EU Clinical Trials Register

Clinical trial results:
Randomised, double-blind (within dose groups), placebo-controlled and parallel group trial to investigate the effects of different doses of oral BI 685509 given over 20 weeks on UACR reduction in patients with non-diabetic kidney disease

Summary

EudraCT number	2020-002930-33
Trial protocol	DK SE PT DE PL ES
Global end of trial date	21 September 2023

Results information

Result version number	v1 (current)
This version publication date	04 October 2024
First version publication date	04 October 2024

Trial information

Trial identification

Sponsor protocol code	1366-0022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04736628
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	
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	22 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2023
Global end of trial reached?	Yes
Global end of trial date	21 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial were to determine the effectiveness of avenciguat and to characterize the dose-response relationship for avenciguat in patients with non-diabetic kidney disease by assessing 3 doses and placebo.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 53
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	China: 19
Country: Number of subjects enrolled	Denmark: 25
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Malaysia: 15
Country: Number of subjects enrolled	Mexico: 21
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Portugal: 19
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 145

Worldwide total number of subjects	489
EEA total number of subjects	109

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)	277
From 65 to 84 years	212
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was a Phase II, randomised, placebo-controlled, double-blind, parallel, multicentre clinical trial in patients with non-diabetic kidney disease (non-DKD) to demonstrate the effectiveness and safety of avenciguat and to characterize the dose-response relationship for avenciguat in patients with non-DKD by assessing 3 doses and placebo.

Pre-assignment

Screening details:

Confirmed eligible at screening, patients continued in a 2-week baseline run-in period. Patients who completed the screening and baseline run-in periods and met the eligibility criteria were randomised equally into 1 of 3 parallel dose groups, and in each dose group to treatment either with avenciguat or matching placebo in a 3:1 ratio.

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, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest except the Trial Pharmacometrician, PK programmer and Trial bioanalyst in this double-blind trial remained blinded with regard to the randomised treatment assignments within each dose group until after database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Avenciguat 1 mg TID

Arm description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Weeks 1 to 20 (included). Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	avenciguat
Investigational medicinal product code	
Other name	BI 685509
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Weeks 1 to 20 (included). Avenciguat had to be taken with a glass of water and could be taken with or without food.

Arm title	Avenciguat 2 mg TID

Arm description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg of avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 20 of treatment. Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	avenciguat
Investigational medicinal product code	
Other name	BI 685509
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg of avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 20 of treatment. Avenciguat had to be taken with a glass of water and could be taken with or without food.

Arm title	Avenciguat 3 mg TID

Arm description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg avenciguat (one film-coated tablet of 3 mg) TID occurred from Week 5 until Week 20. Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	avenciguat
Investigational medicinal product code	
Other name	BI 685509
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg avenciguat (one film-coated tablet of 3 mg) TID occurred from Week 5 until Week 20. Avenciguat had to be taken with a glass of water and could be taken with or without food.

Arm title	Placebo

Arm description:

This arm comprises all placebo treated participants. Participants were administered film-coated tablets of placebo matching avenciguat 1mg, 2mg or 3mg 3 times a day (TID) during 20 weeks of treatment. Placebo matching avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Arm type	Placebo
Investigational medicinal product name	Placebo to avenciguat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

This arm comprises all placebo treated participants. Participants were administered film-coated tablets of placebo matching avenciguat 1mg, 2mg or 3mg 3 times a day (TID) during 20 weeks of treatment. Placebo matching avenciguat had to be taken with a glass of water and could be taken with or without food.

Number of subjects in period 1[1]	Avenciguat 1 mg TID	Avenciguat 2 mg TID	Avenciguat 3 mg TID
Started	64	65	66
Treated	64	65	66
Completed	58	60	60
Not completed	6	5	6
Adverse event, non-fatal	3	2	4
Perceived lack of efficacy	1	-	-
Protocol deviation	-	-	-
Other reason than listed	1	2	2
Burden of study procedures	1	-	-
Change of residence	-	1	-
Not treated	-	-	-

Number of subjects in period 1[1]	Placebo
Started	66
Treated	64
Completed	55
Not completed	11
Adverse event, non-fatal	3
Perceived lack of efficacy	1
Protocol deviation	1
Other reason than listed	3
Burden of study procedures	1
Change of residence	-
Not treated	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 489 patients that were enrolled only 261 were randomized.

