during the run-in period.
► Treatment with insulin within 12 weeks prior to informed consent.
► Impaired cognitive ability as supported by MMSE-J (defined as ≤23) and verified by the investigator at screening.
► ACS (STEMI, non-STEMI and unstable angina pectoris), stroke or transient ischaemic attack within 12 weeks prior to informed consent.
► Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT) or ALP>3×ULN during screening and run-in period.
► Impaired renal function, defined as an eGFR of <45 mL/min/1.73 m^2 (severe renal impairment, MDRD formula) during the screening and run-in period.
► Low grip strength defined as <28 kg for men or as <18 kg for women.
► Short length of calf circumference defined as <34 cm for men or 33 cm for women at screening.
► Inability to perform five times chair stand test according trial protocol.
► Already confirmed diagnosis of sarcopenia (based on Asian Working Group for Sarcopenia 2019 algorithm[19]).
► History of diabetic ketoacidosis.
► Contraindications to empagliflozin according to the Japanese label.
► Disorders causing haemolysis or unstable red blood cells.
► Any previous (within 2 years prior to informed consent) or planned bariatric surgery (or any other weight loss surgery) or other gastrointestinal surgery that induces chronic malabsorption.
► Medical history of cancer (except for resected non-invasive basal cell or squamous carcinoma) and/or treatment for cancer within the last 5 years.
► Treatment with antiobesity drugs within 12 weeks prior to informed consent or any other treatment at the time of screening (ie, surgery and aggressive diet regimen (eg, low-carbohydrate diet)) leading to unstable body weight.
► Current treatment with systemic steroids (other than inhaled or topical steroids) at informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM.
► Known or suspected allergy or hypersensitivity to trial products or related products (eg, SGLT2 inhibitors).
► Alcohol or drug abuse prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to trial procedures or trial drug intake, in the opinion of the investigator.
► Intake of an investigational drug in another trial within 30 days prior to screening or participation in the follow-up period of another trial (participation in observational studies is permitted).
► Any other clinical condition that, in the opinion of the investigator, would jeopardise patient's safety while participating in this clinical trial.

*Patient with parents who are Japanese.
†No antidiabetes drugs for ≥12 weeks prior to informed consent.
ACS, acute coronary syndrome; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; ICH-GCP, International Conference on Harmonisation Good Clinical Practice; MDRD, Modification of Diet in Renal Disease study; MMSE-J, Japanese version of the Mini-Mental State Examination; OAD, oral antidiabetes drug; SGLT2, sodium–glucose cotransporter-2; SGOT, serum glutamic–oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; STEMI, ST-elevation myocardial infarction; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione; ULN, upper limit of normal.

adherence to the study drug and to train them to use a self-monitoring of blood glucose device. Following the placebo run-in period, patients still meeting the inclusion criteria and not meeting any exclusion criteria will be randomised in a 1:1 ratio to receive once per day oral treatment with empagliflozin 10 mg or matching placebo in a double-blind manner for 52 weeks (figure 1).

Randomisation will use a third-party, web-based, interactive response system to assign patients to treatment, and will be stratified by HbA1c level (<8.5% vs ≥8.5%) and age (<75 years vs ≥75 years). The randomisation list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation of study drug will be both reproducible and non-predictable. The block size will be documented in the clinical trial report. Patients, investigators, central reviewers and personnel involved in trial conduct or analysis will be blinded to the randomised treatment assignments until after the database is locked. Access to the randomisation code will be kept restricted
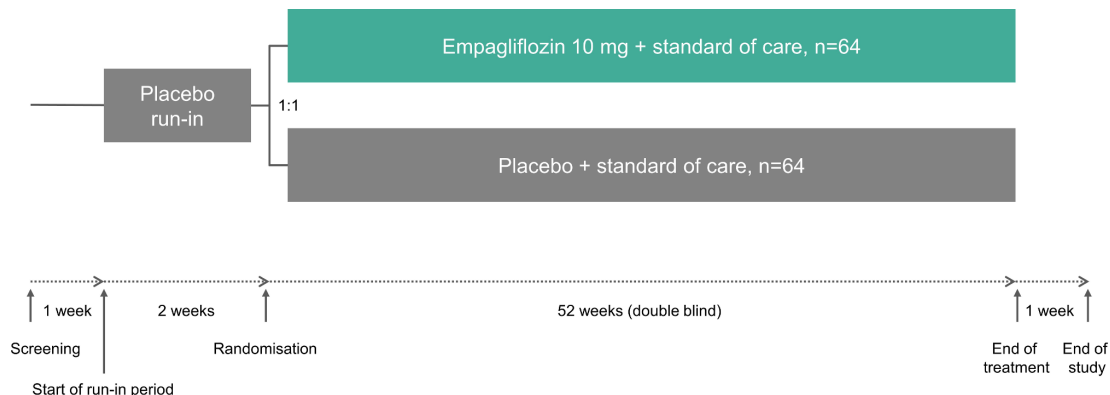
Figure 1 Design of the EMPA-ELDERLY (Empagliflozin in Elderly T2DM Patients) trial.

