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

Subject analysis set description:

All CKD participants with Placebo that fulfill the criteria of full analysis set

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	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Eyelid naevus			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Vascular disorders			
Peripheral vascular disorder			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	1 / 59 (1.69%)	7 / 184 (3.80%)	
occurrences (all)	1	8	
Hypotension			
subjects affected / exposed	0 / 59 (0.00%)	8 / 184 (4.35%)	
occurrences (all)	0	13	
Intermittent claudication			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Pallor			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Endodontic procedure			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Knee arthroplasty			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	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	2 / 59 (3.39%)	22 / 184 (11.96%)	
occurrences (all)	2	25	
Peripheral swelling			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 59 (1.69%)	2 / 184 (1.09%)	
occurrences (all)	1	2	
Unevaluable event			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchial irritation			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 59 (1.69%)	5 / 184 (2.72%)	
occurrences (all)	1	5	
Epistaxis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	

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

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	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Supraventricular tachycardia			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 59 (0.00%)	2 / 184 (1.09%)	
occurrences (all)	0	2	
Ventricular extrasystoles			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Balance disorder			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Cognitive disorder			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	4 / 59 (6.78%)	15 / 184 (8.15%)	
occurrences (all)	4	17	
Extrapyramidal disorder			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 59 (3.39%)	11 / 184 (5.98%)	
occurrences (all)	2	11	
Lethargy			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	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	1 / 59 (1.69%)	0 / 184 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 59 (1.69%)	2 / 184 (1.09%)	
occurrences (all)	1	2	
Renal impairment			
subjects affected / exposed	1 / 59 (1.69%)	4 / 184 (2.17%)	
occurrences (all)	1	4	
Urethral stenosis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 184 (0.00%)	
occurrences (all)	1	0	
Urine flow decreased			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Bladder pain			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	3	
Pollakiuria			
subjects affected / exposed	2 / 59 (3.39%)	1 / 184 (0.54%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	3 / 59 (5.08%)	2 / 184 (1.09%)	
occurrences (all)	3	2	
Joint swelling			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	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	
Polyarthritis			
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	1 / 59 (1.69%)	0 / 184 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Subcutaneous abscess			
subjects affected / exposed	1 / 59 (1.69%)	0 / 184 (0.00%)	
occurrences (all)	1	0	
Tinea pedis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	1 / 59 (1.69%)	0 / 184 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 59 (0.00%)	2 / 184 (1.09%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	1 / 59 (1.69%)	1 / 184 (0.54%)	
occurrences (all)	1	1	
COVID-19			
subjects affected / exposed	2 / 59 (3.39%)	6 / 184 (3.26%)	
occurrences (all)	2	6	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 59 (0.00%)	1 / 184 (0.54%)	
occurrences (all)	0	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