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 diabetic kidney disease

Summary

EudraCT number	2020-002929-28
Trial protocol	DK NL PT PL ES
Global end of trial date	27 December 2022

Results information

Result version number	v3 (current)
This version publication date	18 July 2024
First version publication date	07 January 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1366-0005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04750577
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)	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 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2022
Global end of trial reached?	Yes
Global end of trial date	27 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial were to demonstrate the effectiveness of BI 685509 and to characterise the dose-response relationship for BI 685509 in patients with diabetic kidney disease (DKD) 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. Rescue medication was allowed for all subjects as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 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: 41
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	China: 8
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Hong Kong: 11
Country: Number of subjects enrolled	Japan: 31
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	243
EEA total number of subjects	48

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)	96
From 65 to 84 years	146
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was a phase II, randomized, double-blind (within dose groups), placebo controlled and parallel group trial in patients with diabetic kidney disease (DKD) to demonstrate the effectiveness of BI 685509 and to characterize the dose-response relationship for BI 685509 in patients with DKD by assessing 3 doses and placebo.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

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 the database lock. The access to the randomisation code was kept restricted until its release for analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 685509 1 mg TID

Arm description:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during 20 weeks of treatment in total, with water and 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	BI 685509
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during 20 weeks of treatment in total, with water and taken with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Arm title	BI 685509 2mg TID

Arm description:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 20 of treatment. The tablets were taken with water, 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	BI 685509
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 20 of treatment. The tablets were taken with water, with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Arm title	BI 685509 3 mg TID

Arm description:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg TID BI 685509 occurred from Week 5 until Week 20. The tablets were taken with water, 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	BI 685509
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg TID BI 685509 occurred from Week 5 until Week 20. The tablets were taken with water, with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Arm title	Placebo

Arm description:

This arm comprises all placebo treated participants. Participants were randomized in the dose group in a 3:1 ratio (test treatment to placebo). Participants were administered film-coated tablets of matching placebo 3 times a day during 20 weeks of treatment. The tablets were taken with water, 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
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 randomized in the dose group in a 3:1 ratio (test treatment to placebo). Participants were administered film-coated tablets of matching placebo 3 times a day during 20 weeks of treatment. The tablets were taken with water, with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Number of subjects in period 1	BI 685509 1 mg TID	BI 685509 2mg TID	BI 685509 3 mg TID
Started	61	61	61
Treated	61	61	61
Completed	55	46	47
Not completed	6	15	14
Adverse event, non-fatal	2	10	8
Protocol deviation	1	1	1
No reason available	-	-	-
Burden of study procedures	-	2	2
Patients prematurely discontinued	3	2	2
Change of residence	-	-	1
Not treated	-	-	-

Number of subjects in period 1	Placebo
Started	60
Treated	58
Completed	53
Not completed	7
Adverse event, non-fatal	1
Protocol deviation	1
No reason available	2
Burden of study procedures	-
Patients prematurely discontinued	1
Change of residence	-
Not treated	2

Baseline characteristics

Reporting groups	
Reporting group title	BI 685509 1 mg TID
Reporting group description:	
The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during 20 weeks of treatment in total, with water and 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	BI 685509 2mg TID
Reporting group description:	
The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 20 of treatment. The tablets were taken with water, with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.	
Reporting group title	BI 685509 3 mg TID
Reporting group description:	
The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg TID BI 685509 occurred from Week 5 until Week 20. The tablets were taken with water, 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 randomized in the dose group in a 3:1 ratio (test treatment to placebo). Participants were administered film-coated tablets of matching placebo 3 times a day during 20 weeks of treatment. The tablets were taken with water, with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.	

