



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