



A registry-based randomised trial comparing an SGLT2 inhibitor and metformin as standard treatment of early stage type 2 diabetes (SMARTTEST): Rationale, design and protocol

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ABSTRACT

Aim: SGLT2 inhibitors have been shown to reduce cardiovascular and renal complications in type 2 diabetes (T2D) patients at high cardiovascular risk. Metformin is currently widely used as initial monotherapy in T2D but lacks convincing data to show that it reduces risk of complications. We aim to compare the SGLT2 inhibitor dapagliflozin and metformin as first-line T2D medication with regard to development of complications in a registry-based randomised controlled trial.

Methods: The SGLT2 inhibitor or metformin as standard treatment of early stage type 2 diabetes (SMARTTEST) trial will enrol 4300 subjects at 30–40 study sites in Sweden who will be randomised 1:1 to either metformin or dapagliflozin. Participants must have T2D duration <4 years, no prior cardiovascular disease, and be either drug-naïve or on monotherapy for T2D.

Results: The primary endpoint is a composite of all-cause death, major adverse cardiovascular events and occurrence or progression of microvascular complications (retinopathy, nephropathy, diabetic foot lesions). Secondary endpoints include individual components of the primary endpoint, start of insulin therapy, risk factor biomarkers, patient-reported outcome measures, and cost-effectiveness analysis. Outcomes will primarily be assessed using nationwide healthcare registries.

Conclusions: The SMARTTEST trial will investigate whether dapagliflozin is superior to metformin in preventing complications in early stage T2D. ([Clinicaltrials.gov](https://clinicaltrials.gov) identifier NCT03982381, EudraCT 2019-001046-17).

1. Introduction

The prevalence of diabetes in 2019 was estimated at 9.3% of the global population, about 460 million people, and type 2 diabetes (T2D) accounts for around 90% of cases.¹ Furthermore, the prevalence is estimated to increase to about 700 million people by the year 2045.¹ The heavy disease burden of diabetes is largely due to its long-term vascular

complications² that are expected to become more common as both the prevalence and average duration of diabetes will continue to increase,³ and the absolute global economic burden of diabetes is projected to rise to between 2.1 and 2.5 trillion US dollars by 2030 (2.1–2.2% of global GDP).⁴ Therefore, it is of critical importance to both individuals living with the disease and to society as a whole to explore novel treatment strategies that might decrease the risk of complications already at an

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early disease stage.

The biguanide drug metformin has been used clinically in T2D as an oral glucose-lowering drug (GLD) for several decades.⁵ According to the latest joint European-American guidelines on management of T2D, it is recommended as first-line therapy, alongside comprehensive lifestyle changes including weight management and physical activity.⁶ The widespread use of metformin as the initial GLD of choice is due to its several favourable properties, such as efficient glucose-lowering effect, low cost, weight neutrality and a good safety profile, not least lack of hypoglycaemia when used as monotherapy.⁷ However, the scientific support for the assumption that metformin de facto reduces the risk of cardiovascular disease is questionable. The largest study to date that provided evidence of protective effects was the UK Prospective Diabetes Study (UKPDS) from 1997. In this study, a subset of 753 overweight patients was randomised to either conventional diet intervention ($n = 411$) or metformin ($n = 342$), and metformin led to a relative risk reduction of 32% for any diabetes-related endpoint, 42% for diabetes-related death and 36% for all-cause mortality.⁸ There were also less diabetes-related events in those receiving metformin compared to those receiving sulphonylurea or insulin treatment.⁸ Systematic reviews of the totality of the evidence have not conclusively shown protective effects of metformin on clinically important outcomes when compared to diet or placebo^{9,10} or other classes of GLDs.¹¹

In the past few years, several important, large-scale cardiovascular outcome trials have shown beneficial effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors in patients with T2D and either established or high risk of cardiovascular disease, primarily reductions in heart failure hospitalisation and decline in renal function.^{12–16} However, their effects on clinical outcomes at earlier stages of diabetes is still unknown. Consequently, it is imperative to study the potential of monotherapy with SGLT2 inhibitors compared with metformin as first-line treatment in early stage type 2 diabetes.

We here describe the ongoing SGLT2 inhibitor or metformin as standard treatment of early stage T2D (SMARTTEST) trial, which aims to determine whether dapagliflozin treatment, as compared to metformin, is beneficial in patients with early T2D in promoting progression-free survival. The trial is designed as a registry-based randomised controlled trial (RRCT), which represents a novel concept in the field of diabetes trials and is further described below.

2. Materials and methods

2.1. Study design

This is a multicentre, parallel-group, open-label RRCT conducted in Sweden to assess superiority of dapagliflozin over metformin as first-line treatment for early-stage T2D. Outcomes to be assessed include occurrence of macro- and microvascular events, mortality, risk markers for comorbidities, safety, quality of life and healthcare costs. An overview of the study is presented in Fig. 1. Study enrolment began in September

2019. A total of 4300 patients with T2D will be enrolled at 30–40 local study sites and randomised in a 1:1 manner to either metformin 1000–3000 mg/day or dapagliflozin 10 mg/day as monotherapy. Follow-up will mainly take place within the context of regular follow-up visits at patients' regular healthcare providers and outcome data will be collected from nationwide healthcare registries. The trial is event-driven and will be stopped when 844 events of the primary efficacy endpoint have occurred. Based on prior data of event rates in similar populations, this is estimated to take around 4 years but since the trial is event-driven, may also take a longer time.

