A Phase 2b Multicentre, Randomised, Double-Blind, Active Controlled, Parallel Group Dose-Ranging Study to Assess the Efficacy, Safety and Tolerability of Zibotentan and Dapagliflozin in Patients with Chronic Kidney Disease with Estimated Glomerular Filtration Rate (eGFR) Between 20 and 60 mL/min/1.73 m2

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· To evaluate the effect of zibotentan anddapagliflozin in combination and alone versusplacebo on UACR.

Ethical review	Approved WMO
Status	Completed
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON52170

Source
ToetsingOnline

Brief title
Zenith-CKD

Condition

- Renal disorders (excl nephropathies)

Synonym
Chronic Kidney Disease, Kidney Failure

Research involving
Human

Sponsors and support

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

Intervention

Keyword: CKD, Dapafliglozin, Phase 2b, Zibotentan

Outcome measures

Primary outcome

· Change in log-transformed UACR from

baseline to Week 12.

The primary estimand is a hypothetical estimand such that the treatment effect

is quantified in the optimal situation where any potential confounder is

avoided.

The population of interest is the Full Analysis population. Participants will

be included in the analysis if they have a non-missing baseline and at least

one post-treatment visit UACR measurement.

For the intercurrent events, if a participant is lost to follow up, prematurely

discontinues study treatment or uses a prohibited medication, the

UACR data are treated as missing after the event and no imputation is

performed. The summary measure being evaluated is the geometric mean reduction

of

UACR from baseline to Week 12.

Secondary outcome

Change in log-transformed UACR from baseline to Week 12.

Change in BP from baseline (Visit 2) to Week 12.

The least squares mean change of UACR at

Week 12 from the Zibo/Dapa dose arms and the dapagliflozin monotherapy arm.

Change in eGFR from baseline to Week 1.

Change in eGFR from baseline to Week 12.

Change in eGFR from baseline to Week 14.

Change in eGFR from Week 1 to Week 12.

Study description

Background summary

Chronic kidney disease (CKD) is a common health problem that can cause a number of complications and may reduce your life expectancy. Kidneys are the body*s filtration units - they keep important things your body needs inside your blood, like proteins and remove things your body doesn't need, like wastes and extra water. A major indicator of kidney health is the level of a protein called albumin (normally found in blood) in urine and its ratio with creatinine, a chemical waste product of a protein called creatine (normally found in urine). A high urine albumin-to-creatinine ratio means that albumin is *leaking* out through your kidneys as their function has been affected. Diabetes mellitus is one of the major causes of CKD. High blood sugar is shown to affect and cause loss of kidney function over time.
Zibotentan works by blocking the activation of proteins that help in narrowing of the blood vessels thus controlling blood pressure. This in turn increases blood flow to the kidney to maintain the health of the kidney.
Dapagliflozin changes how the kidneys handle sugar, salt, and water. This in turn helps maintain the overall health of the body, the heart and the kidneys.
The study aims to measure the effect of zibotentan and dapagliflozin on the amount of albumin present in the urine of patients with CKD and will measure

how safe and tolerable these drugs are in CKD patients.
Zibotentan, dapagliflozin, and placebo will be referred to as *study treatment* in the rest of this document.

Study objective

· To evaluate the effect of zibotentan and dapagliflozin in combination and alone versus placebo on UACR.

Study design

This is a Phase 2b, multicentre, randomised, double-blind, active-controlled, parallel group dose-ranging study to assess the efficacy, safety and tolerability of zibotentan and dapagliflozin in participants with CKD with eGFR > 20 mL/min/1.73 m2 and UACR >= 150 mg/g and <= 5000 mg/g.
The study will be conducted in approximately 220 sites in North America, South America, Africa, Asia/Pacific, and European countries.

Participants will be randomised to 12 weeks of treatment plus 2 weeks follow-up. Participants who meet the eligibility criteria will be randomised to study treatments in addition to receiving background local SoC therapy. Participants who were previously randomised cannot be re-randomized.

Participants will be stratified by diabetes (diabetic kidney disease [DKD] versus non-diabetes mellitus [non-DM] CKD) and baseline eGFR (below or equal versus above
45 mL/min/1.73m2) at the time of randomisation to ensure an approximate balance between
treatment arms within each sub--population. The number of randomised participants in each stratum will be monitored to ensure the non-DM CKD sub-population is approximately a minimum of 30% and a maximum of 50% of the total number of participants randomised.

Intervention

Eligible participants will be randomised to either of the following treatments, in addition to receiving background local SoC therapy:

• Zibotentan 0.25 mg + Dapagliflozin 10 mg once daily.
• Zibotentan 1.5 mg + Dapagliflozin 10 mg once daily.
• Dapagliflozin 10 mg once daily.

To ensure blinding to treatment and zibotentan dose, daily dosing will consist of one dapagliflozin tablet, containing dapagliflozin 10 mg; and one zibotentan

capsule containing zibotentan 1.5 mg, zibotentan 0.25 mg or placebo.
For each participant, the total duration of participation will be approximately 17 to 19 weeks. The screening period can be up to approximately 4 weeks in duration prior to randomisation. The first dose will be taken after randomisation at the baseline visit on Day 1. In addition to the baseline visit, the participant will visit the clinic 5 times during the following 12 weeks of treatment. Approximately 2 weeks after the last dose, the participant will visit the clinic again for a follow-up assessment.

Study burden and risks

A total of 8 blood draws of approximately 50mL at a time.
8 visits.
To investigate
Keeping diaries
wearing blood pressure monitor and heart rate monitor
Risks of the investigations
Side effects

Contacts

Public
Astra Zeneca

Forskargatan 18
Sodertalje SE-15185
SE
Scientific
Astra Zeneca

Forskargatan 18
Sodertalje SE-15185
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:
Age
1 Participant must be 18 years of age or older at the time of signing the informed consent.
Type of Participant and Disease Characteristics / Laboratory Parameters
2 Diagnosis of CKD, defined as:
(a) eGFR (CKD-EPI) >= 20 mL/min/1.73 m2 (by CKD-EPI formula, see Section 8.1.2.2) AND
(b) Urine albumin to creatinine ratio (UACR) >= 150 and <= 5000 mg albumin/g creatinine,
based on a single first morning void spot urine sample at screening.
Medical Treatment
3 No current or prior (within 1 month of screening) medical treatment with an SGLT2i or
any FDC with SGLT2i (such as SGLT2i + metformin).
4 If ACEi and/or ARB and/or MRA are prescribed, the dose must be stable >= 4 weeks
before screening. Participants who have been deemed unable to tolerate ACEi or ARB therapy due to allergy or complications can be enrolled.
5 No current or prior treatment within 6 months prior to screening with cytotoxic therapy,
immunosuppressive therapy or other immunotherapy for primary or secondary kidney disease.
Weight
6 Body mass index (BMI) <= 40 kg/m2.
Sex
7 Male or female of non-childbearing potential.

Reproduction
8 Female participants must have a negative pregnancy test at screening, must not be
lactating, and must be of non-childbearing potential, confirmed at screening by fulfilling one of the following criteria:
(a) Postmenopausal defined as amenorrhoea for at least 12 months or more following
cessation of all exogenous hormonal treatments and FSH and LH levels in the

postmenopausal range.
(b) Documentation of irreversible surgical sterilisation by hysterectomy, bilateral
oophorectomy, or bilateral salpingectomy but not tubal ligation.
9 Male participants must be surgically sterile, abstinent, or in conjunction with a female
sexual partner, using a highly effective method of contraception for the duration of the study (from the time they sign consent) and for 3 months after the last dose of investigational product to prevent any pregnancies. Male study participants must not donate or bank sperm during this same time period (see Section 8.3.8.2).
Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective birth control methods such as:
• Combined (oestrogen and progesterone containing) hormonal contraception associated
with inhibition of ovulation:
* Oral.
* Intravaginal.
* Transdermal.
• Progesterone-only hormonal contraception associated with inhibition of ovulation:
* Oral.
* Injectable.
* Implantable.
• Intrauterine device (IUD).
• Intrauterine hormone-releasing system (IUS).
• Bilateral tubal occlusion of female partner.
• Male vasectomy.
• True sexual abstinence.
True abstinence refers to: when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Informed Consent
10 Capable of giving signed informed consent, as described in Appendix A, which includes
compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
11 Provision of signed and dated, written ICF prior to any mandatory study-specific
procedures, sampling, and analyses.
12 Provision of signed and dated written Genetic informed consent prior to collection of
samples (optional) for genetic analysis.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:
Medical Conditions
1 Minimal change disease, unstable rapidly progressing renal disease, and/or renal disease
requiring significant immunosuppression, autosomal dominant or autosomal recessive polycystic kidney disease.
2 Participants with NYHA functional HF class III or IV.
3 Acute coronary syndrome (ACS) events within 3 months prior to screening.
4 Participants with a BNP >= 200 pg/mL or NT-proBNP >= 600 pg/mL (BNP >= 400 pg/mL or NT-proBNP >= 1200 pg/mL, respectively, if associated with atrial fibrillation) measured by local laboratory at screening (Visit 1).
5 Participants with unstable HF requiring hospitalisation for optimisation of HF treatment
and/or who have not been stable on HF therapy within 6 months prior to screening.
6 Heart failure due to cardiomyopathies that would primarily require other specific
treatment: eg, cardiomyopathy due to pericardial disease, amyloidosis or other infiltrative diseases, cardiomyopathy related to congenital heart disease, primary hypertrophic cardiomyopathy, cardiomyopathy related to toxic or infective conditions (ie, chemotherapy, infective myocarditis, septic cardiomyopathy).
7 High output HF (eg, due to hyperthyroidism or Paget*s disease).
8 Heart failure due to primary cardiac valvular disease/dysfunction, severe functional mitral
or tricuspid valve insufficiency, or planned cardiac valve repair/replacement.
9 Participants with uncontrolled diabetes mellitus (HbA1c > 12%).
10 Participants with T1DM.
11 Hyponatremia, defined as serum Na+ < 135 mmol/L at the time of screening (Visit 1).
12 Intermittent or persistent second or third degree atrioventricular (AV) block after sinus
node dysfunction, with clinically significant bradycardia or sinus pause when not treated with pacemaker.
13 Prolonged QT interval (QTcF > 470ms) on ECG at screening (Visit 1) or randomisation
visit (Visit 2), known congenital long QT syndrome or history of QT prolongation associated with other medications.
14 History of any life-threatening cardiac dysrhythmia (continuous or paroxysmal or
uncontrolled ventricular rate in participants with atrial fibrillation or atrial flutter).
15 Cardiac surgery or non-elective percutaneous coronary interventions (PCI/TAVI) (within

3 months) or open chest coronary artery bypass grafting or valvular repair/replacement (within 3 months) prior to screening or is planned to undergo any of these procedures after randomisation.
16 Heart transplantation or left ventricular assist device at any time.
17 Kidney or any organ transplantation.
18 History or ongoing allergy/hypersensitivity, as judged by the investigator, to SGLT2i (eg,
dapagliflozin, canagliflozin, empagliflozin) or drugs with a similar chemical structure to zibotentan.
19 Any clinically significant disease or disorder (eg, cardiovascular, gastrointestinal, liver,
renal, neurological, musculoskeletal, endocrine, metabolic, psychiatric, major physical impairment) which, as judged by the investigator, might put the participant at risk because of participation in the study, or probable alternative primary reason for participant*s symptoms in judgment of investigator, including but not limited to:
(a) Isolated pulmonary arterial hypertension (defined as mean PAP >= 25 mmHg at rest)
or right ventricular failure; in the absence of left-sided HF.
(b) Anaemia defined as haemoglobin (Hb) level < 100 g/L or 10 g/dL at screening (Visit 1).
(c) Severe chronic obstructive pulmonary disease (COPD) or other lung disease including but not limited to pulmonary fibrosis requiring chronic O2 therapy, regular nebuliser use, or oral steroid therapy.
20 Stroke, transient ischemic attack, carotid surgery, or carotid angioplasty within previous
3 months prior to screening.
21 Active malignancy requiring treatment (except for basal cell or squamous cell carcinomas
of the skin) and malignancies 5 years prior to screening.
22 Severe hepatic impairment (Child-Pugh class C Hepatic impairment), aspartate transaminase [AST] or alanine transaminase [ALT] > 2x the upper limit of normal [ULN]; or total bilirubin > 2x ULN at time of screening. An isolated increase in bilirubin in participants with known Gilbert*s syndrome is not a reason for exclusion.
23 Participants with newly detected pathological laboratory values or an ongoing disease
condition requiring investigation and/or initiation or adjustment of current treatment (in the opinion of the investigator).
24 Drug or alcohol abuse, either current or within 12 months before screening.
25 Positive hepatitis C antibody or hepatitis B virus surface antigen at screening.
26 Positive human immunodeficiency virus (HIV) test.
27 Participants treated with strong or moderate CYP3A4 inhibitor or inducer.
28 Any condition outside the renal and CV disease area, such as but not limited to
malignancy, with a life expectancy of less than 2 years based on investigator*s

clinical judgment.
29 Confirmation of COVID-19 infection:
(a) Participant has a positive test result for SARS-CoV-2 during screening. Participants
who are not hospitalised for COVID-19 infections can be re-screened 4 weeks after they have recovered.
(b) Participant has been previously hospitalised with COVID-19 infection.
30 Ejection fraction < 50% measured by ECHO at screening.
Prior/Concurrent Clinical Study Experience
31 Participation in another clinical study with an investigational product administered in the
last 3 months prior to screening.
Other Exclusions
32 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca
staff and/or staff at the study site).
33 Judgment by the investigator that the participant should not participate in the study if the
participant is unlikely to comply with study procedures, restrictions, and requirements.
34 Previous randomisation into the present study.
35 Plasma donation within 1 month of the visit at the clinic or any blood donation/blood loss
> 500 mL during the 3 months prior to any visit at the clinic.
36 Male participant in a sexually active relation with pregnant or breastfeeding partner.

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:	Completed
Start date (anticipated):	01-02-2021
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dapagliflozin
Generic name:	Farxiga
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Zibotentan
Generic name:	ZD4054

Ethics review

Approved WMO Date:	23-03-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-03-2021
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	24-06-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-06-2021
Application type:	First submission

Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	27-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-06-2021
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Not approved Date:	14-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	14-04-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO Date:	08-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-06-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	04-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-08-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	03-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-11-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	08-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-11-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO	

Date:	16-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-02-2023
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	02-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-03-2023
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2020-004101-32-NL
ClinicalTrials.gov	NCT04724837
CCMO	NL76974.075.21