



Clinical trial results:

A randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of individually titrated oral doses of runcaciguat in subjects with clinical diagnosis of chronic kidney disease with diabetes and/or hypertension and at least one cardiovascular comorbidity

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2019-003297-53 |
| Trial protocol | DE DK IT FI SE ES PL AT BE BG SK |
| Global end of trial date | 05 April 2022 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 16 April 2023 |
| First version publication date | 16 April 2023 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | 18748 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04507061 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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 | 06 May 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 April 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to investigate the change in albuminuria by urinary albumin-to-creatinine ratio (UACR) after treatment with titrated doses of runcaciguat given once daily from baseline to day 57 (± 3). The secondary objective is to investigate the overall safety and tolerability of Runcaciguat.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Standard of care therapy

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 01 September 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Austria: 9 |
| Country: Number of subjects enrolled | Belgium: 15 |
| Country: Number of subjects enrolled | Bulgaria: 44 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Denmark: 22 |
| Country: Number of subjects enrolled | Spain: 36 |
| Country: Number of subjects enrolled | Finland: 14 |
| Country: Number of subjects enrolled | Israel: 30 |
| Country: Number of subjects enrolled | Italy: 22 |
| Country: Number of subjects enrolled | Poland: 1 |
| Country: Number of subjects enrolled | Slovakia: 8 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | Ukraine: 27 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 243 |
| EEA total number of subjects | 186 |

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) | 47 |
| From 65 to 84 years | 195 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Out of the 395 screened participants, 243 were randomized in 3 different strata and started treatment.

Pre-assignment

Screening details:

The reasons of 152 screen failure were, 135 participants not fulfilling inclusion or exclusion criteria, 14 withdrawal and 3 for other reasons.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Runcaciguat |

Arm description:

Subjects of diabetic CKD with ≥ 3 months SGLT2 inhibitor randomized to this group were administered with the titrated doses (up to 120 mg or the maximum individual tolerated dose) of runcaciguat orally once a day on top of respective standard of care treatment in the morning.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Runcaciguat |
| Investigational medicinal product code | BAY1101042 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Individually titrated doses from 30 mg to 120 mg (or individually tolerated maximal dose) once daily

| | |
|------------------|--|
| Arm title | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Placebo |
|------------------|--|

Arm description:

Subjects of diabetic CKD with ≥ 3 months SGLT2 inhibitor randomized to this group were administered with the titrated doses of matching placebo orally once a day on top of respective standard of care treatment in the morning.

| | |
|--|----------|
| 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:

matching placebo

| | |
|------------------|---|
| Arm title | Diabetic CKD without SGLT2 inhibitor, Runcaciguat |
|------------------|---|

Arm description:

Subjects of diabetic CKD without SGLT2 inhibitor randomized to this group were administered with the titrated doses (up to 120 mg or the maximum individual tolerated dose) of runcaciguat orally once a day on top of respective standard of care treatment in the morning.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---|
| Investigational medicinal product name | Runcaciguat |
| Investigational medicinal product code | BAY1101042 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Individually titrated doses from 30 mg to 120 mg (or individually tolerated maximal dose) once daily | |
| Arm title | Diabetic CKD without SGLT2 inhibitor, Placebo |

Arm description:

Subjects of diabetic CKD without SGLT2 inhibitor randomized to this group were administered with the titrated doses of matching placebo orally once a day on top of respective standard of care treatment in the morning.

| | |
|--|-------------------------------|
| 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: | |
| matching placebo | |
| Arm title | Non-diabetic CKD, Runcaciguat |

Arm description:

Subjects of non-diabetic CKD randomized to this group were administered with the titrated doses (up to 120 mg or the maximum individual tolerated dose) of runcaciguat orally once a day on top of respective standard of care treatment in the morning.

| | |
|--|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Runcaciguat |
| Investigational medicinal product code | BAY1101042 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Individually titrated doses from 30 mg to 120 mg (or individually tolerated maximal dose) once daily | |
| Arm title | Non-diabetic CKD, Placebo |

Arm description:

Subjects of non-diabetic CKD randomized to this group were administered with the titrated doses of matching placebo orally once a day on top of respective standard of care treatment in the morning.

| | |
|--|----------|
| 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:

matching placebo

| Number of subjects in period 1 | Diabetic CKD with ≥3 months SGLT2 inhibitor, Runcaciguat | Diabetic CKD with ≥3 months SGLT2 inhibitor, Placebo | Diabetic CKD without SGLT2 inhibitor, Runcaciguat |
|--------------------------------|---|--|--|
| | | | |
| Started | 65 | 19 | 66 |
| Completed | 48 | 15 | 50 |
| Not completed | 17 | 4 | 16 |
| Adverse event, serious fatal | - | - | 1 |
| COVID-19 pandemic | - | - | - |
| Consent withdrawn by subject | 1 | - | 2 |
| Adverse event, non-fatal | 12 | 3 | 10 |
| Other | 1 | - | - |
| Non-compliance with study drug | 1 | - | 2 |
| Protocol deviation | 2 | 1 | 1 |

| Number of subjects in period 1 | Diabetic CKD without SGLT2 inhibitor, Placebo | Non-diabetic CKD, Runcaciguat | Non-diabetic CKD, Placebo |
|--------------------------------|---|----------------------------------|------------------------------|
| | | | |
| Started | 23 | 53 | 17 |
| Completed | 21 | 41 | 14 |
| Not completed | 2 | 12 | 3 |
| Adverse event, serious fatal | - | - | - |
| COVID-19 pandemic | 1 | - | - |
| Consent withdrawn by subject | - | 3 | 1 |
| Adverse event, non-fatal | - | 7 | 1 |
| Other | - | - | - |
| Non-compliance with study drug | 1 | 1 | 1 |
| Protocol deviation | - | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|--|
| Reporting group title | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Runcaciguat |
| Reporting group description: Subjects of diabetic CKD with ≥ 3 months SGLT2 inhibitor randomized to this group were administered with the titrated doses (up to 120 mg or the maximum individual tolerated dose) of runcaciguat orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Placebo |
| Reporting group description: Subjects of diabetic CKD with ≥ 3 months SGLT2 inhibitor randomized to this group were administered with the titrated doses of matching placebo orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Diabetic CKD without SGLT2 inhibitor, Runcaciguat |
| Reporting group description: Subjects of diabetic CKD without SGLT2 inhibitor randomized to this group were administered with the titrated doses (up to 120 mg or the maximum individual tolerated dose) of runcaciguat orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Diabetic CKD without SGLT2 inhibitor, Placebo |
| Reporting group description: Subjects of diabetic CKD without SGLT2 inhibitor randomized to this group were administered with the titrated doses of matching placebo orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Non-diabetic CKD, Runcaciguat |
| Reporting group description: Subjects of non-diabetic CKD randomized to this group were administered with the titrated doses (up to 120 mg or the maximum individual tolerated dose) of runcaciguat orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Non-diabetic CKD, Placebo |
| Reporting group description: Subjects of non-diabetic CKD randomized to this group were administered with the titrated doses of matching placebo orally once a day on top of respective standard of care treatment in the morning. | |

| Reporting group values | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Runcaciguat | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Placebo | Diabetic CKD without SGLT2 inhibitor, Runcaciguat |
|---|--|--|---|
| Number of subjects | 65 | 19 | 66 |
| Age Categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age Continuous Units: years geometric mean | 69.3 | 70.2 | 71.8 |

| | | | |
|--------------------|-------|-------|-------|
| standard deviation | ± 7.0 | ± 6.1 | ± 6.8 |
|--------------------|-------|-------|-------|

| | | | |
|---------------------------------------|----|----|----|
| Gender Categorical Units: Subjects | | | |
| Female | 11 | 2 | 14 |
| Male | 54 | 17 | 52 |

| Reporting group values | Diabetic CKD without SGLT2 inhibitor, Placebo | Non-diabetic CKD, Runcaciguat | Non-diabetic CKD, Placebo |
|---|---|-------------------------------|---------------------------|
| Number of subjects | 23 | 53 | 17 |
| Age Categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age Continuous Units: years | | | |
| geometric mean | 71.7 | 69.9 | 69.8 |
| standard deviation | ± 6.3 | ± 9.6 | ± 8.8 |
| Gender Categorical Units: Subjects | | | |
| Female | 4 | 12 | 6 |
| Male | 19 | 41 | 11 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 243 | | |
| Age Categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age Continuous Units: years | | | |
| geometric mean | - | | |
| standard deviation | | | |

| | | | |
|--------------------|-----|--|--|
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 49 | | |
| Male | 194 | | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Runcaciguat |
| Reporting group description: Subjects of diabetic CKD with ≥ 3 months SGLT2 inhibitor randomized to this group were administered with the titrated doses (up to 120 mg or the maximum individual tolerated dose) of runcaciguat orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Placebo |
| Reporting group description: Subjects of diabetic CKD with ≥ 3 months SGLT2 inhibitor randomized to this group were administered with the titrated doses of matching placebo orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Diabetic CKD without SGLT2 inhibitor, Runcaciguat |
| Reporting group description: Subjects of diabetic CKD without SGLT2 inhibitor randomized to this group were administered with the titrated doses (up to 120 mg or the maximum individual tolerated dose) of runcaciguat orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Diabetic CKD without SGLT2 inhibitor, Placebo |
| Reporting group description: Subjects of diabetic CKD without SGLT2 inhibitor randomized to this group were administered with the titrated doses of matching placebo orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Non-diabetic CKD, Runcaciguat |
| Reporting group description: Subjects of non-diabetic CKD randomized to this group were administered with the titrated doses (up to 120 mg or the maximum individual tolerated dose) of runcaciguat orally once a day on top of respective standard of care treatment in the morning. | |
| Reporting group title | Non-diabetic CKD, Placebo |
| Reporting group description: Subjects of non-diabetic CKD randomized to this group were administered with the titrated doses of matching placebo orally once a day on top of respective standard of care treatment in the morning. | |
| Subject analysis set title | All CKD, Runcaciguat, PPS |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All CKD participants with Runcaciguat that fulfill the criteria of Per-protocol sets | |
| Subject analysis set title | All CKD, Placebo, PPS |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All CKD participants with placebo that fulfill the criteria of Per-protocol set | |
| Subject analysis set title | All CKD, Runcaciguat, SAF |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All CKD participants with Runcaciguat that fulfill the criteria for safety analysis | |
| Subject analysis set title | All CKD, Placebo, SAF |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All CKD participants with placebo that fulfill the criteria for safety analysis | |
| Subject analysis set title | All CKD, Runcaciguat, FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All CKD participants with Runcaciguat that fulfill the criteria of full analysis set | |
| Subject analysis set title | All CKD, Placebo, FAS |
| Subject analysis set type | Full analysis |

Primary: The mean change of the ratio of UACR at Day 22 (Visit 4), Day 29 (Visit 5) and Day 57 (Visit 7) versus the UACR at baseline

| | |
|-----------------|---|
| End point title | The mean change of the ratio of UACR at Day 22 (Visit 4), Day 29 (Visit 5) and Day 57 (Visit 7) versus the UACR at baseline |
|-----------------|---|

End point description:

Data presented in below table is geometric mean (geometric standard deviation), the correct form of SD range would be, for example, the lower value 220.1/3.0 and the upper value 220.1*3.0 instead of 220.1 (± 3.0) which is not properly displayed due to database constraints.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

at baseline, Day 22 (Visit 4), Day 29 (Visit 5) and Day 57 (Visit 7)

| End point values | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Runcaciguat | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Placebo | Diabetic CKD without SGLT2 inhibitor, Runcaciguat | Diabetic CKD without SGLT2 inhibitor, Placebo |
|-------------------------------------|--|--|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 | 12 | 44 | 19 |
| Units: Not Applicable | | | | |
| geometric mean (standard deviation) | | | | |
| Baseline | 220.1 (± 3.0) | 181.0 (± 3.6) | 244.5 (± 3.2) | 187.6 (± 3.3) |
| Day 22 (Visit 4) | 122.6 (± 4.8) | 189.4 (± 3.3) | 145.5 (± 3.7) | 179.9 (± 4.5) |
| Day 29 (Visit 5) | 124.9 (± 4.6) | 254.1 (± 3.1) | 144.6 (± 3.7) | 215.9 (± 4.0) |
| Day 57 (Visit 7) | 148.3 (± 3.8) | 174.0 (± 3.4) | 144.7 (± 3.4) | 202.5 (± 3.5) |