until its release for analysis. Emergency unblinding will be available to the principal investigator via the interactive response system; this is for use in an emergency when the identity of the trial drug must be revealed to the investigator to provide appropriate medical treatment or otherwise assure safety of trial participants.

Although empagliflozin is available in two dose strengths in Japan and other countries (10 and 25 mg), only the 10 mg dose, which is the predominantly prescribed dose in Japan, will be used in EMPA-ELDERLY. This dose selection is in line with ongoing postmarketing surveillance of elderly patients with T2DM receiving empagliflozin in Japan: most patients who started treatment with 10 mg continued at that dose for over a year without uptitration.[18]

Endpoints

The primary endpoint of EMPA-ELDERLY is the change in HbA1c level from baseline at 52 weeks after beginning treatment with empagliflozin or placebo. Secondary endpoints include change from baseline at week 52 in the following parameters: muscle mass, body fat mass, lean body mass (fat-free mass), total body water and bone mineral content (estimated bone mass). These parameters will be measured by bioelectrical impedance analysis (BIA). Change from baseline at week 52 in skeletal muscle index is also a secondary endpoint, which will be calculated by dividing the limb muscle mass measured by BIA by the square of the height (m^2). Additional secondary endpoints are the changes from baseline at week 52 in grip strength and time in the five-time chair stand test.

A further endpoint is the proportion of patients achieving the following target HbA1c levels at 52 weeks: HbA1c <7.5% for those ≥65 to<75 years of age using sulfonylureas or glinides, HbA1c <8.0% for those aged ≥75 years using sulfonylureas or glinides, and HbA1c <7.0% for those not using sulfonylureas or glinides.

Additional endpoints include change from baseline to week 52 in the following parameters: quality of life (assessed by the EuroQoL 5-dimension 5-level (EQ-5D-5L) and The Older Persons and Informal Caregivers Survey– Short Form (TOPICS-SF) 2017 instruments), free-living physical activity (measured with a physical activity

monitor), calorie intake (estimated by a food frequency questionnaire) and cognitive function (evaluated using the MMSE-J). Adverse events, including hypoglycaemia, and changes in laboratory parameters will also be assessed. The following adverse events are prespecified as being of special interest based on pre-existing data on SGLT2 inhibitors: hepatic injury, diabetic ketoacidosis, decreased renal function and lower-limb amputation.

Assessments and schedule

The demographic and clinical characteristics of patients will be recorded at screening, as will their medical history and concomitant diagnoses and therapies. Following randomisation (week 0), patients will be asked to return to their trial site at weeks 4, 12, 24, 36 and 52. A double-blind study drug will be dispensed at all visits except week 52. Physical examination and measurement of body weight and vital signs will be conducted at weeks 0, 24 and 52. At all visits, HbA1c will be measured and diet/exercise counselling will be provided. Blood and urine samples for laboratory testing will be collected at all visits except week 24 after a full overnight fast (nothing to eat or drink except water for ≥10 hours) and before administration of concomitant glucose-lowering drugs and investigational drug. The following assessments will be conducted at baseline and week 52: BIA, grip strength, chair stand test, EQ-5D-5L, TOPICS-SF, free-living physical activity monitoring, food frequency questionnaire and the MMSE-J. Adverse events will be recorded at all visits and during telephone contact at week 50.

During randomised treatment with the study drug, patients will continue to receive standard of care. Glycaemic rescue medication for hyperglycaemia can be prescribed by study investigators for patients with fasting glucose levels of >200 mg/dL (>11.1 mmol/L) in at least two measurements on different days. Any glucose-lowering drugs may be used for glycaemic rescue except SGLT2 inhibitors.

