An exploratory phase 2 study to asses the effect of Dapagliflozin on Glomerular Filtration Rate (GFR) in subjects with type 2 Diabetes who have inadequate glycemic and blood pressure (BP) control.

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

Summary

ID

NL-OMON33243

Source
ToetsingOnline

Brief title
MB102-035

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes Mellitus Type 2

Research involving

Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharma industry

Intervention

Keyword: glomerular filtration rate, plasma volume, red cell mass, Type 2 diabetes

Outcome measures

Primary outcome

The study has exploratory objectives which aim to:

Assess the percent change from baseline in GFR and the changes from baseline in the mean 24-hour daytime and nighttime ambulatory systolic BP achieved with dapagliflozin plus metformin and/or SU versus placebo plus metformin and/or SU OR hydrochlorothiazide (HCTZ) plus metformin and/or SU

Substudy exploratory objective

To assess the percent change from baseline in red cell mass and plasma volume achieved with dapagliflozin plus metformin and/or SU versus HCTZ plus metformin and/or SU OR placebo plus metformin and/or SU

Secondary outcome

• To assess the percent change from baseline in GFR achieved with dapagliflozin 10 mg plus
metformin and/or SU versus placebo plus metformin and/or SU, after 12 weeks of oral

administration of double-blind treatment

• To assess the percent change from baseline in GFR achieved with dapagliflozin 10 mg plus

metformin and/or SU versus hydrochlorothiazide (HCTZ) 25 mg plus metformin and/or SU, after 12 weeks of oral administration of double-blind treatment

• To assess the changes from baseline in the mean 24-hour (hr), daytime (0900 to 2100 hours [hrs]), and nighttime (0100 to 0600 hrs) ambulatory systolic BP achieved with dapagliflozin 10 mg plus metformin and/or SU versus placebo plus metformin and/or SU, after 12 weeks of oral administration of double-blind treatment

• To assess the changes from baseline in the mean 24-hr, daytime (0900 to 2100 hrs), and nighttime (0100 to 0600 hrs) ambulatory systolic BP achieved with dapagliflozin 10 mg plus metformin and/or SU versus HCTZ 25 mg plus metformin and/or SU, after 12 weeks of oral administration of double-blind treatment.

Study description

Background summary

Worldwide there are approximately 150 million people with Type 2 diabetes. Despite many available therapies to treat this condition many patients fail to control their diabetes, therefore additional therapies are warranted. The mechanism of action of Dapagliflozin is in the kidney. Theoretically one would expect a beneficial diuretic effect which should result in lower plasma volume and reversible decrease in GFR, hence the design of the current study.

Study objective

There is no formal research hypothesis for this study. The purpose is to evaluate the effects of dapagliflozin on kidney function (GFR) and the changes from baseline in the ambulatory Blood Pressure.

The effects of dapagliflozin on red cell mass and plasma volume will also be measured in a subset of participants, as part of a substudy.

Study design

A randomised, double-blind, 3-arm, parallel-group, placebo and active-controlled trial. Subjects on metformin and/or SU will be randomised into one of three blinded treatment arms.

Intervention

Subjects on metformin and/or SU will be randomised into one of three blinded treatment arms. Either dapagliflozin 10 mg daily dose (QD) or HCTZ 25 mg QD, or placebo, in a 1:1:1 ratio.

Study burden and risks

Patients will be subject to invasive medical procedures (e.g. blood sampling, ECGs) but these will be performed by trained medical staff so any associated risks or pain should be minimised. Also patients will undergoe a GFR test twice, and if participating in the substudy, measurement of red blood cell mass and plasmavolume (twice). This will be done through 2 intravenous catheters. Blood samples will be taken over a time span of approximately 4 hours (and an additional 2 hours for patients in the substudy) during which the patient will need to remain in the clinic.
One blood sample will be labeled (mixed) with radio-actively labeled ligand and re- injected into the bloodstream in order to measure the Red Blood Cell Mass and Plasma volume.
The most commonly reported toxicities are: urinary tract infection, nausea, dizziness, headache, fatigue, back pain, and nasopharyngitis. Hypoglycemia was reported in about 8% of people taking dapagliflozin. However, these toxicities are manageable and patients will be followed closely and appropriate medical care given.