The study protocol was approved by the Swedish Medical Products Agency and by the Swedish Ethical Review Authority (Dnr 2019–01747, 2020–02824, 2020–06164). The protocol complies with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. The trial is registered with www.clinicaltrials.gov (NCT03982381) and with the European Medicines Agency (EudraCT 2019–001046-17).

2.2. Study population

Eligible subjects must have been diagnosed with T2D less than 4 years before the enrolment date. Subjects may be either drug-naïve or on current monotherapy with any oral GLD except SGLT2 inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists. Ongoing or previous treatment for more than 4 weeks in total with insulin, SGLT2 inhibitors, GLP-1 receptor agonists or combinations of any diabetes medications constitutes an exclusion criterion. Subjects will be classified into two strata according to their medication use at baseline. Stratum A will comprise those who are drug-naïve or have previously received treatment with any diabetes medication for less than 4 weeks in total. Stratum B will comprise those with ongoing or previous oral GLD monotherapy for more than 4 weeks in total (except use of SGLT2 inhibitors or GLP-1 receptor agonists). Each of the two treatment strata must comprise a minimum of 25% of the study subjects ($n = 1075$). Furthermore, study participants must not have a history of established cardiovascular disease, which is defined as previous diagnosis of myocardial infarction, angina pectoris, stroke, heart failure, lower extremity arterial disease or ongoing diabetic foot ulcers. Also, renal function must be sufficient to allow initiation of either metformin or dapagliflozin treatment. All inclusion and exclusion criteria are listed in Table 1.

2.3. Study procedures

Enrolment is carried out at a baseline physical visit to or a video consultation with a local study site. Informed consent is obtained by the local investigator who must be a physician trained in Good Clinical Practice (GCP). Medical history, physical examination and laboratory results are recorded in an electronic case report form (eCRF) at this visit by the local investigator. Laboratory measurements collected less than

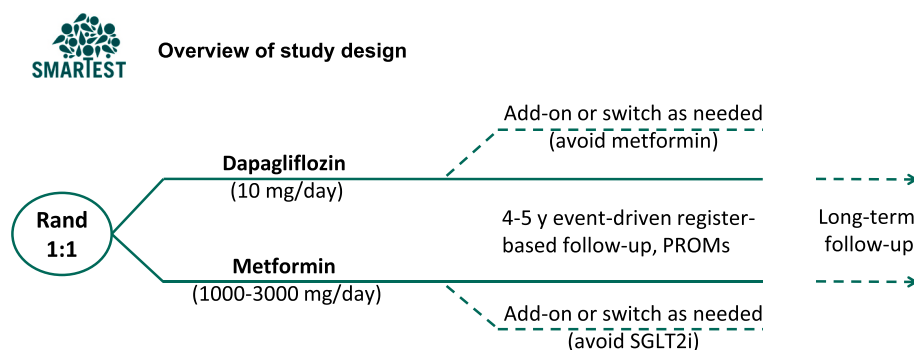


Fig. 1. Schematic overview of study design and treatment arms. PROMs, patient-reported outcome measures. Rand, randomisation. Y, years.

Table 1
Inclusion and exclusion criteria of the SMARTTEST trial.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Diagnosis of T2D (according to WHO criteria) with less than 4 years duration • Age > 18 years 	<ul style="list-style-type: none"> • Known or suspected other form of diabetes than type 2 • Ongoing or > 4 weeks in total of any previous treatment with: insulin, GLP-1 receptor agonists, SGLT2 inhibitors or combination of any diabetes medications • Medical need for any specific GLD treatment, e.g. insulin due to marked hyperglycaemia • HbA1c >70 mmol/mol for patients on monotherapy, >80 mmol/mol in drug naïve
<ul style="list-style-type: none"> • BMI 18.5–45 kg/m² • Diabetes medication: <ul style="list-style-type: none"> a) Drug-naïve, or newly started or short temporary medication^a or b) Ongoing or previous monotherapy with oral GLD medication for more than 4 weeks in total^b • Participation in the Swedish National Diabetes Register (NDR) and accepting individual data collection from this register and those of the National Board of Health and Welfare and Statistics Sweden • Signed informed consent 	<ul style="list-style-type: none"> • Contraindication to either metformin or dapagliflozin, or any unacceptable risk with either treatment as assessed by the investigator • History of established cardiovascular disease: diagnosis of myocardial infarction, angina pectoris, stroke, lower extremity arterial disease, heart failure or ongoing diabetic foot ulcers. • Any serious illness or other condition with short life expectancy (<4 years) • Renal impairment (eGFR <60 ml/min/1.73m² according to CKD-EPI) • Any condition, as judged by the investigator, that suggests that the patient will be non-compliant or otherwise unsuitable to study medication or study participation. E.g. serious psychiatric or alcohol or substance abuse disorders. • Pregnancy or breastfeeding, women of childbearing potential (including perimenopausal women who have had a menstrual period within 1 year) without adequate contraception during any part of the study period • Involvement in the planning and/or conduct of the study • Ongoing participation in another clinical trial

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; GLP-1, glucagon-like peptide 1; HbA1c, glycated haemoglobin; WHO, World Health Organization.