Baseline characteristics

Reporting groups

Reporting group title	Avenciguat 1 mg TID

Reporting group description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Weeks 1 to 20 (included). Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	Avenciguat 2 mg TID

Reporting group description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg of avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 20 of treatment. Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	Avenciguat 3 mg TID

Reporting group description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg avenciguat (one film-coated tablet of 3 mg) TID occurred from Week 5 until Week 20. Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	Placebo

Reporting group description:

This arm comprises all placebo treated participants. Participants were administered film-coated tablets of placebo matching avenciguat 1mg, 2mg or 3mg 3 times a day (TID) during 20 weeks of treatment. Placebo matching avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group values	Avenciguat 1 mg TID	Avenciguat 2 mg TID	Avenciguat 3 mg TID
Number of subjects	64	65	66
Age categorical			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	41	36	39
From 65-84 years	22	28	27
85 years and over	1	1	0
Age Continuous			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: years			
arithmetic mean	54.6	60.4	59.3

standard deviation	± 16.3	± 15.5	± 15.0

Sex: Female, Male			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: Participants			
Female	21	16	26
Male	43	49	40
Ethnicity (NIH/OMB)			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: Subjects			
Hispanic or Latino	18	20	11
Not Hispanic or Latino	46	45	55
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: Subjects			
American Indian or Alaska Native	3	4	1
Asian	18	20	12
Native Hawaiian or Other Pacific Islander	0	0	2
Black or African American	3	1	8
White	39	38	42
More than one race	1	1	0
Unknown or Not Reported	0	1	1
Sodium-glucose cotransporter 2 inhibitor (SGLT2i) use at randomization			
Number of patients in each category sodium-glucose cotransporter 2 inhibitor (SGLT2i) use at randomization. The reported categories of SGLT2i use at randomization are: Yes; No. (RS): this patient set included all entered and randomised patients.			
Units: Subjects			
Category "yes"	17	14	15
Category "No"	47	51	51
Baseline urine albumine creatinine ratio (UACR), 10-hour urine			
Baseline UACR measured in 10-hour urine is reported. UACR is a ratio between two measured substances i.e., albumine and creatinine and it is calculated as: (Urine albumin (milligram (mg)/deciliter (dL)))/(urine creatinine gram (g)/deciliter (dL))= UACR in mg/g. Albuminuria is present when UACR is greater than 30 mg/g and is a marker for chronic kidney disease (CKD). Baseline was defined as the mean of all non-missing assessments from visit 2 (Week -2) until prior to the first intake of trial medication. Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: milligram/gram			
arithmetic mean	1024.1	868.2	941.5
standard deviation	± 920.1	± 727.7	± 1155.2
Baseline Urine Albumine Creatinine Ratio (UACR) in First Morning Void (FMV)			
UACR measured in FMV is reported. UACR is a ratio between two measured substances i.e., albumine and creatinine and it is calculated as: (urine albumin (milligram (mg)/deciliter (dL)))/(urine creatinine gram (g)/deciliter (dL))= UACR in mg/g. Albuminuria is present when UACR is greater than 30 mg/g and is a marker for chronic kidney disease (CKD). Baseline was defined as the mean of all non-missing assessments from visit 2 (Week -2) until prior to the first intake of trial medication. Randomised Set (RS): this patient set included all entered and randomised patients.			

Units: milligram/gram			
arithmetic mean	879.1	745.4	821.3
standard deviation	± 840.8	± 661.9	± 1083.5

Reporting group values	Placebo	Total	
Number of subjects	66	261	
Age categorical			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	42	158	
From 65-84 years	23	100	
85 years and over	1	3	
Age Continuous			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: years			
arithmetic mean	58.1		
standard deviation	± 14.4	-	
Sex: Female, Male			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: Participants			
Female	17	80	
Male	49	181	
Ethnicity (NIH/OMB)			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: Subjects			
Hispanic or Latino	18	67	
Not Hispanic or Latino	48	194	
Unknown or Not Reported	0	0	
Race (NIH/OMB)			
Randomised Set (RS): this patient set included all entered and randomised patients.			
Units: Subjects			
American Indian or Alaska Native	4	12	
Asian	15	65	
Native Hawaiian or Other Pacific Islander	1	3	
Black or African American	5	17	
White	40	159	
More than one race	0	2	
Unknown or Not Reported	1	3	
Sodium-glucose cotransporter 2 inhibitor (SGLT2i) use at randomization			
Number of patients in each category sodium-glucose cotransporter 2 inhibitor (SGLT2i) use at randomization. The reported categories of SGLT2i use at randomization are: Yes; No.			
(RS): this patient set included all entered and randomised patients.			