Statistical analysis

It is calculated that 64 patients per treatment group (128 in total) are required to provide 90% power to detect a difference of 0.5% in HbA1c change from baseline

between the empagliflozin and placebo groups after 52 weeks of treatment, using a two-sided test with a significance level (α) of 5%. This calculation assumes an SD of 0.85% for change in HbA1c and that approximately 3% of patients will not be eligible for analysis of HbA1c change from baseline due to lack of a postbaseline HbA1c value.

The primary endpoint will be evaluated for the full analysis set, which will consist of all randomised patients who were treated with at least one dose of trial drug, had a baseline HbA1c assessment and at least one on-treatment HbA1c assessment. This primary analysis will employ a mixed model for repeated measures (MMRM) that includes fixed classification effects for treatment, gender, baseline renal function, visit and visit-by-treatment interaction, and a linear covariate for baseline HbA1c and age. Only data observed while patients are on treatment will be included in the analysis (the observed cases approach), with missing data handled implicitly by the MMRM rather than being imputed. All HbA1c values measured after introduction of glycaemic rescue medication will be classified as missing in the primary analysis. Planned sensitivity analysis of the primary endpoint will include HbA1c values after introduction of glycaemic rescue medication. Secondary endpoints and further endpoints will be evaluated in an exploratory manner and no hypothesis testing is planned.

Adverse events and laboratory data will be analysed for all randomised patients who were treated with at least one dose of study drug (the treated set). Adverse events will be classified using the version of the Medical Dictionary for Drug Regulatory Activities that is current when the database is locked. All adverse events beginning between the start of double-blind treatment and 7 days after the last dose of trial medication will be evaluated; the latter time point is the period after the last dose of empagliflozin with measurable drug levels and/or pharmacodynamic effects still likely to be present. The analyses will be purely descriptive.

Study oversight and organisation
EMPA-ELDERLY is sponsored by Nippon Boehringer Ingelheim Co., and Eli Lilly K.K. Nippon Boehringer Ingelheim Co., the manufacturer of empagliflozin, is also responsible for operational implementation of the study, data management and statistical analysis. EMPA-ELDERLY has been designed jointly by independent academic investigators and sponsor-employed scientists and physicians with relevant clinical and methodological expertise. The coordinating investigator (Daisuke Yabe, MD; Gifu University, Gifu, Japan) is responsible for coordinating the principal investigators at the different sites participating in this trial. Contract research organisations will be involved in the interactive response technology for randomisation, central laboratory analyses and data monitoring. The trial began on 5 October 2020 and is anticipated to finish on 21 November 2022.

Patient and public involvement
Patients and the public were not involved in the design of this trial.

ETHICS AND DISSEMINATION
EMPA-ELDERLY has been approved by independent ethics committees or institutional review boards at each site. Written informed consent must be obtained from each patient prior to their participation in the trial (online supplemental figure S1). The trial will be conducted according to the ethical principles of the Declaration of Helsinki and in accordance with the Guideline for Good Clinical Practice from the International Conference on Harmonisation and the Japanese Good Clinical Practice (Ministry of Health and Welfare Ordinance No. 28, 27 March 1997), Good Post-Marketing Study Practice and Good Vigilance Practice regulations.

We will submit the trial results to conferences and peer-reviewed journals. The sponsor of the EMPA-ELDERLY trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents and patient-level clinical study data. Researchers are invited to submit inquiries via the website (https://trials.boehringer-ingelheim.com).

DISCUSSION
EMPA-ELDERLY is the first randomised clinical trial of an SGLT2 inhibitor in elderly patients with T2DM designed to evaluate effects on glycaemic control, skeletal muscle mass, muscle strength and physical performance. In the landmark EMPA-REG OUTCOME trial, empagliflozin reduced the risk of cardiovascular (CV) death, all-cause mortality, hospitalisation for heart failure and nephropathy, all of which are more common in elderly patients than younger patients.[20] In addition, this CV and renal risk reduction with empagliflozin was consistent across age groups (<65, 65–<75 and ≥75 years).[21] Thus, the results of EMPA-ELDERLY will be highly important due to the likelihood that elderly patients with T2DM—who have greater risk of cardiorenal–metabolic disease and mortality than younger patients—will be increasingly prescribed SGLT2 inhibitors such as empagliflozin, especially in countries such as Japan, where there is already a high prevalence of elderly patients with T2DM.

Moderate weight loss with empagliflozin and other SGLT2 inhibitors has been observed in overweight or obese patients with T2DM, in whom weight loss from reduction of adipose tissue would be desirable. Indeed, this body weight reduction appears to be mostly due to loss of adipose tissue but may also involve reductions in lean body mass, seemingly from skeletal muscle and water content, although these findings have not been uniform across studies to date.[15 22] In a 104-week clinical trial comparing empagliflozin with the sulfonylurea glimepiride, almost 90% of the empagliflozin-elicited weight loss was due to a reduction in fat mass.[23]

Some short-term (<24 week), non-randomised, mostly uncontrolled clinical studies in Japanese patients have suggested that loss of skeletal muscle mass occurred during treatment with the SGLT2 inhibitors ipragliflozin, luseogliflozin and tofogliflozin[24–30] (although other similar studies did not observe this association, as reviewed elsewhere[15]). Furthermore, 1 week of empagliflozin treatment in Japanese patients in a small, open-label, single-arm study was associated with a slight but significant loss of skeletal muscle mass, among other effects.[31] However, 24-week, randomised, open-label clinical trials of dapagliflozin (n=54) or ipragliflozin (n=49) added to existing diabetes medications versus those medications alone did not find loss of skeletal muscle tissue with these SGLT2 inhibitors in Japanese patients.[32 33] Data in elderly patients susceptible to sarcopenia and frailty, however, still remain limited as none of the studies performed so far were dedicated trials in the elderly.

EMPA-ELDERLY is being conducted in Japan, as East Asian patients tend to have lower BMI than their Western counterparts[34] and thus may be particularly susceptible to muscle loss. To help elucidate the potential effect of SGLT2 inhibitors on muscle in elderly patients, EMPA-ELDERLY will evaluate changes in muscle strength (via assessment of handgrip strength), physical performance (via five-time chair stand test) together with body composition (via BIA) as prespecified secondary endpoints. Handgrip strength is a surrogate measure of upper-limb strength in the elderly, while the five-time chair stand test is commonly used for evaluating lower limb function and physical performance. Both measures are used for the assessment of possible sarcopenia in primary healthcare settings in Asia, based on guidelines from the Asian Working Group for Sarcopenia 2019.[19] EMPA-ELDERLY may be the first clinical trial of an SGLT2 inhibitor to follow these guidelines. A non-randomised study suggested that grip strength increased in both male and female Japanese patients during treatment with SGLT2 inhibitors,[35] which is at odds with the studies described previously suggesting loss of muscle with these drugs,[24–26 36] reinforcing the need for the EMPA-ELDERLY trial. Although EMPA-ELDERLY excludes patients with low handgrip strength in order to avoid enrolling individuals with possible sarcopenia, its evaluation of handgrip strength, five-time chair stand test, and muscle mass before and after treatment with the SGLT2 inhibitor is likely to hold some relevance for sarcopenic patients. EMPA-ELDERLY will also evaluate changes in calorie intake using food frequency questionnaires. An inverse association between calorie intake and sarcopenia was seen in a cross-sectional study in elderly Japanese patients,[37] while longitudinal studies showed increased calorie intake during treatment with empagliflozin and the SGLT2 inhibitor canagliflozin.[38 39]

The patient's sense of well-being and perceived quality of life are increasingly recognised as important outcomes of diabetes care.[40–42] Accordingly, EMPA-ELDERLY will assess patient-reported outcomes using the EQ-5D-5L and TOPICS-SF 2017 instruments. The EQ-5D-5L health questionnaire is a validated and widely used instrument for measuring health outcomes consisting of five questions on different dimensions of health and one visual analogue scale on current health. TOPICS-SF is a newer instrument designed to assess physical and mental health and quality of life in the elderly, for use in evaluating patient-reported outcomes in geriatric care.[43] TOPICS-SF includes questions on general health, pain, cognitive function, mood, activities of daily living and social activities.

In conclusion, EMPA-ELDERLY is the first randomised clinical trial of an SGLT2 inhibitor in elderly patients with T2DM to evaluate both muscle mass and muscle strength. This study has been designed to add to the general evidence base for use of SGLT2 inhibitors, as well as to specifically evaluate effects on body composition and muscle strength, given the uncertainty about the impact of SGLT2 inhibitors on muscle in the elderly. The results will be particularly important as the cardiorenal–metabolic benefits seen with empagliflozin in the EMPA-REG OUTCOME trial[20]—including risk reductions in elderly participants[21]—mean that increasing numbers of elderly patients with T2DM are likely to be prescribed this SGLT2 inhibitor over the next few years.

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