^a Stratum A: no GLD treatment, except for any ongoing or previous treatment for a maximum of 4 weeks in total.

^b Stratum B.

12 weeks before start of study treatment may be used as baseline data if the local investigator deems the subject to be in a stable clinical state.

In order to make trials more cost-effective by allowing remote monitoring of consent forms and allow video inclusions, we developed an electronic informed consent system (Fig. 2). Using safe identifiers widely available in Sweden for both study participants (BankID) and healthcare personnel (HSAID and SITHS), the system ensures that only the valid version of the participant information is online and available for signing, ensures the correct signing sequence (participant signs before the physician), prevents signing of non-valid versions or multiple signatures to the same version, and allows for re-consent to updated versions if required. The online consent database contains participant information versions, digital signatures and certificates, participant's and physician's names, timestamps, and site, and can be monitored online. The system is available as open-source code and through collaboration with Uppsala University.

Enrolment using video consultations utilises the novel electronic informed consent system and the site's ordinary video consultation system (prevalent throughout Swedish healthcare). Necessary baseline visit clinical data will then be obtained by the investigator in collaboration with non-study caregivers (these are all examinations and measures routine to all physicians caring for diabetes patients). Our study is part of a pilot project coordinated by the Swedish Medical Products Agency aiming to establish conditions for how clinical trials may be carried out in a decentralised and virtual manner.¹⁷

After subject eligibility has been established, the eCRF is submitted to the electronic database via the eCRF system and randomisation occurs according to a computer-generated randomisation list. Randomisation is done using large permuted blocks within each of stratum A and B and with a 1:1 ratio to dapagliflozin or metformin. Results of randomisation are immediately provided to the local investigator who then prescribes the randomised drug and informs the patient. Dapagliflozin is prescribed at a fixed dose of 10 mg/day, whereas metformin is prescribed at a dose of 1000–3000 mg/day according to the subject's glycaemic control.

Treatment will not be blinded to either the investigator, patient or other healthcare providers and will be registered in the subject's electronic medical records (EMR). The decision not to blind treatment was made for reasons of feasibility and to keep the study design as pragmatic as possible, allowing subjects to subsequently be followed up at their primary care units (PCU) according to standard clinical practice. At the central study level, the steering committee and persons involved in data review and analysis will be blinded to study treatment until database lock, to exclude risk of bias from unblinded decisions related to the design and conduct of the trial. Although individual investigators will know the treatment of their own patients, only the data monitoring committee (DMC) will have access to the entire study data subdivided by study treatment.

In case samples for laboratory measurements are taken after the visit or if there is delay in obtaining the results, randomisation may occur later, at the most 3 weeks after the visit. Patients may then be informed about treatment allocation via telephone or at an extra visit. Results of retinopathy screening will also be recorded, and if the latest fundus photography was more than 18 months prior to the visit, a referral will be sent to an ophthalmology clinic to arrange for a new fundus examination within 3 months of the visit to be considered as baseline data.

The investigator will arrange for follow-up at the patient's PCU by sending a referral letter containing detailed information about the study and the study treatment. In some cases the patient's study site and PCU may be the same unit. Clinical follow-up visits will take place at the patient's PCU according to national and local guidelines, which includes at least yearly visits to a diabetes nurse and physician. Treating physicians may at any time according to their own clinical judgment decide to discontinue treatment, switch to other GLDs, add other GLDs or modify other non-diabetic medications. They are instructed in the referral letter to avoid switching to or adding the comparator study drug, unless there are specific indications for the patient to receive an SGLT2 inhibitor or metformin. Further follow-up by the study site will only consist of a telephone visit every 12 months to renew the study drug prescription

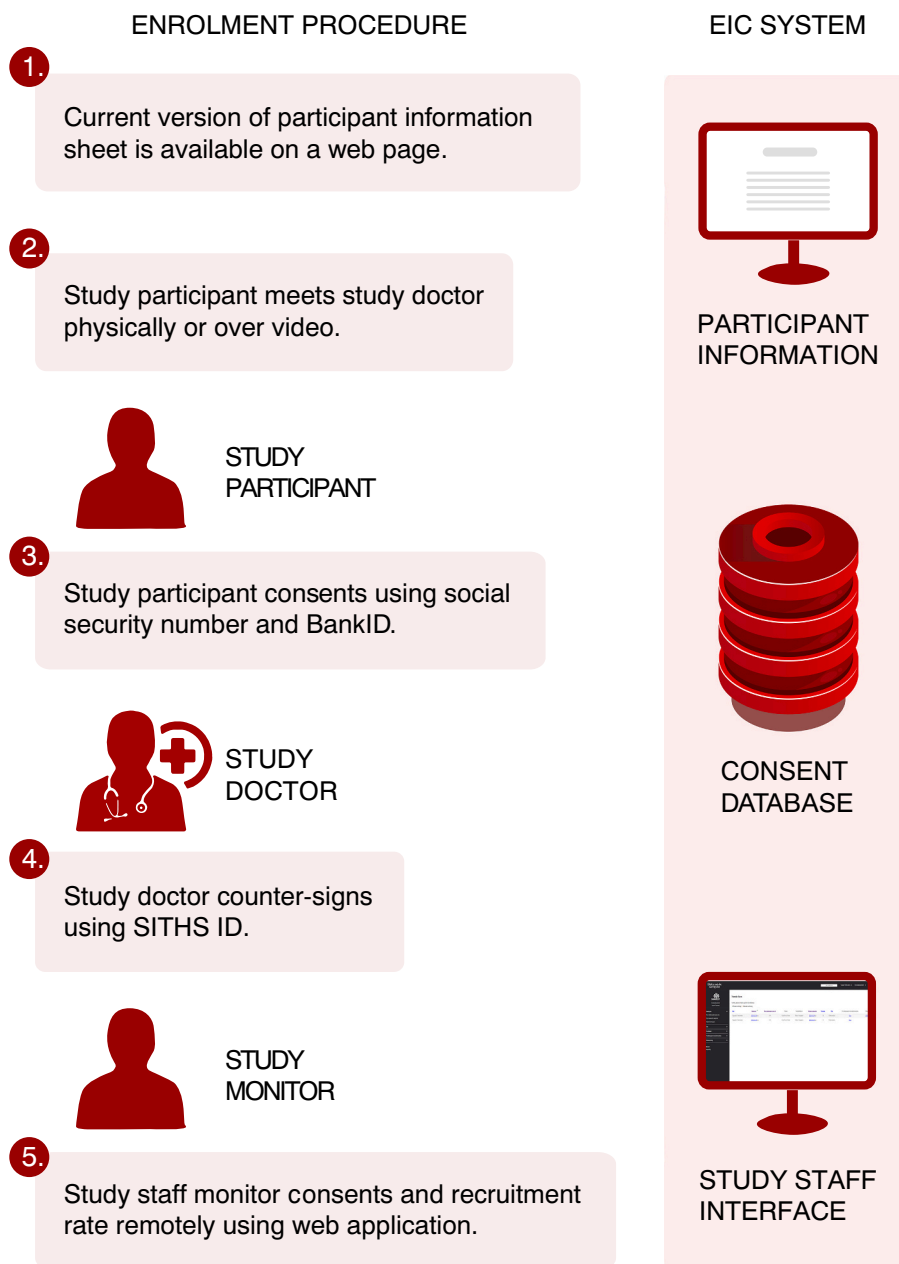


Fig. 2. Overview of participant inclusion using an electronic informed consent system. This is an alternative to traditional, paper-based informed consent which may also be employed in physical inclusion visits.

until the end of the study. Data concerning clinical outcomes will be collected from nationwide healthcare registries and patient-reported outcome measures (PROMs) will be assessed, described further in detail below. At end of study, when 844 events of the primary efficacy endpoint have occurred, a telephone visit will be scheduled within 2 weeks to inform study participants that the study has ended. Study drug treatment will be discontinued and the patient's primary care physician will thereafter decide on appropriate GLD treatment. Subjects who cannot participate in the telephone visit will receive written information by mail instead.

2.3.1. Discontinuation of study treatment and withdrawal from study

Study participants may discontinue active participation and study drug treatment at any time with no influence on further clinical care and treatment. The data collection from registers will continue and be included in the final intention-to-treat analysis. However, if participants

withdraw informed consent or otherwise inform study staff that they do not agree to onward data collection, this will be stopped.

2.4. Data collection

The data flow in the study is shown in Fig. 3 and the main data sources including national registries are summarized in Table 2.

2.4.1. eCRF and data obtained at enrolment or from EMR

At the baseline visit, the subject's weight, height and blood pressure are measured and recorded in the eCRF. Data concerning demographics, medical history, concomitant medications and laboratory results are also recorded in the eCRF, using the patient's EMR as a source of information. The following laboratory measurements are recorded: haemoglobin, white blood cell and platelet count, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, potassium, serum