Units: Subjects			
Category "yes"	16	62	
Category "No"	50	199	

Baseline urine albumine creatinine ratio (UACR), 10-hour urine			

Baseline UACR measured in 10-hour urine is reported. UACR is a ratio between two measured substances i.e., albumine and creatinine and it is calculated as: (Urine albumin (milligram (mg)/deciliter (dL)))/(urine creatinine gram (g)/deciliter (dL))= UACR in mg/g. Albuminuria is present when UACR is greater than 30 mg/g and is a marker for chronic kidney disease (CKD). Baseline was defined as the mean of all non-missing assessments from visit 2 (Week -2) until prior to the first intake of trial medication.

Randomised Set (RS): this patient set included all entered and randomised patients.

Units: milligram/gram			
arithmetic mean	1076.2		
standard deviation	± 1786.2	-	

Baseline Urine Albumine Creatinine Ratio (UACR) in First Morning Void (FMV)			

UACR measured in FMV is reported. UACR is a ratio between two measured substances i.e., albumine and creatinine and it is calculated as: (urine albumin (milligram (mg)/deciliter (dL)))/(urine creatinine gram (g)/deciliter (dL))= UACR in mg/g. Albuminuria is present when UACR is greater than 30 mg/g and is a marker for chronic kidney disease (CKD). Baseline was defined as the mean of all non-missing assessments from visit 2 (Week -2) until prior to the first intake of trial medication.

Randomised Set (RS): this patient set included all entered and randomised patients.

Units: milligram/gram			
arithmetic mean	874.1		
standard deviation	± 1142.0	-	

End points

End points reporting groups

Reporting group title	Avenciguat 1 mg TID

Reporting group description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Weeks 1 to 20 (included). Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	Avenciguat 2 mg TID

Reporting group description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg of avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 20 of treatment. Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	Avenciguat 3 mg TID

Reporting group description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg avenciguat (one film-coated tablet of 3 mg) TID occurred from Week 5 until Week 20. Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	Placebo

Reporting group description:

This arm comprises all placebo treated participants. Participants were administered film-coated tablets of placebo matching avenciguat 1mg, 2mg or 3mg 3 times a day (TID) during 20 weeks of treatment. Placebo matching avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Primary: Change from baseline in log transformed Urine Albumin Creatinine Ratio (UACR) measured in 10-hour urine after 20 weeks of trial treatment

End point title	Change from baseline in log transformed Urine Albumin Creatinine Ratio (UACR) measured in 10-hour urine after 20 weeks of trial treatment

End point description:

Change from baseline in log transformed Urine Albumin Creatinine Ratio (UACR) measured in 10-hour urine after 20 weeks of trial treatment is reported.
Least Squares Mean (Standard error) were estimated by restricted maximum likelihood (REML)−based mixed-effect model for repeated measures (MMRM) including the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12, and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.
Log transformed UACR at Week 20 was log of (average of all available scheduled measurements between week 18 and week 20).
The data in the Outcome Measure Data Table represent the Least Squares Mean (Standard error) at Week 20.

This endpoint reports data for the Full Analysis Set (FAS): included all patients who had at least one baseline measurement of UACR in Week -2, -1, or 0 and at least 1 post-baseline measurement after Week 6.

End point type	Primary

End point timeframe:

The MMRM model is a longitudinal analysis and it incorporated UACR measurements from baseline (Week -2, Week -1, Week 0 pre-dose) and Week 6, Week 12 and Week 20. The data represent the Least

End point values	Avenciguat 1 mg TID	Avenciguat 2 mg TID	Avenciguat 3 mg TID	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64	61	62	62
Units: log (mg/g)				
least squares mean (standard error)	-0.210 (± 0.067)	-0.190 (± 0.068)	-0.217 (± 0.068)	0.018 (± 0.068)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Least Squares Mean differences and 95% confidence intervals were estimated by restricted maximum likelihood (REML)−based mixed-effect model for repeated measures (MMRM) including the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

Comparison groups	Avenciguat 1 mg TID v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0179
Method	Mixed-effect Model repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.228
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.417
upper limit	-0.04

Notes:

[1] - Least Squares Mean of "Avenciguat 1 mg TID" - Least Squares Mean of "Placebo".

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Least Squares Mean differences and 95% confidence intervals were estimated by restricted maximum likelihood (REML)−based mixed-effect model for repeated measures (MMRM) including the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

Comparison groups	Avenciguat 2 mg TID v Placebo

Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0307
Method	Mixed-effect Model repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.398
upper limit	-0.02

Notes:

[2] - Least Squares Mean of "Avenciguat 2 mg TID" - Least Squares Mean of "Placebo".

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Least Squares Mean differences and 95% confidence intervals were estimated by restricted maximum likelihood (REML)−based mixed-effect model for repeated measures (MMRM) including the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

Comparison groups	Avenciguat 3 mg TID v Placebo
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0151
Method	Mixed-effect Model repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.425
upper limit	-0.046

Notes:

[3] - Least Squares Mean of "Avenciguat 3 mg TID" - Least Squares Mean of "Placebo".

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of avenciguat and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (Emax, exponential, linear, quadratic, sigmoid emax) while protecting the overall probability of type I error (one-sided alpha of 0.050). The total daily dose was considered for MCP-Mod analysis (placebo, active avenciguat 3 mg, 6 mg, and 9 mg).

Comparison groups	Avenciguat 1 mg TID v Avenciguat 2 mg TID v Avenciguat 3 mg TID v Placebo

Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0053
Method	MCP-Mod E-max model fit

Notes:

[4] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

MCP-Mod E-max model fit assumption: 80% of the maximum effect is achieved at 6 mg.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of avenciguat and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (Emax, exponential, linear, quadratic, sigmoid emax) while protecting the overall probability of type I error (one-sided alpha of 0.050). The total daily dose was considered for MCP-Mod analysis (placebo, active avenciguat 3 mg, 6 mg, and 9 mg).

Comparison groups	Avenciguat 1 mg TID v Avenciguat 2 mg TID v Avenciguat 3 mg TID v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0102
Method	MCP-Mod quadratic model fit

Notes:

[5] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

MCP-Mod quadratic model fit assumption: 50 % of the maximum effect is achieved at a dose of 3 mg. 90 % of the maximum effect is achieved at a dose of 6 mg.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of avenciguat and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (Emax, exponential, linear, quadratic, sigmoid emax) while protecting the overall probability of type I error (one-sided alpha of 0.050). The total daily dose was considered for MCP-Mod analysis (placebo, active avenciguat 3 mg, 6 mg, and 9 mg).

Comparison groups	Avenciguat 1 mg TID v Avenciguat 2 mg TID v Avenciguat 3 mg TID v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.023
Method	MCP-Mod linear model fit

Notes:

[6] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

MCP-Mod linear model fit assumption: no assumption is needed.

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of avenciguat and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (Emax, exponential, linear, quadratic, sigmoid emax) while protecting the overall probability of type I error (one-sided alpha of 0.050). The total daily dose was considered for MCP-Mod analysis (placebo, active avenciguat 3 mg, 6 mg, and 9 mg).

Comparison groups	Avenciguat 1 mg TID v Avenciguat 2 mg TID v Avenciguat 3 mg TID v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0468
Method	MCP-Mod Exponential model fit

Notes:

[7] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

MCP-Mod Exponential model fit assumption: 20% of the maximum effect is achieved at 3 mg.

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of avenciguat and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (Emax, exponential, linear, quadratic, sigmoid emax) while protecting the overall probability of type I error (one-sided alpha of 0.050). The total daily dose was considered for MCP-Mod analysis (placebo, active avenciguat 3 mg, 6 mg, and 9 mg).

Comparison groups	Avenciguat 1 mg TID v Avenciguat 2 mg TID v Avenciguat 3 mg TID v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.0292
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[8] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

MCP-Mod Sigmoid Emax model fit assumption: 30 % of the maximum effect is achieved at a dose of 3 mg. 90 % of the maximum effect is achieved at a dose of 6 mg.

Secondary: Change from baseline in log transformed UACR measured in First Morning Void urine after 20 weeks of trial treatment

End point title	Change from baseline in log transformed UACR measured in First Morning Void urine after 20 weeks of trial treatment

End point description:

Change from baseline in log transformed UACR measured in First Morning Void urine after 20 weeks of trial treatment is reported.
Least Squares Mean (Standard error) were estimated by restricted maximum likelihood (REML)−based mixed-effect model for repeated measures (MMRM) including the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.
The first morning void (FMV) was the first urination after the patient woke up at their usual time to start their day. Log transformed UACR at Week 20 was log of (average of all available scheduled measurements between week 18 and week 20). The data in the Outcome Measure Data Table represent the Least Squares Mean (Standard error) at Week 20.

This endpoint reports data for the Full Analysis Set (FAS).

End point type	Secondary

End point timeframe:

The MMRM model is a longitudinal analysis and it incorporated UACR measurements from baseline (Week -2 and Week -1) and Week 6, Week 12 and Week 20. The data represent the Least Squares Mean at Week 20.

End point values	Avenciguat 1 mg TID	Avenciguat 2 mg TID	Avenciguat 3 mg TID	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64	61	62	62
Units: log (mg/g)				
least squares mean (standard error)	-0.190 (± 0.071)	-0.180 (± 0.073)	-0.161 (± 0.071)	0.027 (± 0.072)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Least Squares Mean differences and 95% confidence intervals were estimated by restricted maximum likelihood (REML)−based mixed-effect model for repeated measures (MMRM) including the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

Comparison groups	Avenciguat 1 mg TID v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.0327
Method	Mixed-effect Model repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.217
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.416
upper limit	-0.018

Notes:

[9] - Least Squares Mean of "Avenciguat 1 mg TID" - Least Squares Mean of "Placebo".

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Least Squares Mean differences and 95% confidence intervals were estimated by restricted maximum likelihood (REML)−based mixed-effect model for repeated measures (MMRM) including the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

Comparison groups	Avenciguat 2 mg TID v Placebo

Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.0447
Method	Mixed-effect Model repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.206
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.408
upper limit	-0.005

Notes:

[10] - Least Squares Mean of "Avenciguat 2 mg TID" - Least Squares Mean of "Placebo".

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Least Squares Mean differences and 95% confidence intervals were estimated by restricted maximum likelihood (REML)−based mixed-effect model for repeated measures (MMRM) including the fixed, categorical effects of treatment at each visit (baseline, Week 6, Week 12 and Week 20), and the continuous effect of baseline at each visit (Week 6, Week 12, and Week 20) as well as random effects of patient.

Comparison groups	Avenciguat 3 mg TID v Placebo
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.0654
Method	Mixed-effect Model repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.187
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.387
upper limit	0.012

Notes:

[11] - Least Squares Mean of "Avenciguat 3 mg TID" - Least Squares Mean of "Placebo".

Secondary: Number of patients achieving UACR decreases in 10-hour urine of at least 20% from baseline after 20 weeks of trial treatment

End point title	Number of patients achieving UACR decreases in 10-hour urine of at least 20% from baseline after 20 weeks of trial treatment

End point description:

Number of patients achieving urine albumin creatinine ratio (UACR) decreases in 10-hour urine of at least 20% from baseline after 20 weeks of trial treatment.
During the 10-hour period every time the patient urinates, and the patient collected their urine into a provided container. An aliquot of this urine was taken and used as the 10-hour UACR sample.

This endpoint reports data for the Full Analysis Set (FAS): included all patients who had at least one baseline measurement of UACR in Week -2, -1, or 0 and at least 1 post-baseline measurement after Week 6.

End point type	Secondary

End point timeframe:

At baseline (Day -14 and Day -7) and at Week 20 (Day 141) after start of trial treatment.

End point values	Avenciguat 1 mg TID	Avenciguat 2 mg TID	Avenciguat 3 mg TID	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64	61	62	62
Units: Participants	25	27	31	14

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Treatment and sodium-glucose co-transporter-2 inhibitor (SGLT2i) use at randomization were used as covariates in the logistic regression model.	
Comparison groups	Avenciguat 1 mg TID v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.0476 [13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	4.79

Notes:

[12] - Odds ratio (Avenciguat 1 mg vs. Placebo).

[13] - Nominal p-value.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Treatment and sodium-glucose co-transporter-2 inhibitor (SGLT2i) use at randomization were used as covariates in the logistic regression model.	
Comparison groups	Avenciguat 2 mg TID v Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.0119 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	5.94

Notes:

[14] - Odds ratio (Avenciguat 2 mg vs. Placebo).

[15] - Nominal p-value.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Treatment and sodium-glucose co-transporter-2 inhibitor (SGLT2i) use at randomization were used as covariates in the logistic regression model.

Comparison groups	Avenciguat 3 mg TID v Placebo
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.0019 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.58
upper limit	7.45

Notes:

[16] - Odds ratio (Avenciguat 3 mg vs. Placebo).

[17] - Nominal p-value.

Secondary: Number of patients achieving UACR decreases in First Morning Void urine of at least 20% from baseline after 20 weeks of trial treatment

End point title	Number of patients achieving UACR decreases in First Morning Void urine of at least 20% from baseline after 20 weeks of trial treatment

End point description:

Number of patients achieving urine albumin creatinine ratio (UACR) decreases in First Morning Void urine of at least 20% from baseline after 20 weeks of trial treatment is reported. The first morning void (FMV) was the first urination after the patient woke up at their usual time to start their day.

This endpoint reports data for the Full Analysis Set (FAS): included all patients who had at least one baseline measurement of UACR in Week -2, -1, or 0 and at least 1 post-baseline measurement after Week 6.

End point type	Secondary

End point timeframe:

At baseline (Day -14 and Day -7) and at Week 20 (Day 141) after start of trial treatment.

End point values	Avenciguat 1 mg TID	Avenciguat 2 mg TID	Avenciguat 3 mg TID	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64	61	62	62
Units: Participants	27	26	26	16

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment and sodium-glucose co-transporter-2 inhibitor (SGLT2i) use at randomization were used as covariates in the logistic regression model.

Comparison groups	Avenciguat 1 mg TID v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.0497 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	4.55

Notes:

[18] - Odds ratio (Avenciguat 1 mg vs. Placebo).

[19] - Nominal p-value.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Treatment and sodium-glucose co-transporter-2 inhibitor (SGLT2i) use at randomization were used as covariates in the logistic regression model.

Comparison groups	Avenciguat 2 mg TID v Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.0502 [21]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	4.61

Notes:

[20] - Odds ratio (Avenciguat 2 mg vs. Placebo).

[21] - Nominal p-value.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Treatment and sodium-glucose co-transporter-2 inhibitor (SGLT2i) use at randomization were used as covariates in the logistic regression model.

Comparison groups	Avenciguat 3 mg TID v Placebo

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.0572 [23]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	4.49

Notes:

[22] - Odds ratio (Avenciguat 3 mg vs. Placebo).

[23] - Nominal p-value.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

"All-Cause Mortality" "Serious Adverse Events" and "Other Adverse Events": From first avenciguat intake until last avenciguat intake or patient's trial termination date, whichever occurs earlier + 7 days of Residual effect period (REP), up to 148 days.

Adverse event reporting additional description:

Treated Set (TS): this patient set included all patients who received at least 1 dose of trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Avenciguat 1 mg TID

Reporting group description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Weeks 1 to 20 (included). Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	Avenciguat 2 mg TID

Reporting group description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg of avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 20 of treatment. Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	Avenciguat 3 mg TID

Reporting group description:

Patients received daily orally one film-coated tablet of 1 milligram (mg) of avenciguat three times a day (TID) in Week 1 and Week 2. If the 1 mg TID medication was tolerated, up-titration to 2 mg avenciguat (one film-coated tablet of 2 mg) TID occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg avenciguat (one film-coated tablet of 3 mg) TID occurred from Week 5 until Week 20. Avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	Placebo

Reporting group description:

This arm comprises all placebo treated participants. Participants were administered film-coated tablets of placebo matching avenciguat 1mg, 2mg or 3mg 3 times a day (TID) during 20 weeks of treatment. Placebo matching avenciguat had to be taken with a glass of water and could be taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Serious adverse events	Avenciguat 1 mg TID	Avenciguat 2 mg TID	Avenciguat 3 mg TID
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 64 (4.69%)	3 / 65 (4.62%)	6 / 66 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Incision site haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive urgency			
subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemorrhagic diathesis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Appendicitis noninfective			
subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders

Acute kidney injury

subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations

COVID-19

subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia

subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyelonephritis acute

subjects affected / exposed	0 / 64 (0.00%)	0 / 65 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 64 (9.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of lung			

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications

Incision site haemorrhage

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Fall

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vascular disorders

Hypertensive urgency

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hypotension

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders

Acute myocardial infarction

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Angina pectoris

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac failure

subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemorrhagic diathesis			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Appendicitis noninfective			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

COVID-19			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Avenciguat 1 mg TID	Avenciguat 2 mg TID	Avenciguat 3 mg TID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 64 (26.56%)	19 / 65 (29.23%)	26 / 66 (39.39%)
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 64 (4.69%)	6 / 65 (9.23%)	5 / 66 (7.58%)
occurrences (all)	4	7	10
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 64 (7.81%)	1 / 65 (1.54%)	5 / 66 (7.58%)
occurrences (all)	5	1	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	6 / 66 (9.09%)
occurrences (all)	0	2	6
Oedema peripheral			
subjects affected / exposed	0 / 64 (0.00%)	4 / 65 (6.15%)	5 / 66 (7.58%)
occurrences (all)	0	5	5
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	2 / 64 (3.13%)	3 / 65 (4.62%)	6 / 66 (9.09%)
occurrences (all)	2	3	6
Nausea			
subjects affected / exposed	2 / 64 (3.13%)	0 / 65 (0.00%)	4 / 66 (6.06%)
occurrences (all)	4	0	4
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 64 (6.25%)	5 / 65 (7.69%)	3 / 66 (4.55%)
occurrences (all)	4	5	3
Nasopharyngitis			
subjects affected / exposed	4 / 64 (6.25%)	2 / 65 (3.08%)	3 / 66 (4.55%)
occurrences (all)	4	2	3
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 64 (1.56%)	3 / 65 (4.62%)	5 / 66 (7.58%)
occurrences (all)	1	3	5

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 64 (32.81%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 64 (4.69%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 64 (4.69%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	5		
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences (all)	1		
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2021	Global amendment 3 part 1: The following main changes were introduced by the amendment: Modification of flow chart to clarify post-dose electrocardiogram (ECG) at Visit 3 and addition of a footnote explaining the timing of the last dose, for correction and clarification; Extension of the maximum time before randomisation from 28 to 35 days throughout the clinical trial protocol (CTP), to gain more time to allow screening procedures to be repeated where permitted; Specification added for Inclusion Criterion 3 that estimated glomerular filtration rate (eGFR) had to remain ≥20 milliliter (mL)/minute (min)/1.73 square meters (m^2) after Visit 1 up to the start of Visit 3, to ensure patient safety; Rephrasing of Inclusion Criterion 6 from 'stable on anti-hypertensives, non-steroidal anti-inflammatory drug(s) (NSAIDs), endothelin receptor antagonists, systemic steroids, within at least 4 weeks prior to Visit 1 until start of trial treatment, with no planned change of the therapy during the trial' to 'if the patient is taking any of the following medications they should be on a stable dose at least 4 weeks prior to Visit 1 until start of treatment, with no planned change of the therapy during the trial: anti-hypertensives, NSAIDs, endothelin receptor antagonists, systemic steroids or sodium-glucose co-transporter-2 (SGLT2) inhibitors', for clarification; Modification of Exclusion Criterion 3 from 'diabetes mellitus' to 'diagnosed with diabetes mellitus according to local guidelines', for clarification; Specification that trial medication shipments were also allowed for regular visits at the patient's home, for clarification;
15 July 2021	Global amendment 3 part 2: The following main changes were introduced by the amendment: Addition of a footnote to concomitant treatments for clarification on use of restricted nitrates in an emergency; Removal of tablet count recording in the case report forms (CRF) since tablet counts were not required for compliance calculation, but were to be provided through accountability procedures at the site; Replacement of the requirement to test non-sterilized women <65 years of age with the requirement to test women of child-bearing potential for pregnancy as it was considered unnecessary for a women who was not of child-bearing potential to undergo pregnancy testing: Addition of a clarification of why a safety laboratory may not be performed at the central laboratory and addition of requirement to check creatinine to the minimum tests at the local laboratory as an important laboratory parameter to monitor kidney function.

11 October 2021	Global amendment 4 part 1 - the following main changes were introduced by this amendment: Addition of electrocardiogram (ECGs) at visits where there were previously no ECGs in the flow chart and the flow chart for procedures (3 ECGs at Visits 4 and 5 and 1 ECG at Visits 7 and 8; at Visits 3 and 6 an additional ECG was to be done in addition to the 2 already performed) to introduce more frequent ECG monitoring as a response to recent additional data; Addition of eGFR as a test that patients could be pre-screened for if consent was given, to reduce unnecessary screening procedures for patients who would not be eligible due to eGFR; Inclusion of recent data from trial 1366-0020 in the drug profile to include new information and to serve as rationale for additional measures introduced with the amendment; Inclusion of potential QT-interval (QT interval is the time from the start of the Q wave to the end of the T wave) prolongation in the overview of trial related risks, to reflect new available data; Removal of lactose monohydrate as an example of an excipient in Exclusion Criterion 11 since lactose monohydrate was not used in the Phase II formulation; Addition of the following exclusion criteria to ensure that patients with QTc (QTc is the corrected QT interval) prolongation or with the potential for QTc prolongation would not participate: o Exclusion Criterion 17 (QTcF-interval (QT interval corrected for Fridericia formula) >450 milliseconds (ms) in men or >470 ms in women at screening [Visit 1] until start of treatment); o Exclusion Criterion 18 (family history of long QT syndrome); o Exclusion Criterion 19 (concomitant use of therapies with a known risk of Torsade de Pointes at screening [Visit 1] and throughout screening and baseline run-in or planned initiation of such therapies during the trial);
11 October 2021	Global amendment 4 part 2 - the following main changes were introduced by this amendment: Clarification that the Kidney Disease: Improving Global Outcomes (KDIGO) definition should be used 'for guidance' when assessing the criterion for treatment discontinuation in case of Acute Kidney Injury (AKI), to reflect that the KDIGO guidelines are for use within a clinical setting, and patients with low urine output for reasons other than AKI could potentially have been incorrectly discontinued; Modification of the criterion for treatment discontinuation in case of intake of concomitant medication that interferes with the safety of the investigational medicinal product to include sponsor review and decision on a case-by-case basis, to enable patients to remain on trial treatment in exceptional cases if using restricted medication, if there were no safety concerns; Addition of a criterion for treatment discontinuation for patients with a QT or QTcF interval >500 ms, or an increase of QT or QTcF of >60 ms from the pre-dose value at Visit 3 and specification that such cases had to be reported as Adverse Events (AEs), as an additional safety measure; Addition of concomitant therapies with a known risk of Torsade de Pointes as restricted medications, with criteria for temporary stop and re-start of trial medication in the event of temporary concomitant use of such a therapy, to exclude use of medications that could impact QTc; Specification that vital signs were to be assessed prior to ECG and blood sampling, to ensure vital signs were assessed prior to ECG; Addition of high density lipoprotein (HDL) cholesterol laboratory test to correct erroneous omission; Addition of details on ECG timing, review, collection, and storage, to ensure ECGs were accurate and any anomalies were correctly reported, and to include a new storage procedure.

14 February 2022	Global amendment 5 part 1 - the following main changes were introduced by this amendment: Modification of the lay title of the CTP to be consistent with revisions made to the eligibility criteria; Changes of inclusion criteria to allow enrolment of patients with other non-diabetic kidney diseases whose prognosis and treatment were similar, and who therefore may have benefited from treatment with a soluble Guanylate Cyclase (sGC) activator: Expansion of Inclusion Criterion 8 by replacing '...hypertensive kidney disease or chronic glomerulonephritis defined as one of the following (...)' with '...any kind of diagnosed chronic kidney disease1 whose primary cause is clinically not considered to be of diabetic origin' (with footnote indicating that diagnosis could be reached by standard clinical methods, not requiring biopsy); Removal of Inclusion Criterion 7 (diagnosis of CKD as defined by KDIGO definition) due to redundancy with Inclusion Criterion 8; Replacement of 'phosphodiesterase inhibitors' with 'Phosphodiesterase-5-inhibitors, non-specific phosphodiesterase inhibitors (such as dipyridamole and theophylline)' in Exclusion Criterion 1 and in the restricted concomitant medications, since nitric oxide (NO)-sGC- cyclic guanosine monophosphate (cGMP) pathway activating drugs were not to be administered due to possible synergistic effects with avenciguat; Replacement of 'diabetes mellitus' with 'diagnosed with diabetic kidney disease1' in Exclusion Criterion 3 (with footnote indicating that diagnosis could be reached by standard clinical methods, not requiring biopsy) to be consistent with the revised inclusion criteria which allowed patients with diabetes mellitus as long as the primary cause of kidney disease was not of diabetic origin;
14 February 2022	Global amendment 5 part 2 - the following main changes were introduced by this amendment: Addition of Exclusion Criterion 20 (patients with one of the following aetiologies as the underlying cause: Chronic Kidney Disease (CKD) secondary due to malignancy [e.g. cast-nephropathy, AL-amyloidosis], CKD secondary to infectious disease [e.g. hepatitis- or human immunodeficiency virus (HIV)-associated], autosomal-dominant polycystic kidney disease) as a clarification to ensure patients with certain causes of kidney disease, where sufficient benefit of this treatment was not expected, did not participate; Limitation of criterion for treatment discontinuation for patients with severe Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) to those infections that 'precluded their safe participation in the trial' to avoid discontinuing trial treatment if it was deemed safe for patients to continue on treatment; Addition of 'other anti-diabetic treatment (e.g. glucagon-Like Peptide 1 receptor (GLP1R) agonists)' to restricted medications to consider that patients may have been on diabetic treatment due to broadening of inclusion criteria for diagnosis of CKD. This was added to align with restrictions on other anti-diabetic medications and allow treatment if on stable dose; Inclusion of a sentence allowing the option to complete unscheduled visits or visits outside visit window for exceptional home visits or telemedicine contacts in the case that COVID-19 or similar pandemic restrictions were in place, to allow more flexibility.
15 March 2022	Global amendment 6 - the following main change was introduced by this amendment: Modification of Exclusion Criterion 1 to exclude patients treated with NO donors including nitrates and inclusion of NO donors including nitrates as restricted medications, to ensure that no NO-sGC-cGMP pathway-activating drugs were administered due to possible synergistic effects with avenciguat.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

| 25 February 2022 | There was a temporary pause on site initiations and recruitment implemented on 25 Feb 2022 due to study drug resupply issues (not due to safety/efficacy reasons). Recruitment resumed in July 2022 - the pause was lifted in stages based on country and supply depot status with regards to investigational medicinal product (IMP). | 04 July 2022 |

Notes:

Limitations and caveats

None reported