Reporting group values	BI 685509 1 mg TID	BI 685509 2mg TID	BI 685509 3 mg TID
Number of subjects	61	61	61
Age categorical			
Randomised Set (RS): This patient set includes 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)	28	28	21
From 65-84 years	33	32	40
85 years and over	0	1	0
Age Continuous			
Randomised Set (RS): This patient set includes all entered and randomised patients.			
Units: years			
arithmetic mean	65.2	64.8	65.2
standard deviation	± 9.3	± 11.0	± 8.8

Sex: Female, Male			
Randomised Set (RS): This patient set includes all entered and randomised patients.			
Units: Participants			
Female	16	14	13
Male	45	47	48
Race (NIH/OMB)			
Randomised Set (RS): This patient set includes all entered and randomised patients.			
Units: Subjects			
American Indian or Alaska Native	1	3	3
Asian	23	16	16
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	6	11	10
White	30	31	32
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Randomised Set (RS): This patient set includes all entered and randomised patients.			
Units: Subjects			
Hispanic or Latino	16	21	23
Not Hispanic or Latino	45	40	38
Unknown or Not Reported	0	0	0
Urine Albumin Creatinine Ratio (UACR) - 10 Hour			
Urine Albumin Creatinine Ratio (UACR) at baseline. For 10-hour urine. Baseline was defined as the mean of all non-missing assessments from visit 2 until prior to the first intake of trial medication. As soon as the First Morning Void sample was collected the clock starts for the 10-hour urine collection. During the 10-hour period every time the patient urinates, they collected their urine into a provided container. An aliquot of this urine was taken and used as the 10-hour UACR sample.			
Units: milligram/gram (mg/g)			
arithmetic mean	1093.5	1090.7	880.8
standard deviation	± 980.3	± 794.4	± 722.4
Urine Albumin Creatinine Ratio (UACR) FMV			
Urine Albumin Creatinine Ratio (UACR) at baseline. The first morning void (FMV) is the first urination after the patient wakes up at their usual time to start their day. Baseline is defined as the mean of all available samples prior to Visit 2 up to and including those prior to the first intake of trial medication.			
Units: Milligram/gram (mg/g)			
arithmetic mean	991.7	1033	818.4
standard deviation	± 889.0	± 760.4	± 686.9

Reporting group values	Placebo	Total	
Number of subjects	60	243	
Age categorical			
Randomised Set (RS): This patient set includes 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)	19	96	

From 65-84 years	41	146	
85 years and over	0	1	

Age Continuous			
Randomised Set (RS): This patient set includes all entered and randomised patients.			
Units: years			
arithmetic mean	67.6		
standard deviation	± 8.7	-	
Sex: Female, Male			
Randomised Set (RS): This patient set includes all entered and randomised patients.			
Units: Participants			
Female	16	59	
Male	44	184	
Race (NIH/OMB)			
Randomised Set (RS): This patient set includes all entered and randomised patients.			
Units: Subjects			
American Indian or Alaska Native	2	9	
Asian	16	71	
Native Hawaiian or Other Pacific Islander	0	1	
Black or African American	6	33	
White	34	127	
More than one race	2	2	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Randomised Set (RS): This patient set includes all entered and randomised patients.			
Units: Subjects			
Hispanic or Latino	21	81	
Not Hispanic or Latino	39	162	
Unknown or Not Reported	0	0	
Urine Albumin Creatinine Ratio (UACR) - 10 Hour			
Urine Albumin Creatinine Ratio (UACR) at baseline. For 10-hour urine. Baseline was defined as the mean of all non-missing assessments from visit 2 until prior to the first intake of trial medication. As soon as the First Morning Void sample was collected the clock starts for the 10-hour urine collection. During the 10-hour period every time the patient urinates, they collected their urine into a provided container. An aliquot of this urine was taken and used as the 10-hour UACR sample.			
Units: milligram/gram (mg/g)			
arithmetic mean	913.1		
standard deviation	± 657.3	-	
Urine Albumin Creatinine Ratio (UACR) FMV			
Urine Albumin Creatinine Ratio (UACR) at baseline. The first morning void (FMV) is the first urination after the patient wakes up at their usual time to start their day. Baseline is defined as the mean of all available samples prior to Visit 2 up to and including those prior to the first intake of trial medication.			
Units: Milligram/gram (mg/g)			
arithmetic mean	866.1		
standard deviation	± 658.1	-	