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

1) willing and able to give signed and dated written informed consent.
2) type 2 diabetes with inadequate glycemic control, defined as
central laboratory HbA1c >= 6.6% and <= 9.5% obtained at the enrollment visit.
3) metformin (XR or IR) and/or SU for at least 4 weeks prior to enrollment at any stable dose.
4). inadequate BP control, defined as seated SBP >= 130 and < 165 mmHg AND/OR seated DBP >= 80 and < 105 mmHg
5) C-peptide >= 0.8 ng/ml (0.27 nmol/L)
6) BMI <= 45.0 kg/m2 at the enrollment visit.
7) Men and women, ages >= 18 to <= 70 years.
Women of childbearing potential (WOCBP) must be using an adequate method of contraception

Exclusion criteria

Main exclusion criteria:
1) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period.
2) Women who are pregnant or breastfeeding.
3) Women with a positive pregnancy test on enrollment or prior to investigational product administration and/or injection of iohexol, and, for subjects participating in the substudy, prior to administration of radioisotopes for determination of RCM and PV.
4) Estimated GFR (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula <= 60 mL/min/1.73m2 and >= 150 mL/min/1.73m2.

5) Urine albumin to creatinine ratio (UACR) >= 300 mg/g (33.9 mg/mmol/Cr).
6) Aspartate Aminotransferase (AST) > 3X Upper limit of normal (ULN).
7) Alanine aminotransferase (ALT) > 3X ULN.
8) Serum Total Bilirubin > 2 mg/dL (34.2 µmol/L).
9) Serum Creatinine (Scr) >= 1.50 mg/dL (133 µmol/L) for men; SCr >= 1.40 mg/dL (124 µmol/L) for women.
10) Hemoglobin <= 10.0 g/dL (100 g/L) for men; hemoglobin <= 9.0 g/dL (90 g/L) for women.
11) Creatine kinase (CK) > 3X ULN.
12) Positive for hepatitis B surface antigen.
13) Positive for anti-hepatitis C virus antibody.
14) Abnormal free T4 value.
15) History of diabetes insipidus.
16) Symptoms of poorly controlled diabetes that would preclude participation in this trial including, but not limited to, marked polyuria and polydipsia with greater than 10% weight loss during the 3 months prior to enrollment, or other signs and symptoms.
17) History of diabetic ketoacidosis or hyperosmolar nonketotic coma.
CV/Vascular Diseases: Any of the following CV/Vascular Diseases within 6 months of the enrollment visit:
18) Myocardial infarction.
19) Cardiac surgery or revascularization (coronary artery bypass surgry [CABG]/ percutaneous transluminal coronary angioplasty [PTCA]).
20) Unstable angina.
21) Unstable congestive heart failure (CHF).
22) CHF New York Heart Association (NYHA) Class III or IV. (see Appendix 3)
23) Transient ischemic attack (TIA) or significant cerebrovascular disease.
24) Unstable or previously undiagnosed arrhythmia.
25) History of malignant or accelerated hypertension.
26) History of gout.
27) History of unstable or rapidly progressing renal disease.
28) Conditions of congenital renal glucosuria.
29) Significant hepatic disease, including but not limited to, chronic active hepatitis and/or severe hepatic insufficiency.
30) Documented history of hepatotoxicity with any medication.
31) Documented history of severe hepatobiliary disease.
32) History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis.
33) Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring withdrawal of > 400 mL of blood during the 6 weeks prior to the enrollment visit.
34) Malignancy within 5 years of the enrollment visit (with the exception of treated basal cell or treated squamous cell carcinoma of the skin).
35) Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus.
36) Allergies or contraindication to the contents of dapagliflozin tablets.
37) History of adverse reaction to radio-contrast dye.
38) Allergy or contraindication to use of thiazide diuretics.
39) Administration of insulin or any other antihyperglycemic therapy (other than metformin

and/or SU), at any dose and time, during the 4 weeks prior to the enrollment visit.
40) Administration of any diuretics or other drugs approved for the treatment of hypertension (with the exception of either ACEI or ARB), at any dose and time, during the 12 weeks prior to the enrollment visit.
41) Administration of both ACEI and ARB.
42) Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to enrollment visit.
43) Administration of sibutramine, phentermine, rimonabant, benzphetamine, diethylpropion, methamphetamine, and/or phendimetrazine, within 30 days of the enrollment visit.
44) Any unstable endocrine, psychiatric, rheumatic disorders as judged by the Investigator.
45) Subject is, in the judgment of the Investigator, unlikely to comply with the protocol or has any severe concurrent medical or psychological condition that may affect the interpretation of efficacy or safety data.
46) Subject who, in the judgment of the Investigator, may be at risk for dehydration or volume depletion that may affect the interpretation of efficacy or safety data.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2010
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hydrochloorthiazide
Generic name:	Hydrochloorthiazide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog niet bekend
Generic name:	Dapagliflozin

Ethics review

Approved WMO Date:	17-09-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-12-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-01-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2009-010221-39-NL
CCMO	NL29159.042.09