| End point values | Non-diabetic CKD, Runcaciguat | Non-diabetic CKD, Placebo | All CKD, Runcaciguat, PPS | All CKD, Placebo, PPS |
|-------------------------------------|-------------------------------|---------------------------|---------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 10 | 125 | 41 |
| Units: Not Applicable | | | | |
| geometric mean (standard deviation) | | | | |
| Baseline | 227.8 (± 2.7) | 150.4 (± 3.7) | 230.7 (± 2.9) | 175.9 (± 3.4) |
| Day 22 (Visit 4) | 125.9 (± 3.9) | 75.7 (± 6.2) | 131.1 (± 4.1) | 147.9 (± 4.5) |
| Day 29 (Visit 5) | 110.3 (± 4.1) | 43.8 (± 10.5) | 126.8 (± 4.1) | 153.5 (± 5.6) |
| Day 57 (Visit 7) | 123.1 (± 4.0) | 61.1 (± 8.6) | 139.0 (± 3.7) | 144.6 (± 4.7) |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Runcaciguat/Placebo, diabetic CKD with inhibitor |
|-----------------------------------|--|

Statistical analysis description:

Bayesian analysis of treatment effect, the average geometric mean ratio to baseline of Visit 4, 5, 7, diabetic CKD with ≥ 3 months SGLT2 inhibitor (per protocol set)

| | |
|---|---|
| Comparison groups | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Runcaciguat v Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Placebo |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | geometric mean ratio |
| Point estimate | 0.53 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 0.7 |

| | |
|---|---|
| Statistical analysis title | Runcaciguat/Placebo, All CKD |
| Statistical analysis description: Bayesian analysis of treatment effect, the average geometric mean ratio to baseline of Visit 4, 5, 7, all CKD (per protocol set) | |
| Comparison groups | All CKD, Runcaciguat, PPS v All CKD, Placebo, PPS |
| Number of subjects included in analysis | 166 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | geometric mean ratio |
| Point estimate | 0.676 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.584 |
| upper limit | 0.782 |

| | |
|--|---|
| Statistical analysis title | Runcaciguat/Placebo, non-diabetic CKD |
| Statistical analysis description: Bayesian analysis of treatment effect, the average geometric mean ratio to baseline of Visit 4, 5, 7, Non-diabetic CKD (per protocol set) | |
| Comparison groups | Non-diabetic CKD, Runcaciguat v Non-diabetic CKD, Placebo |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | geometric mean ratio |
| Point estimate | 1.307 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.906 |
| upper limit | 1.889 |

| | |
|--|---|
| Statistical analysis title | Runcaciguat/Placebo, diabetic CKD w/o inhibitor |
| Statistical analysis description: Bayesian analysis of treatment effect, the average geometric mean ratio to baseline of Visit 4, 5, 7, diabetic CKD without SGLT2 inhibitor (per protocol set) | |
| Comparison groups | Diabetic CKD without SGLT2 inhibitor, Runcaciguat v Diabetic CKD without SGLT2 inhibitor, Placebo |
| Number of subjects included in analysis | 63 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | geometric mean ratio |
| Point estimate | 0.546 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.479 |
| upper limit | 0.622 |

| | |
|---|---|
| Secondary: Percentage of subjects with treatment emergent adverse event (TEAE) | |
| End point title | Percentage of subjects with treatment emergent adverse event (TEAE) |
| End point description: Adverse events will be considered as treatment-emergent if they occur after the first study intervention intake and until 7 (calendar) days after last study drug intake. | |
| End point type | Secondary |
| End point timeframe: From first treatment administration up to 7 days after end of treatment | |

| | | | | |
|-----------------------------|--|--|---|---|
| End point values | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Runcaciguat | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Placebo | Diabetic CKD without SGLT2 inhibitor, Runcaciguat | Diabetic CKD without SGLT2 inhibitor, Placebo |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 65 ^[1] | 19 ^[2] | 66 ^[3] | 23 ^[4] |
| Units: percentage | | | | |
| number (not applicable) | 67.7 | 57.9 | 77.3 | 60.9 |

Notes:

[1] - SAF

[2] - SAF

[3] - SAF

[4] - SAF

| | | | | |
|-----------------------------|-------------------------------|---------------------------|---------------------------|-----------------------|
| End point values | Non-diabetic CKD, Runcaciguat | Non-diabetic CKD, Placebo | All CKD, Runcaciguat, SAF | All CKD, Placebo, SAF |
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 53 ^[5] | 17 ^[6] | 184 ^[7] | 59 ^[8] |
| Units: percentage | | | | |
| number (not applicable) | 60.4 | 35.3 | 69.0 | 52.5 |

Notes:

[5] - SAF

[6] - SAF

[7] - SAF

[8] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with early discontinuations

| | |
|-----------------|--|
| End point title | Number of subjects with early discontinuations |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first treatment administration up to 7 days after end of treatment

| End point values | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Runcaciguat | Diabetic CKD with ≥ 3 months SGLT2 inhibitor, Placebo | Diabetic CKD without SGLT2 inhibitor, Runcaciguat | Diabetic CKD without SGLT2 inhibitor, Placebo |
|-----------------------------|--|--|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 65 ^[9] | 19 ^[10] | 66 ^[11] | 23 ^[12] |
| Units: subjects | 17 | 4 | 16 | 2 |

Notes:

[9] - SAF

[10] - SAF

[11] - SAF

[12] - SAF

| End point values | Non-diabetic CKD, Runcaciguat | Non-diabetic CKD, Placebo | All CKD, Runcaciguat, SAF | All CKD, Placebo, SAF |
|-----------------------------|-------------------------------|---------------------------|---------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 53 ^[13] | 17 ^[14] | 184 | 59 |
| Units: subjects | 12 | 3 | 45 | 9 |

Notes:

[13] - SAF

[14] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be considered as treatment-emergent if they occur after the first study intervention intake and until 7 (calendar) days after last study drug intake.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Pooled analysis group of all CKD subjects who were administered with matching placebo.

| | |
|-----------------------|-------------|
| Reporting group title | Runcaciguat |
|-----------------------|-------------|

Reporting group description:

Pooled analysis group of all CKD subjects who were administered with runcaciguat.

| Serious adverse events | Placebo | Runcaciguat | |
|---|----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 59 (8.47%) | 12 / 184 (6.52%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | 1 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Concussion | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |

| | | | |
|--|----------------|-----------------|--|
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Leg amputation | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Typhoid fever | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Runcaciguat | |
|---|---------------------|-----------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 30 / 59 (50.85%) | 123 / 184 (66.85%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Melanocytic naevus subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Eyelid naevus subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Vascular disorders Peripheral vascular disorder subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Hypertension subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 7 / 184 (3.80%) 8 | |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 8 / 184 (4.35%) 13 | |
| Intermittent claudication subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Orthostatic hypotension subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Pallor subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Surgical and medical procedures Endodontic procedure subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Knee arthroplasty subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Therapeutic nerve ablation | | | |

| | | | |
|--|----------------|------------------|--|
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vitrectomy | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 6 / 184 (3.26%) | |
| occurrences (all) | 0 | 6 | |
| Chills | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) | |
| occurrences (all) | 0 | 2 | |
| Discomfort | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 11 / 184 (5.98%) | |
| occurrences (all) | 3 | 11 | |
| Feeling abnormal | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) | |
| occurrences (all) | 0 | 2 | |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 5 / 184 (2.72%) | |
| occurrences (all) | 0 | 5 | |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Medical device site erythema | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) | |
| occurrences (all) | 0 | 3 | |
| Oedema peripheral | | | |

| | | | |
|---|---------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 2 | 22 / 184 (11.96%) 25 | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 2 / 184 (1.09%) 2 | |
| Unevaluable event subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Respiratory, thoracic and mediastinal disorders Bronchial irritation subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Cough subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 5 / 184 (2.72%) 5 | |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |

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|--|---------------------|----------------------|--|
| Hiccups subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Nasal congestion subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 184 (0.00%) 0 | |
| Productive cough subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 184 (0.00%) 0 | |
| Psychiatric disorders | | | |
| Restlessness subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 184 (0.00%) 0 | |
| Poor quality sleep subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 2 / 184 (1.09%) 2 | |
| Mood altered subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 184 (0.00%) 0 | |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 3 / 184 (1.63%) 3 | |
| Disorientation subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Agitation subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Investigations | | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 2 | 4 / 184 (2.17%) 4 | |
| Blood fibrinogen increased subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Blood glucose fluctuation | | | |

| | | |
|--|----------------|-----------------|
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) |
| occurrences (all) | 0 | 2 |
| Blood pressure decreased | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 1 / 184 (0.54%) |
| occurrences (all) | 1 | 1 |
| Blood pressure increased | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 5 / 184 (2.72%) |
| occurrences (all) | 0 | 7 |
| Colonoscopy | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) |
| occurrences (all) | 1 | 0 |
| Culture urine positive | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Electrocardiogram PR prolongation | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Electrocardiogram QT prolonged | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Endoscopy upper gastrointestinal tract | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Weight increased | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) |
| occurrences (all) | 0 | 3 |
| Transaminases increased | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 2 |
| Product residue present | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) |
| occurrences (all) | 1 | 0 |
| International normalised ratio decreased | | |

| | | | |
|--|----------------|-----------------|--|
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Glutamate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 5 / 184 (2.72%) | |
| occurrences (all) | 0 | 11 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Skin wound | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Stab wound | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 1 / 184 (0.54%) | |
| occurrences (all) | 1 | 2 | |
| Fall | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 184 (1.09%) | |
| occurrences (all) | 1 | 2 | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Inflammation of wound | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Limb injury | | | |

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|--------------------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) | |
| occurrences (all) | 0 | 2 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Nodal rhythm | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 1 / 184 (0.54%) | |
| occurrences (all) | 1 | 1 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 1 / 184 (0.54%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|--|---------------------|------------------------|--|
| Supraventricular extrasystoles subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Supraventricular tachycardia subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 2 / 184 (1.09%) 2 | |
| Ventricular extrasystoles subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Nervous system disorders | | | |
| Carpal tunnel syndrome subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Balance disorder subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Cognitive disorder subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 59 (6.78%) 4 | 15 / 184 (8.15%) 17 | |
| Extrapyramidal disorder subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 2 | 11 / 184 (5.98%) 11 | |
| Lethargy subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Migraine | | | |

| | | | |
|--------------------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) | |
| occurrences (all) | 0 | 2 | |
| Taste disorder | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 2 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) | |
| occurrences (all) | 0 | 3 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 3 / 184 (1.63%) | |
| occurrences (all) | 1 | 3 | |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 6 / 184 (3.26%) | |
| occurrences (all) | 0 | 8 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Lymph node pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 2 / 59 (3.39%) | 7 / 184 (3.80%) | |
| occurrences (all) | 2 | 8 | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Eye irritation | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) | |
| occurrences (all) | 0 | 2 | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) | |
| occurrences (all) | 0 | 3 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal pain upper | | | |

| | | |
|----------------------------------|----------------|------------------|
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) |
| occurrences (all) | 0 | 4 |
| Constipation | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) |
| occurrences (all) | 0 | 3 |
| Diarrhoea | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 13 / 184 (7.07%) |
| occurrences (all) | 2 | 17 |
| Dry mouth | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 1 / 184 (0.54%) |
| occurrences (all) | 1 | 1 |
| Dyspepsia | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) |
| occurrences (all) | 0 | 2 |
| Epigastric discomfort | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 184 (1.09%) |
| occurrences (all) | 1 | 2 |
| Eructation | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) |
| occurrences (all) | 0 | 2 |
| Flatulence | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) |
| occurrences (all) | 0 | 2 |
| Gastric dilatation | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gastrointestinal haemorrhage | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Gastrointestinal sounds abnormal | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Impaired gastric emptying | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Irritable bowel syndrome | | |

| | | | |
|--|----------------|-----------------|--|
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Toothache | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 1 / 184 (0.54%) | |
| occurrences (all) | 1 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 4 / 184 (2.17%) | |
| occurrences (all) | 3 | 4 | |
| Nausea | | | |
| subjects affected / exposed | 5 / 59 (8.47%) | 7 / 184 (3.80%) | |
| occurrences (all) | 5 | 7 | |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) | |
| occurrences (all) | 0 | 2 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 4 / 184 (2.17%) | |
| occurrences (all) | 0 | 4 | |
| Rash macular | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Skin haemorrhage | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|---------------------|----------------------|--|
| Skin ulcer subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 184 (0.00%) 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 2 / 184 (1.09%) 2 | |
| Renal impairment subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 4 / 184 (2.17%) 4 | |
| Urethral stenosis subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 184 (0.00%) 0 | |
| Urine flow decreased subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Bladder pain subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 3 | |
| Pollakiuria subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 2 | 1 / 184 (0.54%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal discomfort subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 3 | 2 / 184 (1.09%) 2 | |
| Joint swelling subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Groin pain | | | |

| | | |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Gouty arthritis | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Flank pain | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) |
| occurrences (all) | 1 | 0 |
| Calcification of muscle | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Bone pain | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Back pain | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 8 / 184 (4.35%) |
| occurrences (all) | 2 | 8 |
| Arthralgia | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 3 / 184 (1.63%) |
| occurrences (all) | 1 | 3 |
| Myalgia | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 1 / 184 (0.54%) |
| occurrences (all) | 3 | 1 |
| Tendonitis | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Tendon pain | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Rotator cuff syndrome | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Polyarthrititis | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Pain in extremity | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 184 (1.09%) | |
| occurrences (all) | 0 | 2 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) | |
| occurrences (all) | 0 | 3 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 2 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Gangrene | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) | |
| occurrences (all) | 0 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 184 (1.09%) | |
| occurrences (all) | 1 | 2 | |

| | | | |
|--|---------------------|----------------------|--|
| Pyelonephritis chronic subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 184 (0.00%) 0 | |
| Respiratory tract infection viral subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Subcutaneous abscess subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 184 (0.00%) 0 | |
| Tinea pedis subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Tooth abscess subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Tooth infection subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 184 (0.00%) 0 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 2 / 184 (1.09%) 2 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 1 / 184 (0.54%) 1 | |
| COVID-19 subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 2 | 6 / 184 (3.26%) 6 | |
| Metabolism and nutrition disorders Diabetes mellitus inadequate control subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 184 (0.54%) 1 | |
| Iron deficiency | | | |

| | | |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) |
| occurrences (all) | 0 | 3 |
| Decreased appetite | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 184 (1.63%) |
| occurrences (all) | 0 | 3 |
| Food refusal | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Gout | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 184 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hyperglycaemia | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Hyperkalaemia | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 184 (1.09%) |
| occurrences (all) | 1 | 2 |
| Hypervolaemia | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Hypocalcaemia | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Hypoglycaemia | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Hypokalaemia | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |
| Increased appetite | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 2 |
| Dehydration | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 184 (0.54%) |
| occurrences (all) | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 03 September 2020 | The following main modifications were introduced in amendment 1: • Exclusion criterion 2 was modified to exclude any significant heart diseases. • Exclusion criterion 10 was modified to exclude participants with diagnosis of COVID-19 within 3 months before signing the ICF. • A new exclusion criterion 12 was added to exclude Diabetes Mellitus type 1 patients from the study. • Exclusion criterion 19 was modified to exclude only participants in another study who have received at least 1 dose of study intervention. • A new exclusion criterion 25 was added to exclude participants with a known hypersensitivity to any ingredient of the study intervention. • Participants diagnosed with COVID-19 must be permanently withdrawn from the study intervention. • Primary analysis of UACR is to be based on UACR measured at Visit 4, Visit 5, and Visit 7. |
| 09 June 2021 | The major modification in amendment 2 was the addition of possibility of evaluation by closed strata. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported