DAPASALT: An Open Label, Phase IV, Mechanistic, Three-Arm Study to Evaluate the Natriuretic Effect of 2-Week Dapagliflozin treatment in Type 2 Diabetes Mellitus Patients with Either Preserved or Impaired Renal Function and Non-Diabetics with Impaired Renal Function

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Primary:To investigate change in 24-hr sodium excretion during dapagliflozintreatment between Baseline (average of Days *3 to *1) and averageof Days 2 to 4 within each study group in patients withtype 2 diabetes mellitus (T2DM) with preserved or...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON49588

Source
ToetsingOnline

Brief title
DAPASALT

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Renal disorders (excl nephropathies)

Synonym
diabetes mellitus, renal failure

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Dapagliflozin, Diabetes Mellitus 2, Impaired Renal function, Natriuretic Effect

Outcome measures

Primary outcome

Average change in 24-hr sodium excretion from average baseline to average

values at Day 2 to 4 within each study group.

Secondary outcome

see paragraph 'criteria of evaluation of efficacy' in the synopsis of Protocol

V5.0

The secondary endpoints to be evaluated during or following

dapagliflozin treatment within each study group are:

• Average change in 24-hr sodium excretion from average

Baseline values to average end of treatment values (Day 12 to

14); and from average end of treatment values (Day 12 to 14) to

average values during follow-up (Day 15 to 17).

• Average change in 24-hr glucose excretion from average

Baseline values to average values at Day 2 to 4; from average

Baseline values to average end of treatment values (Day 12 to

14); and from average end of treatment values (Day 12 to 14) to

average values during follow-up (Day 15 to 17).

• Change in mean 24-hr systolic blood pressure from Baseline to

Day 4; from Baseline to end of treatment (Day 13); and from end

of treatment (Day 13) to end of follow-up (Day 18).

• Change in plasma volume, from Baseline to Day 4; from Baseline to end of

treatment (Day 14); and from end of treatment (Day 14) to end

of follow-up (Day 18).

• Change in extracellular volume, from Baseline to Day 4;

from Baseline to end of treatment (Day 14); and from end of treatment (Day 14)

to end of follow-up (Day 18).

• Dapagliflozin pharmacokinetics on Day 4 and Day 14.

• Average change in mean 24-hr UACR from average Baseline to

Day 4; from average Baseline values to average end of treatment

values (Day 12 to 14).

Study description

Background summary

T2DM is associated with an elevated risk of cardiovascular morbidity and mortality as
well as renal failure. The cardiovascular benefit of SGLT2 inhibition was demonstrated
in the EMPA-REG study by showing a lower rate of the primary composite cardiovascular outcome and of death in the active empagliflozin treatment arm (Zinman
et al, 2015 [3]). There is also a growing body of evidence indicating that SGLT2 inhibition is nephroprotective. Post-hoc analysis from the dapagliflozin phase II and

phase III programme have shown in T2DM patients with moderate renal impairment on
top of renin-angiotensin-aldosterone system (RAAS) blockade reduction around 40% in
albuminuria and stabilization of eGFR decline for up to 1 year (Sjöström et al, 2015 [4])
and 2 years (Fioretto et al, 2015 [5]). After an initial drop in eGFR, kidney function was
stable over time while a progressive decrease in eGFR was seen in the placebo group. In
another trial with the SGLT2 inhibitor empagliflozin, a 38%, 44% and 55% risk
reduction was found in new onset of macroalbuminuria, doubling of serum creatinine and
initiation of dialysis treatment respectively. Moreover, the overall risk reduction in
cardiovascular death was 22% in patients with chronic kidney disease (CKD) 3
(eGFR 30 to 59 mL/min) (Wanner et al, 2016 [6]).
The nephroprotective effect is thought to be achieved by mechanisms independent of
blood glucose reduction (Rajasekeran et al, 2016 [7]), such as by reduced
intra-glomerular pressure through an enhanced tubuloglomerular feedback mechanism
(De Nicola, et al 2014 [8] and Thomas, 2014 [9]), reduced glucose and sodium transport
over the proximal tubule cells (Pollock, et al 1991 [10] and Komala, et al 2013
[11]),increased natriuresis (Heerspink et al, 2013 [12]) and reduced systemic blood pressure
(Baker et al, 2015 [13]).
Since the sodium/volume related effects are believed to be independent of HbA1c
reduction this trial will include both patients with and without T2DM.

See protocol V5.0

Study objective

Primary:
To investigate change in 24-hr sodium excretion during dapagliflozin
treatment between Baseline (average of Days *3 to *1) and average
of Days 2 to 4 within each study group in patients with
type 2 diabetes mellitus (T2DM) with preserved or impaired renal
function and in non-diabetics with impaired renal function.

Secondary:
The secondary objectives to be evaluated within each study group
during or following dapagliflozin treatment are:
• To evaluate the change in 24-hr sodium excretion during
dapagliflozin treatment from Baseline to end of treatment, and

during follow-up.
• To evaluate the change in 24-hr glucose excretion.
• To evaluate the change in mean 24-hr systolic blood pressure.
• To evaluate the change in plasma volume.
• To evaluate the change in extracellular volume.
• To evaluate pharmacokinetics of dapagliflozin.
• To evaluate the change in 24-hr urine albumin: creatinine ratio (UACR)

Exploratory:
The exploratory objectives to be evaluated within each study group, during or following dapagliflozin treatment are:
• To assess change in day (0600 - 2200):night (2200 - 0600) ratio of systolic blood pressure.
•To evaluate change in the following:
- Hormones of the renin-angiotensin-aldosterone system (RAAS) (plasma/urine renin, urine aldosterone, plasma Angiotensin II [AngII], urine angiotensinogen [uAngiotensinogen]).
- N-terminal pro b-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP).
- Urinary adenosine.
- Plasma Co-peptin.
• To evaluate change in 24-hr urinary volume, uric acid, creatinine, cortisol, isoprostanes, and electrolytes.
• To evaluate changes in serum/plasma biomarkers of metabolism, renal and cardiovascular function, electrolytes, uric acid, and haematocrit.
• To evaluate changes in body weight.
• To evaluate changes in calculated intracellular red blood cell concentrations of electrolytes.
• To evaluate change in intracellular volume.
• To evaluate change in total body water.
• To assess the changes in extracellular volume and intracellular volume over a 4-hr time course after 2 weeks of dapagliflozin treatment in relation to pharmacokinetics measurements.
• To collect samples for analysis of urinary exosomes obtained from samples from 24-hr urine collections for changes in specific solute transporters present in the exosomes as well as to test for changes in their phosphorylation state.
• To collect data on body composition analysis for later exploratory analysis.
• To collect serum/plasma samples for later exploratory analysis of metabolic, cardiovascular, and renal biomarkers.
• To collect 24-hr urine samples for later exploratory analysis of metabolic, cardiovascular, and renal biomarkers.
• To collect samples for analysis of urinary exosomes obtained from samples from 24-hr urine collections for changes in specific solute transporters present in the exosomes as well as to test for

changes in their phosphorylation state.

Safety:
• To evaluate the safety and tolerability of dapagliflozin in each of the target patient populations

Study design

This is an open label, mechanistic, three-arm study to evaluate the natriuretic effect of 2 weeks dapagliflozin treatment in T2DM patients with either preserved or impaired renal function and in non-diabetic patients with impaired renal function. The study population will comprise 3 groups of patients as described in study population below. The maximum duration of the study will be 62 days including the allowed window periods for the study (±1 day for Day -6 and for Visit 7 at Day 13). The study will allow for an up to 6-week Screening and Run-in Period. The Run-in Period should always last 6 days (Day -6 to Day -1) for patients not on insulin (Group 2 and 3). ; however, for patients on insulin (Group 1) the Run-in Period may be longer (Day -20 to Day *1). Patients on insulin may require a longer Run-in Period in order to be able to adjust their insulin requirements according to the caloric content of the food boxes, if needed. However, it is not mandatory for the patient on insulin to use the entire extended Run-in Period. Based on the Investigator*s judgement, the Run-in Period may be shortened once each patient (on insulin) has had sufficient time to adapt to the food boxes, and it is determined that the patient*s insulin requirement has stabilised sufficiently to continue in the study.The study will then include a 2-week Treatment Period (Day 1 to Day 14) and a 5-day Follow-up Period: Day 15 to Day 19. Patients will consume food from standardised food boxes (with sodium content 150 mmol) starting on Day *6 (patients not on insulin) or Day *20 at the earliest (patients on insulin) of the study until Day 18 (inclusive). Eligibility will be confirmed on Day *1 based on 24-hr urinary assessments performed on Days *3 and *2 (stable urinary sodium excretion on 2 successive 24-hr urinary sodium excretion measurements ie, <20% difference between Days *3 and *2). Eligible patients will receive dapagliflozin 10 mg tablets once daily for 14±1 days starting on Day 1. This will be followed by a Follow-up Period of 5 days.

Intervention

Patients will receive dapagliflozin 10 mg tablets per day for a total period of 13-15 days. This dose is the recommended dose for monotherapy and for add-on combination therapy with other glucose-lowering medicinal products including insulin to improve glycaemic control in T2DM.

Study burden and risks

Disadvantages of participation in the study may be the possible side effects of dapagliflozin (as described above), the procedures of blood plasma volume measurement involve drawing of blood using catheters inserted in the forearm of the patient. You may experience minor discomfort from these procedures and occasionally some bruising or irritation of the veins used for blood sampling. Also, allergic reactions due to the injections are known to occur in some people. These effects normally clear up completely in a few days.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Based on Protocol amendment 5.0, 1. In the diabetic arms - a diagnosis of T2DM with glycosylated haemoglobin (HbA1c) >=6.5% (>=48 mmol/mol) and <10% (<86 mmol/mol); and eGFR (CKD-EPI) between >=25 and <=50 mL/min/1.73m2 or between >90 and <=130 mL/min/1.73m2 for patients aged 59 or younger, between >85 and <=130 mL/min/1.73m2 for patients aged 60 to 69, and between >75 and <=130 mL/min/1.73m2 for patients aged 70 or older at the Screening Visit (Visit 1)., 2. In the non-diabetic arms, HbA1c <6.5% (<48 mmol/mol) and an eGFR (CKD-EPI) between >=25 and <=50 mL/min/1.73m2 at the Screening Visit (Visit 1)., 3. Patient specific optimal antihypertensive dose of an angiotensin receptor blocker (ARB) (as per Investigator*s judgement) for at least 6 weeks prior to Visit 4 (Day 1)., 4. In the diabetic arm (Group 2) an appropriate stable dose of metformin, or sulphonylurea, or metformin+sulphonylurea as anti-diabetic therapy for the last 12 weeks prior to (Visit 4, Day 1)., 5. In the diabetic arm with impaired renal function (Group 1) a stable insulin dosing (intermediate, long*acting, premixed insulin, basal bolus insulin) for the last 12 weeks prior to Visit 4 (Day 1) as judged by the Investigator. Metformin or sulphonylurea, or metformin+sulphonylurea together with insulin would be accepted, but is not mandatory. If used, stable dose of metformin or sulphonylurea, or metformin+sulphonylurea as anti-diabetic therapy for the last 12 weeks prior to Visit 4 (Day 1) is required., 6. Stable urinary sodium excretion on 2 successive 24-hr urinary sodium excretion measurements (<20% difference between Days *3 and *2)., For an extensive description of the inclusion criteria, see Protocol paragraph 4.1

Exclusion criteria

Study-related:
1. Previous enrolment in the present study or participation in another clinical study with an investigational product during the last 6 months prior to Screening Visit (Visit 1, Day *28 until day -8).
2. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff and staff at third party vendor or at the investigational sites).
3. Hypersensitivity to dapagliflozin, indocyanine green, sodium iodide, or iodine, or patients who have poorly tolerated indocyanine green in the past.
4. Pacemaker or other implanted electronic devices.
5. Pregnancy.
6. Breastfeeding., General health-related:
7. Known clinically significant disease or disorder; or clinically relevant abnormal findings in physical examination, clinical chemistry, haematology, and urinalysis; or unstable or rapidly progressing renal disease; or any other condition or minor medical complaint, which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the results, or the patient*s ability to participate in the study and comply with study procedures, restrictions and requirements.

8. Diagnosis of T1DM.
9. Hyperthyroidism or autonomic thyroid adenomas.
10. Abnormal vital signs, after 10 minutes supine rest, defined as any of the following (Visit 1):
- Systolic blood pressure above 180 mmHg.
- Diastolic blood pressure above 110 mmHg.
- Pulse <50 bpm or >100 bpm
11. Any of the following cardiovascular/vascular diseases within 3 months prior to signing the consent at Visit 1, as assessed by the Investigator: myocardial infarction, cardiac surgery or revascularization (coronary artery bypass graft [CABG]/ percutaneous transluminal coronary angioplasty [PTCA]), unstable angina, unstable heart failure, heart failure New York Heart Association Class IV, transient ischemic attack or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmia.
12. Patients with severe hepatic impairment (Child-Pugh C).
13. Ongoing weight-loss diet (hypocaloric diet) or use of weight loss agents, unless the diet or treatment has been stopped at least 3 months before Screening Visit, ensuring patients having a stable body weight with no verified body weight variability of >3 kg during the 3 months before Screening Visit., Renal failure-related:
14. Symptoms/complaints suggestive of established neurogenic bladder and/or incomplete bladder emptying.
15. History of bladder cancer.
16. Diagnosis of polycystic kidney disease.
17. History of or current lupus nephritis.
18. Urinary albumin excretion >1000 mg/g per day at the Screening Visit based on spot urine sample (quantitative assessment)., for further details, see Protocol v5.0 paragraph 4.2.1

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-07-2017
Enrollment:	28
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	01-02-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-05-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-01-2018

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-06-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-09-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-01-2019

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2016-002961-79-NL
CCMO	NL59193.028.17

Study results

Date completed: 15-10-2019

Actual enrolment: 45

Summary results
Trial is onging in other countries