



## 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          | v1              |
| This version publication date  | 07 January 2024 |
| First version publication date | 07 January 2024 |

### 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, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a> |
| Scientific contact           | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a> |

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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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                |
| <b>Arm title</b>             | 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.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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                           | -                  | -                 | -                  |

| <b>Number of subjects in period 1</b> | 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) 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 |
| 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 |

| 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) 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 | -   |  |
| 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 | -   |  |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | BI 685509 1 mg TID |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Baseline (Week -2 and Week -1) and Week 6, Week 12 and 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                    | 52                    | 56                    | 56                   |
| Units: milligram/gram (mg/g)        |                       |                       |                       |                      |
| least squares mean (standard error) | -0.069 ( $\pm$ 0.074) | -0.029 ( $\pm$ 0.079) | -0.217 ( $\pm$ 0.076) | 0.034 ( $\pm$ 0.073) |

## Statistical analyses

| 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 | 221   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[1]</sup>  |
| P-value                                 | = 0.0294  |
| Method                                  | MCP-Mod linear 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. Linear: No assumption was needed.

| Statistical analysis title | Statistical analysis 3 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Quadratic 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 | 221   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[2]</sup>  |
| P-value                                 | = 0.0468 <sup>[3]</sup>   |
| Method                                  | MCP-Mod quadratic model fit   |

Notes:

[2] - 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).

[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, 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 | 221   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[4]</sup>  |
| P-value                                 | = 0.0586  |
| Method                                  | MCP-Mod Emax model fit  |

Notes:

[4] - 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 assumption: 80% of the maximum effect is achieved at 6 mg.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | 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 | 221   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[5]</sup>  |
| P-value                                 | = 0.0245  |
| Method                                  | MCP-Mod exponential model fit   |

Notes:

[5] - 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: 20% of the maximum effect is achieved at 3 mg.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | 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 | 221   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[6]</sup>  |
| P-value                                 | = 0.0659  |
| Method                                  | MCP-Mod Sigmoid emax model fit  |

Notes:

[6] - 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 assumption: Sigmoid emax: 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:<br>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 <sup>[7]</sup>                  |
| 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:

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

| Statistical analysis title   | Statistical analysis 7                |
|--|---------------------------------------|
| Statistical analysis description:<br>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  | 108                                   |
| Analysis specification   | Pre-specified                         |
| Analysis type  | other <sup>[8]</sup>                  |
| 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:

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

| Statistical analysis title  | Statistical analysis 8 |
|---|------------------------|
| Statistical analysis description:<br>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 <sup>[9]</sup>                  |
| 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:

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

## 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:

Baseline (Week -2 and Week -1) and Week 6, Week 12 and 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         | 56                 | 53                | 55                 | 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 | 112                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other <sup>[10]</sup>        |
| 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"

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | 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 | 111                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other <sup>[11]</sup>        |
| 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"

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[12]</sup> |
| 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 <sup>[13]</sup> |
| 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.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>   | 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 <sup>[14]</sup>       |
| 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.

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>   | 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 <sup>[15]</sup>        |
| 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 <sup>[16]</sup>        |
| 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:<br>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 <sup>[17]</sup>       |
| 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:<br>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 <sup>[18]</sup>        |
| 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 | 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 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 | 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 | Placebo        | BI 685509 3mg TID |
|---|-------------------|----------------|-------------------|
| Total subjects affected by serious adverse events |                   |                |                   |
| subjects affected / exposed                       | 4 / 61 (6.56%)    | 4 / 58 (6.90%) | 7 / 61 (11.48%)   |
| number of deaths (all causes)                     | 0                 | 0              | 2                 |
| number of deaths resulting from adverse events    | 0                 | 0              | 0                 |
| Vascular disorders                                |                   |                |                   |
| Extremity necrosis                                |                   |                |                   |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 0 / 61 (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 / 58 (0.00%) | 0 / 61 (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%) | 0 / 58 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                       |                |                |                |
| Protein urine present                                |                |                |                |
| subjects affected / exposed                          | 1 / 61 (1.64%) | 0 / 58 (0.00%) | 0 / 61 (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 / 58 (0.00%) | 0 / 61 (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                                    |                |                |                |
| Atrial fibrillation                                  |                |                |                |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 1 / 61 (1.64%) |
| 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                          | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                          |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 61 (1.64%) | 1 / 58 (1.72%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Angina unstable                                 |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nodal rhythm                                    |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 58 (1.72%) | 0 / 61 (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          |
| Myocardial ischaemia                            |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 0 / 61 (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 failure congestive                      |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 58 (0.00%) | 0 / 61 (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                        |                |                |                |
| Normal pressure hydrocephalus                   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 0 / 61 (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%) | 0 / 58 (0.00%) | 1 / 61 (1.64%) |
| 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                      |                |                |                |
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 58 (0.00%) | 0 / 61 (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%) | 1 / 58 (1.72%) | 0 / 61 (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          |
| Hepatobiliary disorders                         |                |                |                |
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 0 / 61 (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 / 58 (0.00%) | 0 / 61 (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 / 58 (0.00%) | 0 / 61 (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 / 58 (0.00%) | 0 / 61 (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%) | 0 / 58 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute kidney injury                             |                |                |                |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 58 (0.00%) | 0 / 61 (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                     |                |                |                |
| Gastroenteritis                                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 58 (0.00%) | 0 / 61 (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          |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 1 / 61 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Influenza                                       |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 0 / 61 (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 / 58 (0.00%) | 0 / 61 (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          |
| Osteomyelitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 0 / 58 (0.00%) | 0 / 61 (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          |
| Metabolism and nutrition disorders              |                |                |                |
| Hypoglycaemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 58 (1.72%) | 0 / 61 (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          |

|   |                   |  |  |
|---|-------------------|--|--|
| <b>Serious adverse events</b>                     | 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                                    |                |  |  |
| 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                                      |                |  |  |
| 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          |  |  |
| 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          |  |  |
| 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          |  |  |
| 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          |  |  |
| 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                     |                |  |  |
| Gastroenteritis                                 |                |  |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cellulitis                                      |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| 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          |  |  |
| 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          |  |  |
| Osteomyelitis                                   |                |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| 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 %

| <b>Non-serious adverse events</b>                     | BI 685509 1mg TID | Placebo          | BI 685509 3mg TID |
|---|-------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events |                   |                  |                   |
| subjects affected / exposed                           | 13 / 61 (21.31%)  | 14 / 58 (24.14%) | 15 / 61 (24.59%)  |
| Vascular disorders                                    |                   |                  |                   |
| Hypertension  |                   |                  |                   |
| subjects affected / exposed                           | 3 / 61 (4.92%)    | 6 / 58 (10.34%)  | 3 / 61 (4.92%)    |
| occurrences (all)                                     | 3                 | 8                | 4                 |
| Hypotension   |                   |                  |                   |
| subjects affected / exposed                           | 3 / 61 (4.92%)    | 0 / 58 (0.00%)   | 5 / 61 (8.20%)    |
| occurrences (all)                                     | 3                 | 0                | 8                 |
| General disorders and administration site conditions  |                   |                  |                   |

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

|   |  |  |  |
|---|--|--|--|
| <b>Non-serious adverse events</b>   | BI 685509 2mg TID                              |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 15 / 61 (24.59%)                               |  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypotension<br>subjects affected / exposed<br>occurrences (all) | 2 / 61 (3.28%)<br>2<br><br>6 / 61 (9.84%)<br>6 |  |  |
| General disorders and administration site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)                                 | 5 / 61 (8.20%)<br>5                            |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 61 (1.64%)<br>1                            |  |  |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all)   | 3 / 61 (4.92%)<br>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 $\geq 20$ mL/min/1.73 m <sup>2</sup> 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-dose value 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.  |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported