



## Clinical trial results:

**A randomized, double-blind, placebo-controlled, parallel groups study to investigate the safety and tolerability, efficacy, pharmacokinetics and pharmacodynamics of three BI 187004 doses given once daily as monotherapy and of the highest BI 187004 dose given once daily as add on treatment to metformin over 28 days in patients with type 2 diabetes mellitus**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-003646-16 |
| Trial protocol           | DE             |
| Global end of trial date | 02 August 2015 |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 13 August 2016 |
| First version publication date | 13 August 2016 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 1307.4 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02150824 |
| 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               | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , +1 8002430127, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a> |
| Scientific contact           | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , +1 8002430127, <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                       | 10 September 2015 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 12 July 2015      |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 02 August 2015    |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the current study is to investigate the safety and tolerability of a once daily oral dose of 20 mg, 80 mg or 240 mg BI 187004 as mono-therapy and 240 mg BI 187004 on a stable metformin background over 28 days in patients with type 2 diabetes mellitus.

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 patients as required.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 11 July 2014 |
| 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 | Germany: 103 |
| Worldwide total number of subjects   | 103          |
| EEA total number of subjects         | 103          |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |

|                      |    |
|----------------------|----|
| Adults (18-64 years) | 72 |
| From 65 to 84 years  | 31 |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

This was a randomised, double-blind, placebo-controlled study with parallel groups to investigate the safety, tolerability, efficacy, pharmacokinetics & pharmacodynamics of BI 187004 administered as once daily oral dose of 20mg, 80mg or 240mg monotherapy, or as 240mg add-on to a metformin background, over 28 days in patients with type 2 diabetes mellitus.

### Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the subjects) met all implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial drug if any of the specific entry criteria was violated. In this study, 216 enrolled & 103 entered & treated.

### Period 1

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

Blinding implementation details:

This is a randomised, placebo-controlled, double-blind and parallel-group study.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 oral antidiabetic drug (OAD) (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablet(s) once daily over 28 days.

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

Dosage and administration details:

Subjects were orally administered placebo tablet(s) once daily over 28 days.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | 20 mg BI 187004 |
|------------------|-----------------|

Arm description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 20 mg BI 187004 tablet once daily over 28 days.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | BI 187004 20 mg |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Tablet          |
| Routes of administration               | Oral use        |

Dosage and administration details:

Subjects were orally administered 20 mg BI 187004 tablet once daily over 28 days.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | 80 mg BI 187004 |
|------------------|-----------------|

**Arm description:**

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 80 mg BI 187004 tablet once daily over 28 days.

|                                        |                |
|----------------------------------------|----------------|
| Arm type                               | Experimental   |
| Investigational medicinal product name | BI 187004 80mg |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Oral use       |

**Dosage and administration details:**

Subjects were orally administered 80 mg BI 187004 tablet once daily over 28 days.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | 240 mg BI 187004 |
|------------------|------------------|

**Arm description:**

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | BI 187004 240mg |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Tablet          |
| Routes of administration               | Oral use        |

**Dosage and administration details:**

Subjects were orally administered 240 mg BI 187004 once daily over 28 days.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Placebo + met |
|------------------|---------------|

**Arm description:**

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablets once daily over 28 days with metformin as background therapy.

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

**Dosage and administration details:**

The patients were orally administered placebo tablets once daily over 28 days.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

**Dosage and administration details:**

The patients were orally administered Metformin as a background therapy once daily over 28 days.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | 240 mg BI 187004 + met |
|------------------|------------------------|

**Arm description:**

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days with metformin as background therapy.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | 240 mg BI 187004 |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

The patients on a stable background monotherapy treatment with metformin and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.

|                                        |           |
|----------------------------------------|-----------|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

The patients were orally administered Metformin as a background therapy once daily over 28 days.

| <b>Number of subjects in period 1</b> | Placebo | 20 mg BI 187004 | 80 mg BI 187004 |
|---------------------------------------|---------|-----------------|-----------------|
| Started                               | 15      | 16              | 16              |
| Completed                             | 15      | 16              | 16              |

| <b>Number of subjects in period 1</b> | 240 mg BI 187004 | Placebo + met | 240 mg BI 187004 + met |
|---------------------------------------|------------------|---------------|------------------------|
| Started                               | 15               | 21            | 20                     |
| Completed                             | 15               | 21            | 20                     |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                  |                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | Placebo                |
| Reporting group description:<br>The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 oral antidiabetic drug (OAD) (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablet(s) once daily over 28 days. |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | 20 mg BI 187004        |
| Reporting group description:<br>The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 20 mg BI 187004 tablet once daily over 28 days.                     |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | 80 mg BI 187004        |
| Reporting group description:<br>The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 80 mg BI 187004 tablet once daily over 28 days.                     |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | 240 mg BI 187004       |
| Reporting group description:<br>The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.                           |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | Placebo + met          |
| Reporting group description:<br>The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablets once daily over 28 days with metformin as background therapy.                                                                                      |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | 240 mg BI 187004 + met |
| Reporting group description:<br>The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days with metformin as background therapy.                                                                                     |                        |

| Reporting group values                                                                                                      | Placebo   | 20 mg BI 187004 | 80 mg BI 187004 |
|-----------------------------------------------------------------------------------------------------------------------------|-----------|-----------------|-----------------|
| Number of subjects                                                                                                          | 15        | 16              | 16              |
| Age categorical<br>Units: Subjects                                                                                          |           |                 |                 |
| Age continuous                                                                                                              |           |                 |                 |
| Treated Set(TS): The patients who were treated with $\geq 1$ dose of study medication were all included in the Treated Set. |           |                 |                 |
| Units: years                                                                                                                |           |                 |                 |
| arithmetic mean                                                                                                             | 57.6      | 58.6            | 59.4            |
| standard deviation                                                                                                          | $\pm 7.3$ | $\pm 11.6$      | $\pm 8.6$       |
| Gender categorical<br>Units: Subjects                                                                                       |           |                 |                 |
| Female                                                                                                                      | 4         | 3               | 5               |
| Male                                                                                                                        | 11        | 13              | 11              |

| Reporting group values                                                                                                      | 240 mg BI 187004  | Placebo + met     | 240 mg BI 187004 + met |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------|------------------------|
| Number of subjects                                                                                                          | 15                | 21                | 20                     |
| Age categorical<br>Units: Subjects                                                                                          |                   |                   |                        |
| Age continuous                                                                                                              |                   |                   |                        |
| Treated Set(TS): The patients who were treated with $\geq 1$ dose of study medication were all included in the Treated Set. |                   |                   |                        |
| Units: years<br>arithmetic mean<br>standard deviation                                                                       | 55.7<br>$\pm 7.8$ | 57.2<br>$\pm 9.8$ | 62.1<br>$\pm 7.8$      |
| Gender categorical<br>Units: Subjects                                                                                       |                   |                   |                        |
| Female                                                                                                                      | 3                 | 5                 | 2                      |
| Male                                                                                                                        | 12                | 16                | 18                     |

  

| Reporting group values                                                                                                      | Total |  |  |
|-----------------------------------------------------------------------------------------------------------------------------|-------|--|--|
| Number of subjects                                                                                                          | 103   |  |  |
| Age categorical<br>Units: Subjects                                                                                          |       |  |  |
| Age continuous                                                                                                              |       |  |  |
| Treated Set(TS): The patients who were treated with $\geq 1$ dose of study medication were all included in the Treated Set. |       |  |  |
| Units: years<br>arithmetic mean<br>standard deviation                                                                       | -     |  |  |
| Gender categorical<br>Units: Subjects                                                                                       |       |  |  |
| Female                                                                                                                      | 22    |  |  |
| Male                                                                                                                        | 81    |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                  |                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | Placebo                |
| Reporting group description:<br>The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 oral antidiabetic drug (OAD) (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablet(s) once daily over 28 days. |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | 20 mg BI 187004        |
| Reporting group description:<br>The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 20 mg BI 187004 tablet once daily over 28 days.                     |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | 80 mg BI 187004        |
| Reporting group description:<br>The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 80 mg BI 187004 tablet once daily over 28 days.                     |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | 240 mg BI 187004       |
| Reporting group description:<br>The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.                           |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | Placebo + met          |
| Reporting group description:<br>The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablets once daily over 28 days with metformin as background therapy.                                                                                      |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                            | 240 mg BI 187004 + met |
| Reporting group description:<br>The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days with metformin as background therapy.                                                                                     |                        |