End points

End points reporting groups

Reporting group title	BI 685509 1 mg TID

Reporting group description:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during 20 weeks of treatment in total, with water and 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	BI 685509 2mg TID

Reporting group description:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 20 of treatment. The tablets were taken with water, with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	BI 685509 3 mg TID

Reporting group description:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg TID BI 685509 occurred from Week 5 until Week 20. The tablets were taken with water, 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 randomized in the dose group in a 3:1 ratio (test treatment to placebo). Participants were administered film-coated tablets of matching placebo 3 times a day during 20 weeks of treatment. The tablets were taken with water, 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) after 20 weeks is reported. As soon as the First Morning Void sample was collected the clock starts for the 10-hour urine collection. During the 10-hour period every time the patient urinates, they collected their urine into a provided container. An aliquot of this urine was taken and used as the 10-hour UACR sample. Least Square Means and Standard error were estimated by restricted maximum likelihood based Mixed-effect Model for Repeated Measures ((REML)−based 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 Least Squares Mean (Standard error) at Week 20 is reported.

End point type	Primary

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	BI 685509 1 mg TID	BI 685509 2mg TID	BI 685509 3 mg TID	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	53	56	56
Units: milligram/gram (mg/g)				
least squares mean (standard error)	-0.069 (± 0.074)	-0.029 (± 0.079)	-0.217 (± 0.076)	0.034 (± 0.073)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of BI 685509 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, quadratic, Emax and 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 BI 685509 3 mg, 6 mg, and 9 mg).

Comparison groups	BI 685509 1 mg TID v BI 685509 2mg TID v BI 685509 3 mg TID v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0245
Method	MCP-Mod exponential model fit

Notes:

[1] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. 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.
Exponential model assumption: 20% of the maximum effect is achieved at 3 mg.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of BI 685509 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, quadratic, Emax and 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 BI 685509 3 mg, 6 mg, and 9 mg).

Comparison groups	BI 685509 1 mg TID v BI 685509 2mg TID v BI 685509 3 mg TID v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0294
Method	MCP-Mod linear model fit

Notes:

[2] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. 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.
Linear model assumption: No assumption was needed.

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of BI 685509 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, quadratic, Emax and 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 BI 685509 3 mg, 6 mg, and 9 mg).

Comparison groups	BI 685509 1 mg TID v BI 685509 2mg TID v BI 685509 3 mg TID v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0659
Method	MCP-Mod Sigmoid emax model fit

Notes:

[3] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. 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.
Sigmoid Emax model 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.

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

Least Square Means difference and 95% confidence interval were estimated by restricted maximum likelihood based Mixed-effect Model for Repeated Measures ((REML)−based 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	BI 685509 1 mg TID v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.3224
Method	Mixed-effect Model Repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.309
upper limit	0.102

Notes:

[4] - Least Squares Mean of 1 mg BI 685509 TID"- Least Squares Mean of Placebo

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

Least Square Means difference and 95% confidence interval were estimated by restricted maximum likelihood based Mixed-effect Model for Repeated Measures ((REML)−based 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	BI 685509 2mg TID v Placebo

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.5616
Method	Mixed-effect Model Repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.275
upper limit	0.15

Notes:

[5] - Least Squares Mean of "2 mg BI 685509 TID"- Least Squares Mean of "Placebo"

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

Least Square Means difference and 95% confidence interval were estimated by restricted maximum likelihood based Mixed-effect Model for Repeated Measures ((REML)−based 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	BI 685509 3 mg TID v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0183
Method	Mixed-effect Model Repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.251
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.459
upper limit	-0.043

Notes:

[6] - Least Squares Mean of "3 mg BI 685509 TID"- Least Squares Mean of "Placebo"

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Quadratic model 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.

Comparison groups	BI 685509 1 mg TID v BI 685509 2mg TID v BI 685509 3 mg TID v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0468 [8]
Method	MCP-Mod quadratic model fit

Notes:

[7] - A flat vs. non-flat dose-response relationship across the 3 doses of BI 685509 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, quadratic, Emax and

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 BI 685509 3 mg, 6 mg, and 9 mg).
[8] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. Including the fixed, categorical effects of treatment at each visit, and the continuous effect of baseline at each visit, as well as random effects of patient

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of BI 685509 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, quadratic, Emax and 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 BI 685509 3 mg, 6 mg, and 9 mg).

Comparison groups	BI 685509 1 mg TID v BI 685509 2mg TID v BI 685509 3 mg TID v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.0586
Method	MCP-Mod Emax model fit

Notes:

[9] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. 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. Emax model assumption: 80% of the maximum effect is achieved at 6 mg.

Secondary: Change from baseline in log transformed Urine Albumin Creatinine Ratio (UACR) measured in First Morning Void urine after 20 weeks of trial treatment

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

End point description:

Change from baseline in log transformed Urine Albumin Creatinine Ratio (UACR) measured in First Morning Void urine 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. Least Square Means and Standard error were estimated by restricted maximum likelihood based Mixed-effect Model for Repeated Measures ((REML)−based 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 Least Squares Mean (Standard error) at Week 20 is reported.

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	BI 685509 1 mg TID	BI 685509 2mg TID	BI 685509 3 mg TID	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	53	56	56
Units: milligram/gram (mg/g)				
least squares mean (standard error)	-0.112 (± 0.072)	-0.020 (± 0.076)	-0.258 (± 0.074)	0.099 (± 0.072)

Statistical analyses

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

Least Square Means difference and 95% confidence interval were estimated by restricted maximum likelihood based Mixed-effect Model for Repeated Measures ((REML)−based 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	BI 685509 1 mg TID v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.0396
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.211
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	-0.413
upper limit	-0.01

Notes:

[10] - Least Squares Mean of "1 mg BI 685509 TID"- Least Squares Mean of "Placebo"

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

Least Square Means difference and 95% confidence interval were estimated by restricted maximum likelihood based Mixed-effect Model for Repeated Measures ((REML)−based 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	BI 685509 3 mg TID v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.0006
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.357
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.154

Notes:

[11] - Least Squares Mean of "3 mg BI 685509 TID"- Least Squares Mean of "Placebo"

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

Least Square Means difference and 95% confidence interval were estimated by restricted maximum likelihood based Mixed-effect Model for Repeated Measures ((REML)−based 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	BI 685509 2mg TID v Placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.2568
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.12
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	-0.327
upper limit	0.088

Notes:

[12] - Least Squares Mean of "2 mg BI 685509 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 is reported. As soon as the First Morning Void sample was collected the clock starts for the 10-hour urine collection. During the 10-hour period every time the patient urinates, they collected their urine into a provided container. An aliquot of this urine was taken and used as the 10-hour UACR sample.

End point type	Secondary

End point timeframe:

Baseline (day -14 and -7) and week 20 (day 141)

End point values	BI 685509 1 mg TID	BI 685509 2mg TID	BI 685509 3 mg TID	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	53	56	56
Units: Participants	23	16	26	13

Statistical analyses

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

Treatment, sodium-Glucose co-Transporter-2 Inhibitor (SGLT2i) use at baseline, and type of diabetes were used as covariates in the logistic regression model.

Comparison groups	BI 685509 1 mg TID v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.0519
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	5.1

Notes:

[13] - Odds Ratio was calculated as BI 685509/ Placebo.

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

Treatment, sodium-Glucose co-Transporter-2 Inhibitor (SGLT2i) use at baseline, and type of diabetes were used as covariates in the logistic regression model.

Comparison groups	BI 685509 2mg TID v Placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.4159
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	3.36

Notes:

[14] - Odds Ratio was calculated as BI 685509/ Placebo.

Statistical analysis title	Statistical analysis 14

Statistical analysis description:

Treatment, sodium-Glucose co-Transporter-2 Inhibitor (SGLT2i) use at baseline, and type of diabetes were used as covariates in the logistic regression model.

Comparison groups	BI 685509 3 mg TID v Placebo

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.0106
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	6.55

Notes:

[15] - Odds Ratio was calculated as BI 685509/ Placebo

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 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.

End point type	Secondary

End point timeframe:

Baseline (day -14 and -7) and week 20 (day 141)

End point values	BI 685509 1 mg TID	BI 685509 2mg TID	BI 685509 3 mg TID	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	53	56	56
Units: Participants	23	13	29	11

Statistical analyses

Statistical analysis title	Statistical analysis 15

Statistical analysis description:

Treatment, sodium-Glucose co-Transporter-2 Inhibitor (SGLT2i) use at baseline, and type of diabetes were used as covariates in the logistic regression model.

Comparison groups	BI 685509 1 mg TID v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.0176
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	6.53

Notes:

[16] - Odds Ratio was calculated as BI 685509/ Placebo.

Statistical analysis title	Statistical analysis 16

Statistical analysis description:

Treatment, sodium-Glucose co-Transporter-2 Inhibitor (SGLT2i) use at baseline, and type of diabetes were used as covariates in the logistic regression model.

Comparison groups	BI 685509 2mg TID v Placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.5467
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	3.29

Notes:

[17] - Odds Ratio was calculated as BI 685509/ Placebo

Statistical analysis title	Statistical analysis 17

Statistical analysis description:

Treatment, sodium-Glucose co-Transporter-2 Inhibitor (SGLT2i) use at baseline, and type of diabetes were used as covariates in the logistic regression model.

Comparison groups	BI 685509 3 mg TID v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.0005
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.91
upper limit	10.39

Notes:

[18] - Odds Ratio was calculated as BI 685509/ Placebo

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first BI 685509 intake until last BI 685509 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 set included all patients who were dispensed trial medication (BI 685509) and were documented to have taken at least 1 dose of open-label trial medication (BI 685509).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	BI 685509 1mg TID

Reporting group description:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during 20 weeks of treatment in total, with water and 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	BI 685509 3mg TID

Reporting group description:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 4 of treatment. Then if medication was tolerated, up-titration to 3 mg TID BI 685509 occurred from Week 5 until Week 20. The tablets were taken with water, 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 randomized in the dose group in a 3:1 ratio (test treatment to placebo). Participants were administered film-coated tablets of matching placebo 3 times a day during 20 weeks of treatment. The tablets were taken with water, with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Reporting group title	BI 685509 2mg TID

Reporting group description:

The patients were administered 1 milligram (mg) BI 685509 film-coated tablets 3 times a day during the first 2 weeks of treatment, If the medication was tolerated, up-titration to 2 mg TID BI 685509 occurred after 2 weeks until Week 20 of treatment. The tablets were taken with water, with or without food. Patients continued the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurred first.

Serious adverse events	BI 685509 1mg TID	BI 685509 3mg TID	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 61 (6.56%)	7 / 61 (11.48%)	4 / 58 (6.90%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Extremity necrosis			

subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Investigations			
Protein urine present			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (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			
Procedural haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Acute myocardial infarction			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Cardiac failure congestive			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (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
Cardiac failure			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Nodal rhythm			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Nervous system disorders			
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (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
Epiploic appendagitis			

subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Diabetic bullosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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			
Renal mass			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Chronic kidney disease			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Acute kidney injury			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (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
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Gastroenteritis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (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
Influenza			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Osteomyelitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Pneumonia bacterial			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (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
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 58 (1.72%)
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	BI 685509 2mg TID		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 61 (13.11%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Protein urine present			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 61 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nodal rhythm				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Normal pressure hydrocephalus				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Intestinal obstruction				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epiploic appendagitis				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Cholecystitis				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Diabetic foot				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic bullosis				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal mass				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 61 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypoglycaemia				
subjects affected / exposed	0 / 61 (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	BI 685509 1mg TID	BI 685509 3mg TID	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 61 (21.31%)	15 / 61 (24.59%)	14 / 58 (24.14%)
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 61 (4.92%)	5 / 61 (8.20%)	0 / 58 (0.00%)
occurrences (all)	3	8	0
Hypertension			
subjects affected / exposed	3 / 61 (4.92%)	3 / 61 (4.92%)	6 / 58 (10.34%)
occurrences (all)	3	4	8
General disorders and administration site conditions			

