

**Clinical trial results:****A Study to Assess the Renoprotective Effects of the SGLT2 Inhibitor Dapagliflozin in Non-Diabetic Patients With Proteinuria: a Randomized Double Blind 6-Weeks Cross-Over Trial****Summary**

EudraCT number	2017-001090-16
Trial protocol	NL
Global end of trial date	07 October 2019

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	DIAMOND (DIAMOND_2020.pdf)

Trial information**Trial identification**

Sponsor protocol code	2017003001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03190694
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center Groningen
Sponsor organisation address	Hanzeplein 1, Groningen, Netherlands, 9713 GZ
Public contact	Hiddo Jan Lambers Heerspink, University Medical Center Groningen, +31 503617859NA, h.j.lambers.heerspink@umcg.nl
Scientific contact	Hiddo Jan Lambers Heerspink, University Medical Center Groningen, +31 503617859NA, h.j.lambers.heerspink@umcg.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2019
Global end of trial reached?	Yes
Global end of trial date	07 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary:

- To assess the change baseline in 24-hr proteinuria with dapagliflozin for six weeks relative to placebo treatment in patients with non-diabetic kidney disease and proteinuria > 500 mg/day on stable ACEi or ARB treatment.

Protection of trial subjects:

The safety of the subjects was safeguarded by the site investigators and local standard procedures

Background therapy:

N.ap.

Evidence for comparator:

N.ap.

Actual start date of recruitment	22 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 22
Country: Number of subjects enrolled	Malaysia: 11
Country: Number of subjects enrolled	Netherlands: 20
Worldwide total number of subjects	53
EEA total number of subjects	20

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	48

From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Prior to their visit to the outpatient clinic, patients will be invited by local investigators to participate in the study by verbal invitation when they attend the clinic or by sending an invitation letter.

Pre-assignment

Screening details:

Male and female subjects with Chronic Kidney Disease aged between 18 and 75 years, proteinuria levels between 500 and 3500 mg/24-hour, and an eGFR ≥ 25 ml/min/1.73m² will be enrolled.

Period 1

Period 1 title	treatment period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

The randomisation codes were provided by an unmasked pharmacist employed by the study sponsor (UMCG, Groningen, Netherlands). The study medication was labelled on the basis of the generated codes. The generated codes were used by the unmasked data manager to set up the randomisation module.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin

Arm description:

active

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg per day, oral

Arm title	Placebo
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Arm description:

placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10mg matching placebo, oral, tablet

Number of subjects in period 1	Dapagliflozin	Placebo
Started	27	26
Completed	26	26
Not completed	1	0
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

The randomisation codes were provided by an unmasked pharmacist employed by the study sponsor (University Medical Centre Groningen, Groningen, Netherlands). The study medication was labelled on the basis of the generated codes. The generated codes were used by the unmasked data manager to set up the randomisation module.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin

Arm description:

active

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg per day, oral

Arm title	Placebo
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Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10mg matching placebo, oral, tablet

Number of subjects in period 2	Dapagliflozin	Placebo
Started	26	26
Completed	26	24
Not completed	0	2
Adverse event, non-fatal	-	1
personal	-	1

Baseline characteristics

Reporting groups

Reporting group title	treatment period 1
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Reporting group description: -

Reporting group values	treatment period 1	Total	
Number of subjects	53	53	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	50	50	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous			
Units: years			
geometric mean	51.3		
standard deviation	± 13.26	-	
Gender categorical			
Units: Subjects			
Female	17	17	
Male	36	36	

End points

End points reporting groups

Reporting group title	Dapagliflozin
Reporting group description:	active
Reporting group title	Placebo
Reporting group description:	placebo
Reporting group title	Dapagliflozin
Reporting group description:	active
Reporting group title	Placebo
Reporting group description:	Placebo

Primary: Change in 24-hr proteinuria

End point title	Change in 24-hr proteinuria
End point description:	
End point type	Primary
End point timeframe:	24hr

End point values	Dapagliflozin	Placebo	Dapagliflozin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	26	26
Units: mg per 24h				
arithmetic mean (standard deviation)	1344.0 ($\pm$ 707.60)	1272.9 ($\pm$ 808.33)	1122.3 ($\pm$ 831.39)	1352.4 ($\pm$ 837.04)

Statistical analyses

Statistical analysis title	mixed-effects linear regression model
Comparison groups	Dapagliflozin v Placebo
Number of subjects included in analysis	53
Analysis specification	Post-hoc
Analysis type	other ^[1]
P-value	= 0.93
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.6
upper limit	22.1

Notes:

[1] - mixed-effects linear regression model

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing ICF until final follow up visit

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Dapagliflozin
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Reporting group description:

Subjects receiving dapagliflozin during either period 1 or period 2

Reporting group title	Placebo
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Reporting group description:

Subject receiving placebo during either period 1 or period 2

Serious adverse events	Dapagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Dapagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 53 (32.08%)	13 / 52 (25.00%)	

Neoplasms benign, malignant and unspecified (incl cysts and polyps) Colon cancer subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	
General disorders and administration site conditions Thirst subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) Chills alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) Swelling face alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Peripheral swelling alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 1 / 53 (1.89%) 1 1 / 53 (1.89%) 1	1 / 52 (1.92%) 1 1 / 52 (1.92%) 1 1 / 52 (1.92%) 2 1 / 52 (1.92%) 1 0 / 52 (0.00%) 0 0 / 52 (0.00%) 0	
Immune system disorders Influenza subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	
Reproductive system and breast disorders			

Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0 1 / 53 (1.89%) 1	1 / 52 (1.92%) 1 1 / 52 (1.92%) 1	
Investigations Urine output increased alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) Blood creatinine increased alternative dictionary used: MedDRA 21.0 subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1 1 / 53 (1.89%) 1	0 / 52 (0.00%) 0 0 / 52 (0.00%) 0	
Injury, poisoning and procedural complications Joint injury alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) Foot fracture subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1 1 / 53 (1.89%) 1	0 / 52 (0.00%) 0 0 / 52 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) Headache	0 / 53 (0.00%) 0 1 / 53 (1.89%) 1	1 / 52 (1.92%) 1 0 / 52 (0.00%) 0	

alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3	1 / 52 (1.92%) 1	
Lethargy subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain lower alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 1 / 53 (1.89%) 1	1 / 52 (1.92%) 1 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1	
Skin and subcutaneous tissue disorders Dry skin alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1 1 / 53 (1.89%) 1	0 / 52 (0.00%) 0 1 / 52 (1.92%) 2	
Renal and urinary disorders Acute kidney injury alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	

Pollakiuria alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 5	3 / 52 (5.77%) 3	
Chromaturia alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	
Dysuria alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2	1 / 52 (1.92%) 1	
Arthralgia subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	
Back pain subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	1 / 52 (1.92%) 1	
Pain in extremity alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	
Infections and infestations Vaginal infection subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	
Cellulitis alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Diverticulitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Nasopharyngitis			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	
occurrences (all)	2	2	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 53 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Decreased appetite			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Diabetes mellitus			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Increased appetite			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2018	Page 13: Added assessment during screening visit: Medical History/Kidney Diagnosis; rationale: subject safety Page 14: Time & Events table: Visit 6: additional pregnancy test for Canadian sites; rationale: Per local regulatory requirement Page 19: Added exclusion criteria: 'peripheral vascular disease'; rationale: Subject safety Page 20: Added exclusion criteria: 'history of hypersensitivity or contraindications to iodinated contrast media'; rationale: Subject safety Page 22: Use of NSAIDs. 'Continuous NSAID use is not permitted during the study. NSAIDs use for several days for pain management is permitted as long as it is not during the days prior to GFR / proteinuria assessments'; rationale: Subject safety Page 27: Store temperature medications <25°C instead of 30°C; rationale: Drug Accountability, updated information from AstraZeneca Page 36: Modified AE handling for Canadian sites; rationale: Per local regulatory requirement Page 42-43: Modified unblinding procedure; rationale: Updated information Page 44: Added information reporting overdose procedure; rationale: Subject safety

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

sample size was small
the primary outcome was based on single 24-h urine collections
the study follow-up was too short to fully characterise the safety of dapagliflozin in this population

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32559474>