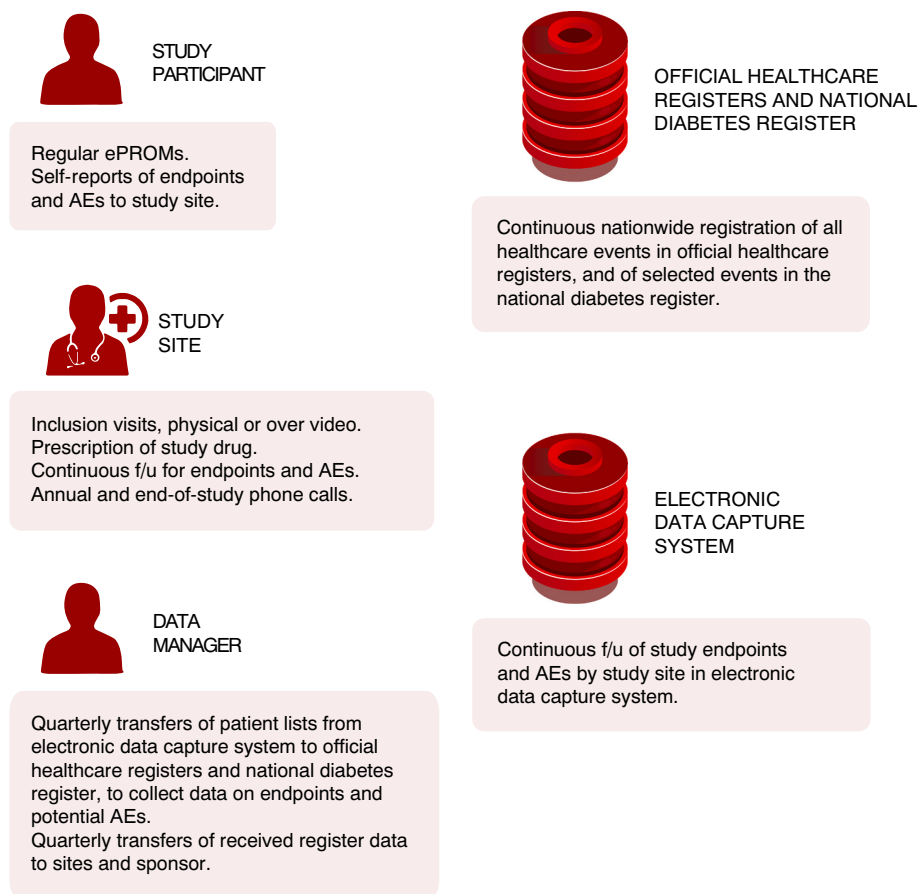


Fig. 3. Overview of data flow and management in the SMARTEST study. AE, adverse events. ePROMs, electronic patient-reported outcome measures. F/u, follow-up.

creatinine, eGFR and urinary albumin-creatinine ratio.

2.4.2. Swedish National Diabetes Register (NDR)

Virtually all primary and secondary healthcare providers in Sweden that treat patients with diabetes submit data to this nationwide registry. In 2019, the registry was estimated to provide a coverage of around 87% of all diabetes patients in Sweden.¹⁸ Data are submitted no less than every 12 months and include diabetes type, lifestyle factors (BMI, physical activity, smoking), complications (retinopathy, nephropathy, foot lesions) and risk factor measurements (HbA1c, blood pressure, blood lipids, eGFR, urinary albumin-creatinine ratio). Monitoring of microvascular complications will take place as per national guidelines in primary care. Retinopathy is assessed by means of fundus photography and is graded according to standardised international classification as none, mild, moderate, severe or proliferative (numerically 1–5 in increasing severity). Follow-up examinations are typically scheduled by ophthalmology clinics at maximum three-year intervals, or more frequently if clinically warranted. Nephropathy is graded in the NDR as either none, microalbuminuria or macroalbuminuria (numerically 1–3 in increasing severity). If eGFR is below 60 ml/min/1.73m², CKD stage also has to be provided (2–5). Foot lesions are graded as none, neuropathy/angiopathy, previous foot ulcer or ongoing foot ulcer/other severe foot lesion (e.g. Charcot foot, osteomyelitis, critical ischaemia, gangrene) and this is graded numerically as 1–4 in increasing severity.¹⁹

2.4.3. National Patient Register

This register contains data from all inpatient and outpatient secondary care contacts involving a physician. Coverage is nationwide and close to 100%. The register is updated monthly. Data include date of admission/visit, length of stay and primary as well as secondary

diagnosis according to the International Classification of Diseases, Tenth Revision (ICD-10) and Diagnosis Related Groups (DRG). All data are stored with the National Board of Health and Welfare. Data will be assessed continuously during follow-up and contribute to efficacy and safety endpoints.

2.4.4. Swedish Population Register

Upon the death of an individual in Sweden, the physician who confirmed the death is obliged to submit a death certificate within 4 days to the Swedish Tax Agency. The Population Register hosted by this agency is updated continuously and will be used to assess death of any cause.

2.4.5. Cause of Death Register

Within 4 weeks of a person dying in Sweden, the physician who confirmed the death is required to submit a cause-of-death certificate to the National Board of Health and Welfare. The information regarding cause of death is based on the clinical details surrounding the death, prior medical history and autopsy results, if undertaken. The cause of death is stored in this register, and this will be used in the study collect information.

2.4.6. Swedish Prescribed Drugs Register

All Swedish pharmacies are bound by law to report all expedited prescriptions to the Swedish eHealth Agency, which then submits this information to the Prescribed Drugs Register hosted by the National Board of Health and Welfare.

2.4.7. Patient-reported outcome measures

The assessment of PROMs is essential for evaluating the efficacy of

Table 2
Data sources including national registries.

Data source	Outcomes
eCRF/EMR	Baseline anthropometric and lab measurements
NDR	Follow-up lab measurements; degree of retinopathy, nephropathy, foot disease
NPR	Secondary care in- and outpatient contacts, e.g. hospitalisations, MACE
SPR	Mortality
CoDR	Cause of death
PDR	Drug treatment
RAND-36 and DTSQ	Patient-reported outcome measures

eCRF, electronic case report form; EMR, electronic medical records; NDR, Swedish National Diabetes Register; NPR, National Patient Register; SPR, Swedish Population Register; CoDR, Cause of Death Register; PDR, Prescribed Drug Register; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

novel GLDs and assessing the glucose-lowering effect related to for example HbA1c levels.²⁰ Improvement in patient satisfaction has previously been shown in patients treated with incretin-based therapies and SGLT2 inhibitors.^{21,22} PROMs are collected using two questionnaires, RAND-36 and the Diabetes Treatment Satisfaction Questionnaire (DTSQ). RAND-36 will be completed by all subjects at baseline, at 1 year and at 2 years after study enrolment. Subjects may choose to complete the questionnaire either digitally or on paper. The DTSQ will be completed in a subset of around 400 study participants at selected sites, only on paper at baseline, 3 months and 1 year of follow-up. These questionnaires are well-validated for the assessment of health-related quality of life in general and as related to diabetes treatment satisfaction, respectively.^{23,24}

2.5. Study outcomes

The primary objective of the trial is to determine whether treatment with dapagliflozin, as compared to metformin, is beneficial in patients with early T2D to promote progression-free survival. The primary composite efficacy endpoint consists of all-cause death, major adverse cardiovascular events (MACE; myocardial infarction, stroke, heart failure) and microvascular events defined as occurrence or progression of retinopathy, nephropathy or diabetic foot lesions. Microvascular complications are graded according to the Swedish National Diabetes

Table 3
Primary and secondary efficacy and safety outcomes of the SMARTTEST trial.

Primary efficacy composite endpoint	Secondary efficacy composite endpoints
<ul style="list-style-type: none"> Time to first of: <ol style="list-style-type: none"> All-cause death Major adverse cardiovascular events (MACE; myocardial infarction, stroke, heart failure) Microvascular events (occurrence or progression of retinopathy, nephropathy, or diabetic foot lesions) 	<ul style="list-style-type: none"> Modified composite endpoint with weighted components 1–3 of primary endpoint based on their individual degrees of severity (falling in that order). Ordinal analysis at 2 years of follow-up. Time to first event among: individual components of the primary endpoint or initiation of insulin treatment.
	<p>Secondary efficacy endpoints</p> <ul style="list-style-type: none"> Time to first of: non-fatal myocardial infarction, stroke, heart failure, unstable angina or cardiovascular death Time to first of: heart failure or cardiovascular death Time to event of death Time to first microvascular event; occurrence or progression of retinopathy, nephropathy, diabetic foot lesions Time to initiation of insulin treatment Time to any treatment failure, defined as add-on or switch to another GLD Change in: 1) HbA1c 2) total cholesterol 3) LDL cholesterol 4) HDL cholesterol 5) Triglycerides 6) Urinary albumin/creatinine ratio 7) BMI 8) Systolic blood pressure 9) Diastolic blood pressure Diagnosis-based costs for all health care during study period plus medication cost Results from RAND-36 and DTSQ questionnaires.
<p>Primary safety endpoint</p> <ul style="list-style-type: none"> Occurrence of serious adverse events (all non-elective hospitalisations or other serious adverse events). 	<p>Secondary safety endpoint</p> <ul style="list-style-type: none"> Occurrence of diabetes- and treatment-specific serious adverse events (hospitalisations for diabetes, severe hypoglycaemia, ketoacidosis, lactic acidosis, diabetic coma, non-traumatic amputations, fractures).

Register categories defined above. Either new occurrence of a microvascular complication or, if present at baseline, an increase in its severity (i.e. progressing from a lower to a higher grade) will be considered a microvascular event.

Key secondary outcomes includes an ordinal analysis of primary endpoint components after 2 years of follow-up and a composite of primary endpoints and initiation of insulin treatment. Other secondary outcomes include separate outcomes of the primary composite endpoint, changes in various risk factors, rates of treatment failure, patient-reported outcomes and cost-effectiveness analysis of the study drugs. Safety endpoints will consist of serious adverse events (SAE). All outcomes are presented in detail in Table 3.

There will be no adjudication of register-based endpoint event collection. A pre-defined hierarchy of data sources will be used to resolve any possible cases of discrepancy between different data sources. However, subgroup analyses may be performed in certain geographical regions or patient groups to validate register data versus EMR and to obtain more detailed information on specific outcomes. Such analyses may include assessment of fundus photography and laboratory measurements obtained in regular health care. The National Patient Register will provide results on primary and secondary endpoints by pre-defined ICD-10 codes for the various diagnoses. Definitions of results obtained from the NDR are the same as used in regular NDR reporting by health care units. For the Prescribed Drug Register, dispensed drugs are reported using Anatomical Therapeutic Classification (ATC) codes (Table 2).

2.5.1. Ancillary studies

The pragmatic study design and large cohort make it possible to conduct several ancillary studies. It has been suggested that SGLT2 inhibitors may at least partly exert their beneficial effects through inhibition of the sympathetic nervous system, which was recently shown in a mouse model,²⁵ though clinical data are scarce.²⁶ The ancillary study SMARTTEST-HRV will assess the effects of dapagliflozin and metformin on heart rate variability, a commonly used surrogate of autonomic nervous system activity, after 3 months and 1 year of follow-up in some 200 participants. Measurements will consist of 15 min resting ECG recordings in both supine and standing positions. Furthermore, the effects of genetic, epigenetic and metabolomic factors as well as biomarkers on the development of complications and efficacy of the study drugs will be further explored by drawing blood samples at baseline, 3 months and 1

year of follow-up. This project is termed SMARTTEST-PRECISION.

We are also in the process of starting a study on myocardial function in a subset of participants, with echocardiography performed at baseline and at 12 months of treatment, to identify possible differences between dapagliflozin and metformin treatment with respect to occurrence of early signs of left ventricular systolic or diastolic dysfunction.

Eye, kidney and foot complications are reported in the NDR but there have been no studies performed to validate those NDR data. We plan to do this by comparing EMR and fundoscopic images with NDR data in a smaller cohort of patients. Occurrence of cardiovascular complications including venous thrombosis will also be examined in this cohort.

2.5.2. Safety reporting

Since the safety profiles of the study drugs are well-documented, mandatory reporting of adverse events (AE) is restricted to SAEs that are not part of the primary efficacy endpoint and any AE that is the reason for withdrawal from the study or discontinuation of a study drug. Information on SAEs may be collected in four different ways: (i) diagnosis codes will be retrieved every three months from the National Patient Register, (ii) subjects are asked to contact the study site to report any SAE, (iii) any healthcare providers involved in a possible SAE are asked to notify the study site (patients carry leaflets with this information) and (iv) at yearly and end-of-study telephone visits. While reporting non-serious AEs is not mandatory, study participants and their healthcare providers may report these to the local investigator should they wish to and may also ask for advice on clinical management in such cases.

2.5.3. Data monitoring committee

The DMC evaluates serious adverse event rates and other outcomes at regular intervals, at least every 12 months, throughout the study. They are provided with unblinded data and have access to all study data. If there is convincing evidence of harm in the dapagliflozin compared to the metformin treatment arm, and this is considered to jeopardise participants' safety, the committee will recommend study discontinuation. However, this will not be applicable vice versa as metformin is the current standard therapy. Preparation of data for the DMC will be performed by independent experts not otherwise involved in the trial. All other persons involved in data review and analysis will remain blinded to study treatment throughout the study until database lock.

2.6. Statistical considerations

2.6.1. Sample size

Using the Schoenfeld formula, the total number of events needed to detect a hazard ratio of 0.8 for dapagliflozin compared to metformin at a two-sided alpha level of 0.05, with 90% power, was calculated to 844 events for the primary composite efficacy endpoint. For the two key secondary composite efficacy endpoints, the power to detect a similar effect is estimated to 90% or above. No adjustment in sample size will be done due to drop-outs since endpoints will be collected from registries providing near-complete coverage of events. Based on event rates from NDR and previous studies^{27–30} the annual event rate for the primary composite endpoint is estimated to be 7% and based on these assumptions, the aim is to recruit 4300 patients for a follow-up of approximately 24–48 months (mean 36 months), until 844 primary composite events have been observed.

2.6.2. Statistical analyses

Analyses will be performed according to an intention-to-treat approach. Exploratory on-treatment analyses, including Prescribed Drug Register data, may be performed at a later stage. The primary endpoint and all other time-to-event endpoints will be analyzed using Cox regression adjusted for previous diabetes medication (naïve/monotherapy), current smoking at baseline (yes/no), sex, and age as a linear covariate on the log-hazard scale, and presented as hazard ratios with

95% confidence intervals and *p*-values. We expect complete follow-up using register data, but any known loss to follow-up will be handled as censoring. Missing adjustment variables will be imputed as the arithmetic mean.

At 2 years of follow-up, ordinal regression of the individual components of the primary endpoint (i.e. the first key secondary endpoint), weighted based on severity, will be carried out using a proportional odds model with the same adjustment variables as for the primary outcome. Any patients with less than 2 years of follow-up at end of study are excluded from this analysis.

Multiplicity in outcomes is handled by gatekeeping by the primary endpoint which must be significant at $p < 0.05$ (two-sided) for claims to be made for key secondary endpoints. Other secondary endpoints will be analyzed in an exploratory manner.

No interim analyses will be performed. Subgroup and interaction analyses to assess homogeneity of effect will be performed for the primary and key secondary outcomes. Pre-specified subgroups are defined by age, diabetes duration, HbA1c, eGFR, BMI, previous diabetes medication (naïve/monotherapy, i.e. the two randomisation strata), sex (male/female), and pre-existing diabetes complications (none/any of retinopathy, nephropathy or diabetic foot lesion). In addition, pre-defined continuous interaction analyses include age, diabetes duration, eGFR, BMI and HbA1c. For metformin the dose levels will also be monitored and a possible impact on outcomes will be explored.

Statistical analyses will be performed using SAS software, SAS Institute Inc., Cary, NC, USA. The full statistical analysis plan will be compiled after patient recruitment has finished, before central unblinding.

3. Discussion

The recently launched SMARTTEST trial will evaluate the effect of the SGLT2 inhibitor dapagliflozin as monotherapy in patients with T2D at an early stage with no manifest macrovascular complications. In contrast to the previous large-scale SGLT2 inhibitor trials which largely included patients with established cardiovascular disease¹² or at high cardiovascular risk,^{14,16} our study sample will consist of patients with no established cardiovascular disease and it is anticipated that many subjects will have a low-to-intermediate cardiovascular risk. This is important as several observational studies have shown that a large proportion of unselected T2D patients would not have been eligible for inclusion in any of the cardiovascular outcome trials, thus limiting the external validity of these studies for general T2D patient populations.^{31–34} Furthermore, the relationships of treatment with SGLT2 inhibitors and some microvascular complications remain unclear and warrant further investigation. For example, in the case of retinopathy, some observational data have suggested a beneficial effect of SGLT2 inhibitors,³⁵ but this has not been conclusively shown in RCTs³⁶ and clearly there is a need for more data. The impact of SGLT2 inhibitors on diabetic foot disease remains controversial, with canagliflozin unexpectedly showing an increase in risk of amputation in the CANVAS program,¹⁴ though the subsequent CREDESCENCE trial showed no increase in risk¹⁵ and neither did the other large-scale SGLT2 inhibitor trials.³⁷ Our trial will not only monitor amputation rates but also assess the progression of diabetic foot lesions as an outcome.

Large simple trials are RCTs designed to quickly enrol a large number of patients in a short time by simplifying and reducing study procedures “per patient” in the clinic. RRCT designs using routinely collected patient data and automated prospective patient identification provide an efficient method for large simple trials. The RRCT is a strong pragmatic clinical trial approach as it utilises standardised prospectively designed data collection. Benefits of an RRCT study design as compared to a traditional prospective randomised controlled trial include the ability to enrol a large number of patients in a relatively short time, a possibility of indefinite follow-up, and substantially lower costs.³⁸ Sweden has an abundance of public registries with a very high level of coverage and so

is well-suited to perform such trials. This has been demonstrated by several Swedish RRCTs in the field of interventional cardiology which have been published in recent years.^{39–41} With our primary intention-to-treat analyses we do not expect issues with confounding. However, exploratory on-treatment analyses may do so by introducing selection bias.

To the best of our knowledge, the SMARTTEST trial is the first RRCT within the field of diabetes. In the SMARTTEST trial, we will use a combination of the national diabetes quality registry NDR along with other mandatory healthcare registries to collect data on a wide range of outcomes. This will also provide an opportunity for ancillary studies to examine the validity of the NDR by comparing NDR data with patients' EMRs for some outcomes such as retinopathy and nephropathy. The registry-based design will also allow for future long-term follow-up of the study cohort. With this trial, we have further added to the strengths of the Swedish clinical trial landscape by developing an electronic informed consent system that can be monitored online, and that allows enrolment using video consultations. This will cut costs and bolster recruitment rates and representativeness from areas previously overlooked in RCTs.

The study started recruitment in the autumn of 2019. The unforeseen circumstances of the COVID-19 pandemic have hampered recruitment, partly due to a greater difficulty in reaching potential study participants and partly due to difficulties in expanding the number of study sites as many PCUs face a great share in tackling the COVID-19 burden. Nonetheless, by May 2021, some 500 patients had been included at around 20 study sites across Sweden. Around 30% were drug-naïve at inclusion and in the group with previous monotherapy, virtually all were on metformin. It is estimated that an additional 18 months of recruitment time will be required in order to reach the goal of 4300 study participants.

4. Conclusion

The SMARTTEST trial will evaluate the effect of dapagliflozin compared to metformin to prevent diabetes-related complications at an early stage of T2D in a real-world setting. The registry-based study design is pragmatic and will allow collection of data regarding a wide range of complications and other effects.

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CRedit authorship contribution statement

Johan Sundström: Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Robin Kristófi:** Writing – original draft, Investigation. **Ollie Östlund:** Formal analysis, Data curation, Writing – review & editing, Supervision. **Louise Bennet:** Investigation, Writing – review & editing. **Björn Eliasson:** Investigation, Writing – review & editing. **Stefan Jansson:** Investigation, Writing – review & editing. **Janeth Leksell:** Investigation, Writing – review & editing. **Kristina Almy:** Investigation, Writing – review & editing. **Martin Lundqvist:** Investigation, Writing – review & editing. **Jan W. Eriksson:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

JS reports ownership in companies providing services to Itrim, Amgen, Janssen, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Bayer, Pfizer and AstraZeneca, outside the submitted work.

BE reports personal fees (expert panels, lectures) from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Navamedic, Novo Nordisk, RLS Global, and grants and personal fees from Sanofi, all outside the submitted work.

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RK, OÖ, LB, SJ, JL, KA and ML declare no conflicts of interest.

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Appendix A. Supplementary material

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