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

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

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

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

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 (± 707.60)	1272.9 (± 808.33)	1122.3 (± 831.39)	1352.4 (± 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
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	Dapagliflozin
Reporting group description: Subjects receiving dapagliflozin during either period 1 or period 2	
Reporting group title	Placebo
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	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Thirst			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Chills			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Swelling face			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Influenza			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

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

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

Pollakiuria			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	5 / 53 (9.43%)	3 / 52 (5.77%)	
occurrences (all)	5	3	
Chromaturia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Dysuria			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 53 (3.77%)	1 / 52 (1.92%)	
occurrences (all)	2	1	
Arthralgia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Pain in extremity			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Vaginal infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	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: Modificated AE handling for Canadian sites; rationale: Per local regulatory requirement Page 42-43: Modificated 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