### Primary: The percentage of patients with drug-related AEs

|                                                                                                                                                                                                                                                                                                   |                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                   | The percentage of patients with drug-related AEs <sup>[1]</sup> |
| End point description:<br>The percentage of patients with drug-related AEs.                                                                                                                                                                                                                       |                                                                 |
| End point type                                                                                                                                                                                                                                                                                    | Primary                                                         |
| End point timeframe:<br>from first drug administration until 14 days after the last drug administration, up to 42 days.                                                                                                                                                                           |                                                                 |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis test were tested. |                                                                 |

| End point values                  | Placebo           | 20 mg BI<br>187004 | 80 mg BI<br>187004 | 240 mg BI<br>187004 |
|-----------------------------------|-------------------|--------------------|--------------------|---------------------|
| Subject group type                | Reporting group   | Reporting group    | Reporting group    | Reporting group     |
| Number of subjects analysed       | 15 <sup>[2]</sup> | 16 <sup>[3]</sup>  | 16 <sup>[4]</sup>  | 15 <sup>[5]</sup>   |
| Units: Percentage of participants |                   |                    |                    |                     |
| number (not applicable)           | 33.3              | 0                  | 31.3               | 26.7                |

Notes:

[2] - Treated Set

[3] - Treated Set

[4] - Treated Set

[5] - Treated Set

| End point values                  | Placebo + met     | 240 mg BI<br>187004 + met |  |  |
|-----------------------------------|-------------------|---------------------------|--|--|
| Subject group type                | Reporting group   | Reporting group           |  |  |
| Number of subjects analysed       | 21 <sup>[6]</sup> | 20 <sup>[7]</sup>         |  |  |
| Units: Percentage of participants |                   |                           |  |  |
| number (not applicable)           | 19                | 30                        |  |  |

Notes:

[6] - Treated Set

[7] - Treated Set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in FPG after 28 days of treatment

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | Change from baseline in FPG after 28 days of treatment |
|-----------------|--------------------------------------------------------|

End point description:

Change from baseline in fasting plasma glucose (FPG) after 28 days of treatment. The ANCOVA model was used to calculate the least squares mean and standard error.

Observed case analysis for FPG (OC-G): This method was used to impute the missing values.

The number of participants analysed displays the number of participants with available data at the timepoint of interest.

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

End point timeframe:

Baseline and Day 29

| End point values                    | Placebo           | 20 mg BI<br>187004 | 80 mg BI<br>187004 | 240 mg BI<br>187004 |
|-------------------------------------|-------------------|--------------------|--------------------|---------------------|
| Subject group type                  | Reporting group   | Reporting group    | Reporting group    | Reporting group     |
| Number of subjects analysed         | 15 <sup>[8]</sup> | 16 <sup>[9]</sup>  | 16 <sup>[10]</sup> | 14 <sup>[11]</sup>  |
| Units: mg/dL                        |                   |                    |                    |                     |
| least squares mean (standard error) | 0.9 (± 5.2)       | 6.6 (± 5)          | 8 (± 5)            | 6.8 (± 5.4)         |

Notes:

[8] - TS (OC-G)

[9] - TS (OC-G)

[10] - TS (OC-G)

[11] - TS (OC-G)

| End point values                    | Placebo + met      | 240 mg BI 187004 + met |  |  |
|-------------------------------------|--------------------|------------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group        |  |  |
| Number of subjects analysed         | 21 <sup>[12]</sup> | 20 <sup>[13]</sup>     |  |  |
| Units: mg/dL                        |                    |                        |  |  |
| least squares mean (standard error) | 4.5 (± 4.4)        | 6.1 (± 4.5)            |  |  |

Notes:

[12] - TS (OC-G)

[13] - TS (OC-G)

## Statistical analyses

| Statistical analysis title | All groups |
|----------------------------|------------|
|----------------------------|------------|

Statistical analysis description:

The statistical model used for the analysis of change from baseline (Day 1 of Visit 3) in FPG after 28 days of treatment was an Analysis of Covariance (ANCOVA) model. In model, the treatment was considered as a categorical effect, baseline FPG was included as a continuous covariate. Missing FPG values after 28 days of treatment were not replaced, whereas values after the potential introduction of another antidiabetic drug were not included in the primary analysis.

|                                         |                                                                                                         |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------|
| Comparison groups                       | Placebo v 20 mg BI 187004 v 80 mg BI 187004 v 240 mg BI 187004 v Placebo + met v 240 mg BI 187004 + met |
| Number of subjects included in analysis | 102                                                                                                     |
| Analysis specification                  | Pre-specified                                                                                           |
| Analysis type                           | superiority                                                                                             |
| P-value                                 | = 0.9414                                                                                                |
| Method                                  | ANCOVA                                                                                                  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from first drug administration until 14 days after the last drug administration, upto 42 days.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablet(s) once daily over 28 days.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | 20 mg BI 187004 |
|-----------------------|-----------------|

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 20 mg BI 187004 tablet once daily over 28 days.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | 80 mg BI 187004 |
|-----------------------|-----------------|

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 80 mg BI 187004 tablet once daily over 28 days.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | 240 mg BI 187004 |
|-----------------------|------------------|

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.

|                       |               |
|-----------------------|---------------|
| Reporting group title | Placebo + met |
|-----------------------|---------------|

Reporting group description:

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablets once daily over 28 days with metformin as background therapy.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | 240 mg BI 187004 + met |
|-----------------------|------------------------|

Reporting group description:

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days with metformin as background therapy.

| Serious adverse events                            | Placebo        | 20 mg BI 187004 | 80 mg BI 187004 |
|---------------------------------------------------|----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events |                |                 |                 |
| subjects affected / exposed                       | 0 / 15 (0.00%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| number of deaths (all causes)                     | 0              | 0               | 0               |
| number of deaths resulting from adverse events    | 0              | 0               | 0               |

| <b>Serious adverse events</b>                     | 240 mg BI 187004 | Placebo + met  | 240 mg BI 187004 + met |
|---------------------------------------------------|------------------|----------------|------------------------|
| Total subjects affected by serious adverse events |                  |                |                        |
| subjects affected / exposed                       | 0 / 15 (0.00%)   | 0 / 21 (0.00%) | 0 / 20 (0.00%)         |
| number of deaths (all causes)                     | 0                | 0              | 0                      |
| number of deaths resulting from adverse events    | 0                | 0              | 0                      |

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

| <b>Non-serious adverse events</b>                     | Placebo          | 20 mg BI 187004  | 80 mg BI 187004  |
|-------------------------------------------------------|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events |                  |                  |                  |
| subjects affected / exposed                           | 13 / 15 (86.67%) | 14 / 16 (87.50%) | 15 / 16 (93.75%) |
| Vascular disorders                                    |                  |                  |                  |
| Flushing                                              |                  |                  |                  |
| subjects affected / exposed                           | 10 / 15 (66.67%) | 14 / 16 (87.50%) | 12 / 16 (75.00%) |
| occurrences (all)                                     | 10               | 14               | 12               |
| Orthostatic hypotension                               |                  |                  |                  |
| subjects affected / exposed                           | 0 / 15 (0.00%)   | 0 / 16 (0.00%)   | 1 / 16 (6.25%)   |
| occurrences (all)                                     | 0                | 0                | 2                |
| Peripheral coldness                                   |                  |                  |                  |
| subjects affected / exposed                           | 0 / 15 (0.00%)   | 0 / 16 (0.00%)   | 1 / 16 (6.25%)   |
| occurrences (all)                                     | 0                | 0                | 1                |
| General disorders and administration site conditions  |                  |                  |                  |
| Chest pain                                            |                  |                  |                  |
| subjects affected / exposed                           | 0 / 15 (0.00%)   | 0 / 16 (0.00%)   | 1 / 16 (6.25%)   |
| occurrences (all)                                     | 0                | 0                | 1                |
| Chills                                                |                  |                  |                  |
| subjects affected / exposed                           | 0 / 15 (0.00%)   | 0 / 16 (0.00%)   | 1 / 16 (6.25%)   |
| occurrences (all)                                     | 0                | 0                | 1                |
| Fatigue                                               |                  |                  |                  |
| subjects affected / exposed                           | 0 / 15 (0.00%)   | 0 / 16 (0.00%)   | 1 / 16 (6.25%)   |
| occurrences (all)                                     | 0                | 0                | 1                |
| Feeling abnormal                                      |                  |                  |                  |

|                                                                                                              |                     |                     |                     |
|--------------------------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                                             | 0 / 15 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 15 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                 | 1 / 15 (6.67%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Psychiatric disorders<br>Listless<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 15 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Mood swings<br>subjects affected / exposed<br>occurrences (all)                                              | 1 / 15 (6.67%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Investigations<br>Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)               | 0 / 15 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 15 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| Nervous system disorders<br>Disturbance in attention<br>subjects affected / exposed<br>occurrences (all)     | 0 / 15 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Dysgeusia                                                                                                    |                     |                     |                     |

|                                        |                |                |                 |
|----------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed            | 1 / 15 (6.67%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Headache                               |                |                |                 |
| subjects affected / exposed            | 1 / 15 (6.67%) | 0 / 16 (0.00%) | 6 / 16 (37.50%) |
| occurrences (all)                      | 1              | 0              | 8               |
| Hypogeusia                             |                |                |                 |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Gastrointestinal disorders             |                |                |                 |
| Abdominal discomfort                   |                |                |                 |
| subjects affected / exposed            | 1 / 15 (6.67%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Abdominal pain upper                   |                |                |                 |
| subjects affected / exposed            | 1 / 15 (6.67%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Constipation                           |                |                |                 |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                      | 0              | 0              | 1               |
| Diarrhoea                              |                |                |                 |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Epigastric discomfort                  |                |                |                 |
| subjects affected / exposed            | 1 / 15 (6.67%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Flatulence                             |                |                |                 |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                      | 0              | 0              | 1               |
| Nausea                                 |                |                |                 |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Toothache                              |                |                |                 |
| subjects affected / exposed            | 0 / 15 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                      | 0              | 0              | 1               |
| Skin and subcutaneous tissue disorders |                |                |                 |
| Dermatitis contact                     |                |                |                 |

|                                                                                                                   |                      |                     |                      |
|-------------------------------------------------------------------------------------------------------------------|----------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                                                  | 0 / 15 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 15 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)                                                        | 0 / 15 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 15 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  |
| Rash generalised<br>subjects affected / exposed<br>occurrences (all)                                              | 1 / 15 (6.67%)<br>1  | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Renal and urinary disorders<br>Nocturia<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 15 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                     | 2 / 15 (13.33%)<br>2 | 0 / 16 (0.00%)<br>0 | 2 / 16 (12.50%)<br>2 |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)                                          | 1 / 15 (6.67%)<br>2  | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Infections and infestations<br>Adenoviral conjunctivitis<br>subjects affected / exposed<br>occurrences (all)      | 0 / 15 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                               | 1 / 15 (6.67%)<br>1  | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0  |
| Metabolism and nutrition disorders                                                                                |                      |                     |                      |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Hyperglycaemia              |                |                |                |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Polydipsia                  |                |                |                |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |

| <b>Non-serious adverse events</b>                     | 240 mg BI 187004  | Placebo + met    | 240 mg BI 187004 + met |
|-------------------------------------------------------|-------------------|------------------|------------------------|
| Total subjects affected by non-serious adverse events |                   |                  |                        |
| subjects affected / exposed                           | 15 / 15 (100.00%) | 18 / 21 (85.71%) | 18 / 20 (90.00%)       |
| Vascular disorders                                    |                   |                  |                        |
| Flushing                                              |                   |                  |                        |
| subjects affected / exposed                           | 14 / 15 (93.33%)  | 17 / 21 (80.95%) | 14 / 20 (70.00%)       |
| occurrences (all)                                     | 14                | 17               | 14                     |
| Orthostatic hypotension                               |                   |                  |                        |
| subjects affected / exposed                           | 0 / 15 (0.00%)    | 2 / 21 (9.52%)   | 2 / 20 (10.00%)        |
| occurrences (all)                                     | 0                 | 3                | 3                      |
| Peripheral coldness                                   |                   |                  |                        |
| subjects affected / exposed                           | 0 / 15 (0.00%)    | 0 / 21 (0.00%)   | 0 / 20 (0.00%)         |
| occurrences (all)                                     | 0                 | 0                | 0                      |
| General disorders and administration site conditions  |                   |                  |                        |
| Chest pain                                            |                   |                  |                        |
| subjects affected / exposed                           | 0 / 15 (0.00%)    | 0 / 21 (0.00%)   | 0 / 20 (0.00%)         |
| occurrences (all)                                     | 0                 | 0                | 0                      |
| Chills                                                |                   |                  |                        |
| subjects affected / exposed                           | 0 / 15 (0.00%)    | 0 / 21 (0.00%)   | 0 / 20 (0.00%)         |
| occurrences (all)                                     | 0                 | 0                | 0                      |
| Fatigue                                               |                   |                  |                        |
| subjects affected / exposed                           | 0 / 15 (0.00%)    | 0 / 21 (0.00%)   | 0 / 20 (0.00%)         |
| occurrences (all)                                     | 0                 | 0                | 0                      |
| Feeling abnormal                                      |                   |                  |                        |
| subjects affected / exposed                           | 1 / 15 (6.67%)    | 0 / 21 (0.00%)   | 0 / 20 (0.00%)         |
| occurrences (all)                                     | 1                 | 0                | 0                      |
| Peripheral swelling                                   |                   |                  |                        |
| subjects affected / exposed                           | 0 / 15 (0.00%)    | 0 / 21 (0.00%)   | 0 / 20 (0.00%)         |
| occurrences (all)                                     | 0                 | 0                | 0                      |

|                                                 |                 |                |                 |
|-------------------------------------------------|-----------------|----------------|-----------------|
| Respiratory, thoracic and mediastinal disorders |                 |                |                 |
| Cough                                           |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 21 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                               | 0               | 0              | 0               |
| Dyspnoea                                        |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 21 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                               | 0               | 0              | 0               |
| Psychiatric disorders                           |                 |                |                 |
| Listless                                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 21 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                               | 1               | 0              | 0               |
| Mood swings                                     |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 21 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                               | 0               | 0              | 0               |
| Investigations                                  |                 |                |                 |
| Blood pressure increased                        |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 21 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                               | 0               | 0              | 0               |
| Injury, poisoning and procedural complications  |                 |                |                 |
| Fall                                            |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 21 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                               | 0               | 0              | 0               |
| Cardiac disorders                               |                 |                |                 |
| Palpitations                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 21 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                               | 1               | 0              | 0               |
| Nervous system disorders                        |                 |                |                 |
| Disturbance in attention                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 21 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                               | 1               | 0              | 0               |
| Dysgeusia                                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 1 / 21 (4.76%) | 0 / 20 (0.00%)  |
| occurrences (all)                               | 0               | 1              | 0               |
| Headache                                        |                 |                |                 |
| subjects affected / exposed                     | 2 / 15 (13.33%) | 0 / 21 (0.00%) | 3 / 20 (15.00%) |
| occurrences (all)                               | 2               | 0              | 3               |
| Hypogeusia                                      |                 |                |                 |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 |
| Gastrointestinal disorders                       |                     |                     |                     |
| Abdominal discomfort                             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 21 (0.00%)      | 1 / 20 (5.00%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Abdominal pain upper                             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 21 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Constipation                                     |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 21 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Diarrhoea                                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 21 (0.00%)      | 3 / 20 (15.00%)     |
| occurrences (all)                                | 0                   | 0                   | 4                   |
| Epigastric discomfort                            |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 21 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Flatulence                                       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 21 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Nausea                                           |                     |                     |                     |
| subjects affected / exposed                      | 1 / 15 (6.67%)      | 0 / 21 (0.00%)      | 1 / 20 (5.00%)      |
| occurrences (all)                                | 1                   | 0                   | 1                   |
| Toothache                                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 15 (0.00%)      | 0 / 21 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Skin and subcutaneous tissue disorders           |                     |                     |                     |
| Dermatitis contact                               |                     |                     |                     |
| subjects affected / exposed                      | 1 / 15 (6.67%)      | 0 / 21 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Dry skin                                         |                     |                     |                     |
| subjects affected / exposed                      | 1 / 15 (6.67%)      | 0 / 21 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Eczema                                           |                     |                     |                     |

|                                                                                                                   |                     |                      |                      |
|-------------------------------------------------------------------------------------------------------------------|---------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                                                  | 1 / 15 (6.67%)<br>1 | 0 / 21 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 15 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0  | 1 / 20 (5.00%)<br>1  |
| Rash generalised<br>subjects affected / exposed<br>occurrences (all)                                              | 0 / 15 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Renal and urinary disorders<br>Nocturia<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 15 (6.67%)<br>1 | 0 / 21 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | 0 / 21 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 15 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)                                          | 0 / 15 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Infections and infestations<br>Adenoviral conjunctivitis<br>subjects affected / exposed<br>occurrences (all)      | 0 / 15 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                               | 1 / 15 (6.67%)<br>1 | 3 / 21 (14.29%)<br>3 | 3 / 20 (15.00%)<br>3 |
| Metabolism and nutrition disorders<br>Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 15 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Polydipsia<br>subjects affected / exposed<br>occurrences (all)                                                    | 0 / 15 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 05 June 2014      | <p>A new statement has been added to clarify on the meaning of the original sentence and make sure it is clear that all statins are allowed as co-medications regardless of their inhibition on the CYP3A4.</p> <p>As proposed and agreed with regulatory bodies, the blood glucose threshold for the initiation of rescue therapy has been lowered. Thus all instances of 270 mg/dL were replaced with 240 mg/dl.</p> <p>The text "(with the exception of GLP-1 receptor agonist)" was added to clarify GLP-1 analogues, though injectable antidiabetics, are allowed rescue medications.</p> <p>As proposed and agreed with Central EC , a process has been added to verify if it is medically acceptable for a patient to continue its participation when more repeated values greater than 140 mg/dL are detected.</p> <p>The clear guidance on where to find detailed instructions on how to handle the urine samples for pharmacodynamic assessments and on how to collect the weight of the containers was added.</p>    |
| 05 September 2014 | <p>Flow chart &amp;all other relevant sections of protocol were updated,In order to provide reliable results, prior to testing cortisol,ACTH &amp;other pituitary axis hormones,resting time of approximately 30 minutes (min) was implemented &amp;In order to accommodate the resting time,60 min window has been introduced &amp; also time interval for the test was increase.</p> <p>An exclusion criterion has been updated based on a publication referenced in protocol.The conversion from mg/dl to mmol/L for blood glucose levels has been changed from 15.0 to 13,3. The µg/l values for cortisol &amp; pg/ml values for Adrenocorticotrophin hormone(ACTH) were removed.The plasma cortisol cut-off point has been updated from 595 nmol/L to 377 nmol/L.</p> <p>A clarification on how to handle the 3 supine measurements &amp;how to perform the comparison to individual standing measurements was updated.</p>                                                                                                |
| 01 April 2015     | <p>Change in sample size was updated.</p> <p>In Sampling flow chart the typographical error was corrected and updated that the Day 28 3:00 am sample for WMG is meant to be at a specific point in time and not relative to the study drug intake.</p> <p>In order to minimized or prevented any bias during the interim analysis as certain functions within Boehringer Ingelheim will be required to be unblinded. It was updated that though certain patient will be unblinded, the unblinded information will not be shared or disclosed with team members that have a significant influence in the conduct of the study. Therefore, any bias will be minimized or prevented. The scope and purpose of the interim analysis was updated.</p> <p>The clarification was provided to emphasize that symptom compatible with low blood pressure or sudden changes in blood pressure are enough to declare the orthostatic test as abnormal.</p> <p>The definition of Postural Orthostatic Tachycardia Syndrome was updated.</p> |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported