Clinical trial results:
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

Summary

EudraCT number	2016-002961-79
Trial protocol	NL SE
Global end of trial date	20 March 2020

Results information

Result version number	v1
This version publication date	02 April 2021
First version publication date	02 April 2021

Trial information

Trial identification

Sponsor protocol code	D1690C00049

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03152084
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, 1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, 1 8772409479, information.center@astrazeneca.com

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	27 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2020
Global end of trial reached?	Yes
Global end of trial date	20 March 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to to evaluate the changes in average 24-hour sodium excretion during dapagliflozin treatment in subjects with T2DM with preserved or impaired kidney function and in non-diabetics with impaired kidney function.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 July 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	Netherlands: 23
Country: Number of subjects enrolled	Sweden: 1
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	11
From 65 to 84 years	13

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 12-Jul-2017 and 20-Mar-2020. Subjects who met all the inclusion and none of the exclusion criteria were enrolled in the study.

Pre-assignment

Screening details:

No subjects in Group 1 (Type 2 diabetes mellitus (T2DM) subjects with impaired kidney function) were enrolled into the Run-in set due to failure to meet inclusion/exclusion criteria, screen failure, or other reasons and it was decided that no more Group 1 subjects would be enrolled in the study.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 2

Arm description:

Type 2 diabetes mellitus (T2DM) subjects with preserved kidney function received oral dose of dapagliflozin 10 mg/day from Day 1 to Day 14, following which they entered Follow-up Period from Day 15 to Day 19.

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Dapagliflozin propanediol monohydrate
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg oral administration

Arm title	Group 3

Arm description:

Non-diabetic subjects with impaired kidney function received oral dose of dapagliflozin 10 mg/day from Day 1 to Day 14, following which they entered Follow-up Period from Day 15 to Day 19.

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Dapagliflozin propanediol monohydrate
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg oral administration

Number of subjects in period 1	Group 2	Group 3
Started	17	7
Completed	17	7

Baseline characteristics

Reporting groups	
Reporting group title	Group 2
Reporting group description:	
Type 2 diabetes mellitus (T2DM) subjects with preserved kidney function received oral dose of dapagliflozin 10 mg/day from Day 1 to Day 14, following which they entered Follow-up Period from Day 15 to Day 19.	
Reporting group title	Group 3
Reporting group description:	
Non-diabetic subjects with impaired kidney function received oral dose of dapagliflozin 10 mg/day from Day 1 to Day 14, following which they entered Follow-up Period from Day 15 to Day 19.	

Reporting group values	Group 2	Group 3	Total
Number of subjects	17	7	24
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 80 years	17	7	24
>=80 years	0	0	0
Age continuous Units: years			
arithmetic mean	64.24	66.00	
standard deviation	± 7.33	± 9.29	-
Sex: Female, Male Units: Participants			
Female	6	2	8
Male	11	5	16
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	16	7	23
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Group 2
Reporting group description:	
Type 2 diabetes mellitus (T2DM) subjects with preserved kidney function received oral dose of dapagliflozin 10 mg/day from Day 1 to Day 14, following which they entered Follow-up Period from Day 15 to Day 19.	
Reporting group title	Group 3
Reporting group description:	
Non-diabetic subjects with impaired kidney function received oral dose of dapagliflozin 10 mg/day from Day 1 to Day 14, following which they entered Follow-up Period from Day 15 to Day 19.	
Subject analysis set title	Group 2
Subject analysis set type	Per protocol
Subject analysis set description:	
Type 2 diabetes mellitus (T2DM) subjects with preserved kidney function received oral dose of dapagliflozin 10 mg/day from Day 1 to Day 14, following which they entered Follow-up Period from Day 15 to Day 19.	

Primary: Change in 24-hour sodium excretion from baseline to start of treatment

End point title	Change in 24-hour sodium excretion from baseline to start of treatment
End point description:	
Average change in 24-hour sodium excretion during dapagliflozin treatment from average baseline to average values at Days 2 to 4 within each study group in subjects with T2DM with preserved kidney function and in non-diabetics with impaired kidney function was assessed.	
End point type	Primary
End point timeframe:	
From baseline (Day -3 to Day -1) to start of treatment (Day 2 to Day 4)	

End point values	Group 2	Group 3	Group 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	6	15	
Units: mmol/24 hour				
median (full range (min-max))	-5.33 (-53.667 to 44.000)	-27.67 (-69.334 to 13.334)	-5.33 (-53.667 to 44.000)	

Statistical analyses

Statistical analysis title	Statistical analysis of change in urine sodium
Statistical analysis description:	
Analysis type is comparison	
Comparison groups	Group 2 v Group 2

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.4462 [2]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	-5.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.542
upper limit	9.12

Notes:

[1] - Within-group change (Group 2): 15 subjects were included in this analysis

[2] - Start of treatment vs baseline

Secondary: Change in 24-hour sodium excretion from baseline to end of treatment and during follow-up

End point title	Change in 24-hour sodium excretion from baseline to end of treatment and during follow-up

End point description:

Average change in 24-hour 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).

End point type	Secondary

End point timeframe:

From baseline (Day -3 to Day -1) to end of treatment (Day 12 to 14); and from end of treatment (Day 12 to 14) to follow-up (Day 15 to 17)

End point values	Group 2	Group 3	Group 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	6	15	
Units: mmol/24 hour				
median (full range (min-max))				
End of treatment vs baseline	2.67 (-64.000 to 143.167)	-23.83 (-107.000 to 0.667)	2.67 (-64.000 to 143.167)	
Follow-up vs end of treatment	1.33 (-135.334 to 25.000)	6.17 (-70.333 to 20.333)	1.33 (-135.334 to 25.000)	

Statistical analyses

Statistical analysis title	Statistical analysis of change in urine sodium

Statistical analysis description:

Analysis type is comparison

Comparison groups	Group 2 v Group 2

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.7842 [4]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	3.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.817
upper limit	32.195

Notes:

[3] - Within-group change (Group 2): 15 subjects were included in this analysis

[4] - End of treatment vs baseline

Statistical analysis title	Statistical analysis of change in urine sodium

Statistical analysis description:

Analysis type is comparison

Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0581 [6]
Method	Regression, Linear
Parameter estimate	Least square mean
Point estimate	-16.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.109
upper limit	0.664

Notes:

[5] - Within-group change (Group 2): 15 subjects were included in this analysis

[6] - Follow-up vs End of treatment

Secondary: Change in 24-hour glucose excretion

End point title	Change in 24-hour glucose excretion

End point description:

Average change in 24-hour 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). Here, n represents subjects with available data that were analyzed for the end point.

End point type	Secondary

End point timeframe:

From baseline (Day -3 to Day -1) to start of treatment (Day 2 to 4); from baseline (Day -3 to Day -1) to end of treatment (Day 12 to 14); and from end of treatment (Day 12 to 14) to follow-up (Day 15 to 17)

End point values	Group 2	Group 3	Group 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	6	15	
Units: mmol/24 hour				
median (full range (min-max))				
Start of treatment vs baseline (n=15;5)	302.61 (191.472 to 635.726)	43.93 (12.050 to 132.333)	302.61 (191.472 to 635.726)	
End of treatment vs baseline (n=15;4)	283.40 (155.876 to 762.801)	29.88 (15.450 to 113.300)	283.40 (155.876 to 762.801)	
Follow-up vs end of treatment (n=15;5)	-168.43 (-376.561 to -107.596)	-37.02 (-74.733 to -10.584)	-168.43 (-376.561 to -107.596)	

Statistical analyses

Statistical analysis title	Statistical Analysis of Change in Urine Glucose
Statistical analysis description: Analysis type is comparison	
Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	344.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	272.785
upper limit	416.905

Notes:

[7] - Within-group change (Group 2): 15 subjects were included in this analysis

[8] - Start of treatment vs baseline

Statistical analysis title	Statistical Analysis of Change in Urine Glucose
Statistical analysis description: Analysis type is comparison	
Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	311.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	224.528
upper limit	398.064

Notes:

[9] - Within-group change (Group 2): 15 subjects were included in this analysis

[10] - End of treatment vs baseline

Statistical analysis title	Statistical Analysis of Change in Urine Glucose

Statistical analysis description:

Analysis type is comparison

Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.0001 [12]
Method	Regression, Linear
Parameter estimate	Least square mean
Point estimate	-203.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-235.983
upper limit	-170.162

Notes:

[11] - Within-group change (Group 2): 15 subjects were included in this analysis

[12] - Follow-up vs end of treatment

Secondary: Change in mean 24-hour systolic blood pressure

End point title	Change in mean 24-hour systolic blood pressure

End point description:

Change in mean 24-hour 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). Here, n represents subjects with available data that were analyzed for the end point.

End point type	Secondary

End point timeframe:

From baseline (Day -1) to start of treatment (Day 4); from baseline (Day -1) to end of treatment (Day 13); and from end of treatment (Day 13) to end of follow-up (Day 18)

End point values	Group 2	Group 3	Group 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	6	15	
Units: mmHg				
median (full range (min-max))				
Start of treatment vs baseline (n=13;6)	-5.4810 (-13.6610 to 5.6100)	-8.9730 (-24.6570 to 2.7210)	-5.4810 (-13.6610 to 5.6100)	
End of treatment vs baseline (n=12;6)	-5.9385 (-16.0060 to 0.9160)	-10.3290 (-23.4160 to 16.2160)	-5.9385 (-16.0060 to 0.9160)	

Follow-up vs end of treatment (n=11;5)	2.5140 (-10.3420 to 8.4590)	-2.6590 (-16.3110 to 7.4680)	2.5140 (-10.3420 to 8.4590)	

Statistical analyses

Statistical analysis title	Statistical Analysis of 24-hour Blood Pressure
Statistical analysis description: Analysis type is comparison	
Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.0047 [14]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	-5.2658
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5459
upper limit	-1.9856

Notes:

[13] - Within-group change (Group 2): 15 subjects were included in this analysis

[14] - Start of treatment vs baseline

Statistical analysis title	Statistical Analysis of 24-hour Blood Pressure
Statistical analysis description: Analysis type is comparison	
Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.0003 [16]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	-7.0987
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.0379
upper limit	-4.1595

Notes:

[15] - Within-group change (Group 2): 15 subjects were included in this analysis

[16] - End of treatment vs baseline

Statistical analysis title	Statistical Analysis of 24-hour Blood Pressure
Statistical analysis description: Analysis type is comparison	

Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.5592 [18]
Method	Regression, Linear
Parameter estimate	Least square mean
Point estimate	0.7287
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9894
upper limit	3.4468

Notes:

[17] - Within-group change (Group 2): 15 subjects were included in this analysis

[18] - Follow-up vs end of treatment

Secondary: Change in plasma volume

End point title	Change in plasma volume

End point description:

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). Arbitrary number 99.99999 represents that data not available as no subjects were evaluated. Here, n represents subjects with available data that were analyzed for the end point.

End point type	Secondary

End point timeframe:

From baseline (Day 1) to start of treatment (Day 4); from baseline (Day 1) to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 18)

End point values	Group 2	Group 3	Group 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	6	15	
Units: Litres				
median (full range (min-max))				
Start of treatment vs baseline (n=13;3)	-0.1440 (-1.7819 to 2.6385)	-0.1139 (-2.0340 to 0.0232)	-0.1440 (-1.7819 to 2.6385)	
End of treatment vs baseline (n=11;1)	-0.2122 (-2.8346 to 1.1073)	2.0557 (2.0557 to 2.0557)	-0.2122 (-2.8346 to 1.1073)	
Follow-up vs end of treatment (n=12;0)	0.6464 (-1.5016 to 1.6410)	99.9999 (99.9999 to 99.9999)	0.6464 (-1.5016 to 1.6410)	

Statistical analyses

Statistical analysis title	Statistical Analysis of Change in Plasma Volume

Statistical analysis description:

Analysis type is comparison

Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.9288 [20]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	0.0315
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7274
upper limit	0.7904

Notes:

[19] - Within-group change (Group 2): 15 subjects were included in this analysis

[20] - Start of treatment vs baseline

Statistical analysis title	Statistical Analysis of Change in Plasma Volume
Statistical analysis description:	
Analysis type is comparison	
Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.1659 [22]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	-0.4318
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.0761
upper limit	0.2125

Notes:

[21] - Within-group change (Group 2): 15 subjects were included in this analysis

[22] - End of treatment vs baseline

Statistical analysis title	Statistical Analysis of Change in Plasma Volume
Statistical analysis description:	
Analysis type is comparison	
Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.019 [24]
Method	Regression, Linear
Parameter estimate	Least square mean
Point estimate	0.4755

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0963
upper limit	0.8548

Notes:

[23] - Within-group change (Group 2): 15 subjects were included in this analysis

[24] - Follow-up vs end of treatment

Secondary: Change in extracellular volume

End point title	Change in extracellular volume

End point description:

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). Here, n represents subjects with available data that were analyzed for the end point.

End point type	Secondary

End point timeframe:

From baseline (Day 1) to start of treatment (Day 4); from baseline (Day 1) to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 18)

End point values	Group 2	Group 3	Group 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	6	15	
Units: Litres				
median (full range (min-max))				
Start of treatment vs baseline (n=14;6)	-0.5783 (-2.7027 to 0.7959)	-0.4553 (-1.3758 to 0.2282)	-0.5783 (-2.7027 to 0.7959)	
End of treatment vs baseline (n=13;6)	0.1248 (-1.4948 to 0.9852)	-0.1427 (-0.6101 to 1.0055)	0.1248 (-1.4948 to 0.9852)	
Follow-up vs end of treatment (n=13;6)	0.1784 (-0.6507 to 0.9780)	0.1394 (-0.3045 to 0.9014)	0.1784 (-0.6507 to 0.9780)	

Statistical analyses

Statistical analysis title	Statistical Analysis of Extracellular Fluid

Statistical analysis description:

Analysis type is comparison

Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.0157 [26]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	-0.6713

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1914
upper limit	-0.1511

Notes:
[25] - Within-group change (Group 2): 15 subjects were included in this analysis
[26] - Start of treatment vs baseline

Statistical analysis title	Statistical Analysis of Extracellular Fluid
Statistical analysis description:	
Analysis type is comparison	
Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.87 [28]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	-0.0324
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4631
upper limit	0.3984

Notes:
[27] - Within-group change (Group 2): 15 subjects were included in this analysis
[28] - End of treatment vs baseline

Statistical analysis title	Statistical Analysis of Extracellular Fluid
Statistical analysis description:	
Analysis type is comparison	
Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.2446 [30]
Method	Regression, Linear
Parameter estimate	Least square mean
Point estimate	0.1718
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1358
upper limit	0.4795

Notes:
[29] - Within-group change (Group 2): 15 subjects were included in this analysis
[30] - Follow-up vs end of treatment

Secondary: Change in 24-hour urine albumin:creatinine ratio (UACR)

End point title	Change in 24-hour urine albumin:creatinine ratio (UACR)

End point description:

Average change in mean 24-hour urine albumin:creatinine ratio (UACR) from average baseline to Day 4; and from average baseline values to average end of treatment values (Day 12 to 14).

End point type	Secondary

End point timeframe:

From baseline (Day -3 to Day -1) to start of treatment (Day 4); and from baseline (Day -3 to Day-1) to end of treatment (Day 12 to 14)

End point values	Group 2	Group 3	Group 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	6	15	
Units: mg/mmol				
median (full range (min-max))				
Start of treatment vs baseline	-0.07 (-30.750 to 6.700)	-5.83 (-35.300 to 0.300)	-0.07 (-30.750 to 6.700)	
End of treatment vs baseline	-0.04 (-17.250 to 0.737)	-7.28 (-35.733 to 0.467)	-0.04 (-17.250 to 0.737)	

Statistical analyses

Statistical analysis title	Statistical Analysis of Change in UACR

Statistical analysis description:

Analysis type is comparison

Comparison groups	Group 2 v Group 2
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.0023 [32]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.299
upper limit	-0.902

Notes:

[31] - Within-group change (Group 2): 15 subjects were included in this analysis

[32] - Start of treatment vs baseline

Statistical analysis title	Statistical Analysis of Change in in UACR

Statistical analysis description:

Analysis type is comparison

Comparison groups	Group 2 v Group 2

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	< 0.0001 [34]
Method	Mixed models analysis
Parameter estimate	Least square mean
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.929
upper limit	-1.256

Notes:

[33] - Within-group change (Group 2): 15 subjects were included in this analysis

[34] - End of treatment vs baseline

Secondary: Pharmacokinetics of dapagliflozin on Day 4 and Day 14

End point title	Pharmacokinetics of dapagliflozin on Day 4 and Day 14

End point description:

Dapagliflozin plasma concentration on Day 4 (pre-dose) and Day 14 (pre-dose, 1h, 2h, 4h post-dose). Here, n represents subjects with available data that were analyzed for the end point.

End point type	Secondary

End point timeframe:

At pre-dose (Day 4) and at pre-dose, 1h, 2h, 4h post-dose (Day 14)

End point values	Group 2	Group 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	7		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 4, Pre-dose (n=17;7)	4.58 (± 134.88)	19.78 (± 116.54)		
Day 14, Pre-dose (n=16;6)	4.54 (± 46.60)	15.26 (± 41.97)		
Day 14, 1 h (n=16;6)	57.46 (± 110.66)	63.83 (± 150.41)		
Day 14, 2 h (n=16;6)	46.47 (± 49.30)	60.41 (± 140.69)		
Day 14, 4 h (n=17;6)	29.71 (± 47.38)	47.83 (± 100.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with AEs and SAEs

End point title	Number of subjects with AEs and SAEs

End point description:

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. SAE is an AE that results in any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability, or is a significant medical event.

End point type	Secondary

End point timeframe:

From Day 1 until Day 18 (FU)

End point values	Group 2	Group 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	7		
Units: Subjects				
Any AE	6	2		
AEs judged as causally related to drug	4	0		
AEs leading to death	0	0		
SAEs (including outcomes = death)	0	0		
SAEs causally related to drug	0	0		
AEs leading to permanent discontinuation of drug	0	0		
SAEs leading to permanent discontinuation of drug	0	0		
Hypoglycaemia AEs	0	0		
Hypoglycaemia AEs = permanent discontinuation drug	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 until Day 18 (FU)

Adverse event reporting additional description:

SAEs and non-SAEs are reported for the Safety Set which comprised of all subjects who received at least one dose of study drug and who had data from at least one post-dose safety assessment available.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Group 2

Reporting group description:

Type 2 diabetes mellitus (T2DM) subjects with preserved kidney function received oral dose of dapagliflozin 10 mg/day from Day 1 to Day 14, following which they entered Follow-up Period from Day 15 to Day 19.

Reporting group title	Group 3

Reporting group description:

Non-diabetic subjects with impaired kidney function received oral dose of dapagliflozin 10 mg/day from Day 1 to Day 14, following which they entered Follow-up Period from Day 15 to Day 19.

Serious adverse events	Group 2	Group 3	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Group 2	Group 3	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 17 (35.29%)	2 / 7 (28.57%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			

Haematoma			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Head discomfort			
subjects affected / exposed	2 / 17 (11.76%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Somnolence			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Infections and infestations			

Genital infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 17 (5.88%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 December 2016	Method change for extracellular volume, from bromo-dilution to Bioimpedance Spectroscopy (BIS). • More in-depth description of study procedures. • More detailed description of potential risks related to use of indocyanine green and BIS. • Additional exploratory variables were introduced.
04 October 2017	Increased Screening Period to allow sufficient time and improve recruitment. • Treatment flexibility +/- 1 day introduced for practical reasons (patient and physician availability).
23 January 2018	Changed study population: From Caucasians only to Caucasians, Asians, Middle Eastern subjects but avoiding sub-Saharan subjects who often have a different Chronic Kidney Disease etiology and may thus respond differently. • Changed age limits: Upper age limits changed from 75 years to 80 years to improve recruitment. • Changed the estimated glomerular filtration rate (eGFR) range for 'normal renal function' (considering normal age related decline in renal function). • Change in exclusion criteria regarding diuretic use – changed from 4 weeks to 2 weeks prior to Screening Visit.
28 April 2018	Allowed insulin use in Group 1 in stable regimen for the last 12 weeks prior to Visit 4 (Day 1). • Rationale to improve recruitment. • Longer Run-in Period with food boxes for subjects on insulin. • Added possibility to proceed with partial (final) analysis of Groups 2 and 3 as recruitment for Group 1 is slower than expected. • Rescreening once per patient is allowed under certain circumstances.
23 January 2020	Inclusion and exclusion criteria modified (angiotensin converting enzyme inhibitor was removed as a prohibited medication and added as an alternative to already approved angiotensin receptor blocker as a required treatment).

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.

Due to unsatisfactory recruitment rate, it was decided that no more Group 1 subjects would be enrolled in the study. In Group 2 and 3, 17 and 7 subjects received the investigational product and completed the study, respectively.

Notes: