DECLARE Dapagliflozin Effect on CardiovascuLAR Events
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes

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ObjectivesPrimary objectiveThe primary objective is to determine the effect of dapagliflozin relative to placebo oncardiovascular outcomes when added to current background therapy in patients with type 2diabetes mellitus (T2DM) with either...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45088

Source
ToetsingOnline

Brief title
DECLARE

Condition

- Other condition
- Diabetic complications

Synonym
cardiovascular disease, diabetes

Health condition

cardiovasculair overlijden, myocard infarct en ischemische beroerte

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: AstraZeneca BV

Intervention

Keyword: cardiovascular events, dapagliflozin, SGLT2 inhibitor, type 2 diabetes mellitus

Outcome measures

Primary outcome

The primary efficacy variable is the time to first event included in the

composite endpoint of CV death, MI, or ischemic stroke.

Secondary outcome

Secondary efficacy is time to secundary event variables.

Study description

Background summary

Cardiovascular disease is the major cause of mortality and an important cause of morbidity in patients with type 2 diabetes mellitus (T2DM).
Dapagliflozin is expected to have consistent effects on glycemic control in a wide spectrum of patients with T2DM, whether used as monotherapy at an early

stage of disease or in combination with other oral anti-diabetes drugs and/or insulin at a later stage. In addition, dapagliflozin has been shown to have a positive effect on cardiovascular risk factors such as blood pressure, body weight, and visceral adipositas. Based on these data, dapagliflozin might be expected to lower cardiovascular risk in patients with T2DM.

Study objective

Objectives
Primary objective
The primary objective is to determine the effect of dapagliflozin relative to placebo on
cardiovascular outcomes when added to current background therapy in patients with type 2
diabetes mellitus (T2DM) with either established cardiovascular disease or at least two
cardiovascular risk factors.

This objective will be evaluated in two steps. The first step will determine if dapagliflozin is
non-inferior to placebo for the incidence of the composite endpoint of cardiovascular death,
myocardial infarction (MI), or ischemic stroke assessed with a non-inferiority margin of 1.3.
If this is met the second step will determine if dapagliflozin reduces the incidence of the coprimary
endpoints: the composite of cardiovascular death, myocardial infarction (MI), or ischemic stroke and the composite of hospitalization for heart failure or CV death compared to
placebo.

Secondary objective
The secondary objective is to determine whether treatment with dapagliflozin compared with
placebo when added to current background therapy in patients with T2DM with either
established cardiovascular disease or at least two cardiovascular risk factors in addition to T2DM
will result in a reduction of:
* Renal composite endpoint: Confirmed sustained *40% decrease in eGFR to eGFR <60
ml/min/1.73m2 and/or ESRD (dialysis *90 days or kidney transplantation, confirmed
sustained eGFR <15ml/min/1.73m2) and/or renal or CV death
* All-cause mortality

Safety objectives

Safety and tolerability will be assessed from overall adverse events, serious adverse events,
adverse events of special interest, and laboratory test results. The assessment will include an
evaluation of the incidence of adjudicated bladder cancer and liver injury.

Exploratory objectives
Other efficacy objectives are to determine whether treatment with dapagliflozin compared with
placebo when added to current background therapy in patients with T2DM and either established
cardiovascular disease or at least two cardiovascular risk factors in addition to T2DM will result
in a reduction of:
* The individual components of the co-primary efficacy endpoints (cardiovascular death, MI, ischemic stroke or hospitalization for heart failure)
* The composite endpoint of cardiovascular death, MI, ischemic stroke, hospitalization
for heart failure, hospitalization for unstable angina pectoris, or hospitalization for
coronary or non-coronary revascularization and the additional individual components
of hospitalization for unstable angina pectoris and hospitalization for coronary or noncoronary
revascularization

Study design

Multicenter, Randomized, Double-Blind, Placebo-Controlled phase 3b Trial

Intervention

Patients will use either dapagliflozin 10 mg or placebo once daily in addition to their current anti-diabetic treatment for a period of maximally 6 years.

Study burden and risks

Patients will visit the hospital minimally 14 times and maximally 26 times during a period of 3-6 years (dependent on the time the patient is included into the study). Median duration of the study is 4.5 years.

Patients will be asked to keep in contact with the investigator for the whole duration of the study.

Physical examination is being performed and blood samples will be collected several times during the study. The taking of a blood sample could cause some

inconvenience.

Women of child bearing potential will have to undergo a pregnancy test several times during the study.

The use of study medication may cause some side effects.

The study is being performed with the expectation that dapagliflozine might prevent the occurrence of cardiovascular events. The information collated in this study may help to better treat future patients with T2DM.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For inclusion in the study patients should fulfill the following criteria:
1. Provision of informed consent prior to any study specific procedures (including run-in);2. Female or male aged * 40 years;3. Diagnosed with T2DM (See Appendix E for details);4. High Risk for CV event defined as having either established CV disease and/or multiple risk factors:
- Established CV Disease (See Appendix E for details)
OR
No known cardiovascular disease AND at least two cardiovascular risk factors in addition to T2DM, defined as:
- Age * 55 years in men and * 60 in women
AND presence of at least 1 of the following additional risk factors (see Appendix E for details)
- Dyslipidemia
- Hypertension
- Current Tobacco use;5. WOCBP must take precautions to avoid pregnancy throughout the study and for 4 weeks after intake of the last dose.
- WOCBP must have a negative urine pregnancy test. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal.
- WOCBP must be willing to use a medically accepted method of contraception that is considered reliable in the judgment of the Investigator.;For inclusion in the optional genetic research, patients must fulfill the criterion specified in Appendix H.

Exclusion criteria

1. Use of the following excluded medications:
- Current or recent (within 24 months) treatment with pioglitazone and/or use of pioglitazone for a total of 2 years or more during lifetime
- Current or recent (within 12 months) treatment with rosiglitazone
- Previous treatment with any SGLT2 inhibitor
- Any patient currently receiving chronic (>30 consecutive days) treatment with an oral steroid at a dose equivalent to oral prednisolone *10 mg (e.g., betamethasone *1.2 mg, dexamethasone *1.5 mg, hydrocortisone *40 mg) per day;2. Acute cardiovascular event (e.g., acute coronary syndrome (ACS), transient ischemic attack (TIA), stroke, any revascularization, decompensated HF, sustained ventricular tachycardia) <8 weeks prior to randomization. Patients with acute cardiovascular events can be enrolled in the run-in period as long as randomization does not occur within 8 weeks of the event. ;3. Systolic BP >180 or diastolic BP >100 mmHg at randomization. Patient should be excluded if either the systolic BP is elevated (>180 mmHg) or the diastolic BP is elevated (>100 mmHg) on both measurements (see section 6.4.8.1);4. Diagnosis of Type 1 diabetes mellitus, MODY, or secondary diabetes mellitus;5. History of bladder cancer or history of radiation therapy to the lower abdomen or pelvis at any time;6. History of any other malignancy within 5 years (with the exception of successfully treated non-melanoma skin cancers);7. Chronic cystitis and/or recurrent urinary tract infections (3 or more in the last year) ;8. Any conditions that, in the

opinion of the Investigator, may render the patient unable to complete the study including but not limited to cardiovascular (NYHA class IV CHF, recurrent ventricular arrhythmias) or non-cardiovascular disease (e.g., active malignancy with the exception of basal cell carcinoma, cirrhosis, chronic lung disease, severe autoimmune disease) and/or a likely fatal outcome within 5 years;9. Pregnant or breast-feeding patients ;10. Involvement in the planning and/or conduct of the study or other dapagliflozin studies (applies to AZ, BMS, Hadassah and Thrombolysis in Myocardial Infarction [TIMI] or representative staff and/or staff at the study site);11. Previous enrollment or randomization in the present study;12. Active participation in another clinical study with IP and/or investigational device;13. Individuals at risk for poor protocol or medication compliance during run-in period (reasonable compliance defined as 80 * 120%, unless a reason for non-compliance is judged acceptable by the Investigator). If for any reason, the Investigator believes that the patient will not tolerate or be compliant with IP or study procedures, the patient should not be randomized and considered a run-in failure.;Patients will be excluded during run-in and should not be randomized if the following are observed from laboratory or observation during enrollment and run-in assessments:;14. HbA1c *12% or HbA1c<6.5% from the central laboratory (nb, the proportion of subjects with HbA1c between 6.5% and < 7.0% will be capped at approximately 5% of the study).;15. AST or ALT >3x ULN or Total bilirubin >2.5 x ULN;16. CrCl < 60 ml/min (based on the Cockroft-Gault equation) ;17. Hematuria (confirmed by microscopy at Visit 1) with no explanation as judged by the Investigator up to randomization. If bladder cancer is identified, patients are not eligible to participate.;18. Any reason the Investigator believes the patient is not likely to be compliant with the study medication and protocol.;Exclusion criteria for the optional genetic research
The exclusion criteria for the optional genetic research are provided in Appendix H.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	12-08-2013
Enrollment:	400
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Forxiga
Generic name:	Dapagliflozin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	31-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2013
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2016
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-000239-28-NL
ClinicalTrials.gov	NCT01730534
CCMO	NL44123.018.13