Oedema peripheral subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2	5 / 61 (8.20%) 6	1 / 58 (1.72%) 1
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4	1 / 61 (1.64%) 1	4 / 58 (6.90%) 4
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2	3 / 61 (4.92%) 3	3 / 58 (5.17%) 4

Non-serious adverse events	BI 685509 2mg TID		
Total subjects affected by non-serious adverse events subjects affected / exposed	15 / 61 (24.59%)		
Vascular disorders Hypotension subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 6 2 / 61 (3.28%) 2		
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2020	Global Amendment 1: Version 2.0 is considered to be the initial version of the CTP and included some modifications after version 1.0 has been archived. The original version 1.0 of this protocol was not submitted to any authorities, ethics committees or institutional review board for approval of the clinical trial.
29 July 2021	Global Amendment 2: -The column header "Post dose" and a cross to indicate post dose ECG at Visit 3 were added to the flow chart.-Extended the maximum time before randomisation from 28 to 35 days throughout the protocol.-Further requirement to inclusion criterion #3 was added: eGFR must remain ≥20 mL/min/1.73 m2 after Visit 1 up to the start of Visit 3, measured by central or any local laboratory analysis.-Adverse events to be summarized by the treatment to which the subject was randomised, and the treatment at the onset of AE for the drug-related AE rather than the treatment at end of the up-titration period as was before.
13 October 2021	Global Amendment 3: Addition of ECGs at visits where there were previously no ECGs: three ECGs at visits 4, 5 and one ECG at Visits 7 and 8. At Visits 3 and 6 an additional ECG to be done to the two already performed. -eGFR has been added as a test that patients can be pre-screened for if consent is given.Potential QT-interval prolongation was added as a risk along with the summary of data, rationale for the risk and the mitigation strategy.-Exclusion criteria 11) Removal of lactose monohydrate as an example of an excipient.Addition of the following exclusion criteria:17. QTcF -interval >450 ms in men or >470 ms in women at any time from screening (Visit 1) until start of treatment. 18. A family history of long QT syndrome. 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.The following was added to Discontinuation of Trial Treatment: Patients with a QT or QTcF interval >500 ms, or an increase of QT or QTcF of >60 ms from the pre-dosevalue at Visit 3 (baseline). Such cases must be reported as AEs.-Text was added to state that ECGs were to be performed prior to blood draws and after the patient has been in the supine position for 5 min.
14 March 2022	Global Amendment 4: Exclusion criterion #1 was changed to: Treatment with Renin Angiotensin Aldosterone System (RAAS) interventions (apart from either ACEi or ARB), phosphodiesterase-5 inhibitors, non-specific phosphodiesterase inhibitors (such as dipyridamole and theophylline), NO donors including nitrates, sGCstimulators/activators (other than trial treatment) or any other restricted medication (including OATP1B1/3 inhibitors, UGT inhibitors/inducers) as provided in the Investigator Site File (ISF) within 4 weeks prior to Visit 1 and throughout screening and baseline run-in. Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial are also excluded.
14 March 2022	Global Amendment 4: Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial are also excluded. 3.3.4.1 Discontinuation of trial treatment: The patient experiences a severe infection e.g. with SARSCoV- 2, as determined by the Investigator. Was changed to: The patient experiences a severe infection, e.g. with SARSCoV-2 that precludes their safe participation in the trial, as determined by the Investigator. 4.2.2.1 Restrictions regarding concomitant treatment: Phosphodiesterase inhibitors Nitrates in table 4.2.2.1:1 replaced with: Phosphodiesterase-5 inhibitors, non-specific phosphodiesterase inhibitors (such as dipyridamole and theophylline). 7.2.1: The TS is used for safety analyses as well as demographics and baseline characteristics. was replaced with: The TS is used for safety analyses and exposure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported