



Clinical trial results:

A Phase II, randomized, parallel group, dose-finding study of subcutaneously administered BI 456906 for 16 weeks, compared with placebo and open-label semaglutide in patients with type 2 diabetes mellitus

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2019-002390-60 |
| Trial protocol | ES DE HU CZ GB IT |
| Global end of trial date | 05 November 2021 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 15 December 2022 |
| First version publication date | 15 December 2022 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 1404-0002 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04153929 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 December 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 October 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 November 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate proof of clinical concept (PoCC) with respect to a non-flat dose response curve and to define a suitable dose escalation scheme and dose range for BI 456906 regarding safety, tolerability, and efficacy.

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 | 09 June 2020 |
| 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 | Australia: 36 |
| Country: Number of subjects enrolled | Austria: 9 |
| Country: Number of subjects enrolled | Canada: 71 |
| Country: Number of subjects enrolled | Czechia: 23 |
| Country: Number of subjects enrolled | Germany: 15 |
| Country: Number of subjects enrolled | Hungary: 70 |
| Country: Number of subjects enrolled | Korea, Republic of: 27 |
| Country: Number of subjects enrolled | New Zealand: 28 |
| Country: Number of subjects enrolled | Poland: 55 |
| Country: Number of subjects enrolled | Spain: 29 |
| Country: Number of subjects enrolled | Taiwan: 13 |
| Country: Number of subjects enrolled | United Kingdom: 25 |
| Country: Number of subjects enrolled | United States: 268 |
| Worldwide total number of subjects | 669 |
| EEA total number of subjects | 201 |

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) | 498 |
| From 65 to 84 years | 171 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This was a randomized, multicenter placebo and active comparator controlled, double-blind within dose groups, parallel-group, 16-week trial in patients with type 2 diabetes mellitus (T2DM). An open-label arm (semaglutide) was included as benchmark to compare response curves and support assumptions for Phase III design.

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 | Randomised |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

Blinding implementation details:

The trial had a double blind design within each dose group. Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this trial will remained blinded with regard to the randomized treatment assignments until after database lock. The semaglutide group was open label.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

This arm comprises all placebo treated patients, regardless of the dose group in which they were treated. Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered solution for subcutaneous injection of placebo matched to BI 456906 once weekly for 16 weeks or twice weekly for 16 weeks.

| | |
|---|------------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | BI 456906 0.3 mg |

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1-Week 16.

| | |
|---|------------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | BI 456906 0.9 mg |

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5-Week 16.

| | |
|---|------------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | BI 456906 1.8 mg |

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI

456906 of 0.3 milligram (mg) on Week 1, 0.6 mg on Week 2, 0.9 mg on Week 3, 1.2 mg on Week 4, 1.5 mg on Week 5, and 1.8 mg on Week 6- Week 16.

| | |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

| | |
|------------------|------------------|
| Arm title | BI 456906 2.7 mg |
|------------------|------------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.6 milligram (mg) on Week 1 and Week 2, 1.2 mg on Week 3 and Week 4, 1.8 mg on Week 5, 2.4 mg on Week 6, 2.7 mg on Week 7- Week 16.

| | |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

| | |
|------------------|-------------------------------------|
| Arm title | BI 456906 1.2 twice weekly (2.4) mg |
|------------------|-------------------------------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2 (total weekly dose=0.6 mg), 0.6 mg on Week 3 and Week 4 (total weekly dose=1.2 mg), 0.9 mg on Week 5 and Week 6 (total weekly dose=1.8 mg), 1.2 mg on Week 7- Week 16 (total weekly dose 2.4 mg).

| | |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

| | |
|------------------|-------------------------------------|
| Arm title | BI 456906 1.8 twice weekly (3.6) mg |
|------------------|-------------------------------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 (total weekly dose=0.6 mg), 0.6 mg on Week 2 (total weekly dose=1.2 mg), 0.9 mg on Week 3 (total weekly dose=1.8 mg), 1.2 mg on Week 4 (total weekly dose 2.4 mg), 1.5 mg on Week 5 and on Week 6 (total weekly dose 3 mg), 1.8 mg on Week 7 -Week 16 (total weekly dose =3.6 mg).

| | |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

| | |
|------------------|-------------|
| Arm title | Semaglutide |
|------------------|-------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of Semaglutide of 0.25 milligram (mg) on Week 1-Week 4, 0.5 mg on Week 5-Week 8, 1.0 mg on Week 9-Week 16

| | |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

| Number of subjects in period 1 | Placebo | BI 456906 0.3 mg | BI 456906 0.9 mg |
|--------------------------------|---------|------------------|------------------|
| Started | 60 | 50 | 50 |
| Completed | 59 | 50 | 50 |
| Not completed | 1 | 0 | 0 |
| No treated | 1 | - | - |

| Number of subjects in period 1 | BI 456906 1.8 mg | BI 456906 2.7 mg | BI 456906 1.2 twice weekly (2.4) mg |
|--------------------------------|------------------|------------------|-------------------------------------|
| Started | 52 | 50 | 51 |
| Completed | 52 | 50 | 51 |
| Not completed | 0 | 0 | 0 |

| | | | |
|------------|---|---|---|
| No treated | - | - | - |
|------------|---|---|---|

| Number of subjects in period 1 | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
|--------------------------------|-------------------------------------|-------------|
| Started | 50 | 50 |
| Completed | 49 | 50 |
| Not completed | 1 | 0 |
| No treated | 1 | - |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Treated |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

Blinding implementation details:

The trial had a double blind design within each dose group. Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this trial will remained blinded with regard to the randomized treatment assignments until after database lock. The semaglutide group was open label.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

This arm comprises all placebo treated patients, regardless of the dose group in which they were treated. Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered solution for subcutaneous injection of placebo matched to BI 456906 once weekly for 16 weeks or twice weekly for 16 weeks.

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | Matching placebo to BI 456906 (isotonic sodium chloride solution) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients with type 2 diabetes mellitus were administered solution for subcutaneous injection of placebo matched to BI 456906 once weekly for 16 weeks or twice weekly for 16 weeks.

| | |
|-----------|------------------|
| Arm title | BI 456906 0.3 mg |
|-----------|------------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1-Week 16.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 456906 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients with type 2 diabetes mellitus were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1-Week 16.

| | |
|------------------|------------------|
| Arm title | BI 456906 0.9 mg |
|------------------|------------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5-Week 16.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 456906 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients with type 2 diabetes mellitus were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5-Week 16.

| | |
|------------------|------------------|
| Arm title | BI 456906 1.8 mg |
|------------------|------------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1, 0.6 mg on Week 2, 0.9 mg on Week 3, 1.2 mg on Week 4, 1.5 mg on Week 5, and 1.8 mg on Week 6- Week 16.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 456906 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients with type 2 diabetes mellitus were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1, 0.6 mg on Week 2, 0.9 mg on Week 3, 1.2 mg on Week 4, 1.5 mg on Week 5, and 1.8 mg on Week 6- Week 16.

| | |
|------------------|------------------|
| Arm title | BI 456906 2.7 mg |
|------------------|------------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.6 milligram (mg) on Week 1 and Week 2, 1.2 mg on Week 3 and Week 4, 1.8 mg on Week 5, 2.4 mg on Week 6, 2.7 mg on Week 7- Week 16.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 456906 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients with type 2 diabetes mellitus were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.6 milligram (mg) on Week 1 and Week 2, 1.2 mg on Week 3 and Week 4, 1.8 mg on Week 5, 2.4 mg on Week 6, 2.7 mg on Week 7- Week 16.

| | |
|------------------|-------------------------------------|
| Arm title | BI 456906 1.2 twice weekly (2.4) mg |
|------------------|-------------------------------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2 (total weekly dose=0.6 mg), 0.6 mg on Week 3 and Week 4 (total weekly dose=1.2 mg), 0.9 mg on Week 5 and Week 6 (total weekly dose=1.8 mg), 1.2 mg on Week 7- Week 16 (total weekly dose 2.4 mg).

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 456906 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients with type 2 diabetes mellitus were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2 (total weekly dose=0.6 mg), 0.6 mg on Week 3 and Week 4 (total weekly dose=1.2 mg), 0.9 mg on Week 5 and Week 6 (total weekly dose=1.8 mg), 1.2 mg on Week 7- Week 16 (total weekly dose 2.4 mg).

| | |
|------------------|-------------------------------------|
| Arm title | BI 456906 1.8 twice weekly (3.6) mg |
|------------------|-------------------------------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 (total weekly dose=0.6 mg), 0.6 mg on Week 2 (total weekly dose=1.2 mg), 0.9 mg on Week 3 (total weekly dose=1.8 mg), 1.2 mg on Week 4 (total weekly dose 2.4 mg), 1.5 mg on Week 5 and on Week 6 (total weekly dose 3 mg), 1.8 mg on Week 7 -Week 16 (total weekly dose =3.6 mg).

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 456906 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients with type 2 diabetes mellitus were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 (total weekly dose=0.6 mg), 0.6 mg on Week 2 (total weekly dose=1.2 mg), 0.9 mg on Week 3 (total weekly dose=1.8 mg), 1.2 mg on Week 4 (total weekly dose 2.4 mg), 1.5 mg on Week 5 and on Week 6 (total weekly dose 3 mg), 1.8 mg on Week 7 - Week 16 (total weekly dose =3.6 mg).

| | |
|------------------|-------------|
| Arm title | Semaglutide |
|------------------|-------------|

Arm description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of Semaglutide of 0.25 milligram (mg) on Week 1-Week 4, 0.5 mg on Week 5-Week 8, 1.0 mg on Week 9-Week 16.

| | |
|--|------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Semaglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients with type 2 diabetes mellitus were administered once weekly subcutaneously a solution for injection of Semaglutide of 0.25 milligram (mg) on Week 1-Week 4, 0.5 mg on Week 5-Week 8, 1.0 mg on Week 9-Week 16.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 are the randomised subjects, period 2 the treated, baseline characteristics are reported for the treated subjects.

| Number of subjects in period 2^[2] | Placebo | BI 456906 0.3 mg | BI 456906 0.9 mg |
|---|---------|------------------|------------------|
| Started | 59 | 50 | 50 |
| Completed | 49 | 41 | 45 |
| Not completed | 10 | 9 | 5 |
| Consent withdrawn by subject | 3 | 1 | - |
| Adverse event, non-fatal | 3 | 5 | 5 |
| Lost to follow-up | 2 | 1 | - |
| Other than listed | 2 | 2 | - |
| Protocol deviation | - | - | - |

| Number of subjects in period 2^[2] | BI 456906 1.8 mg | BI 456906 2.7 mg | BI 456906 1.2 twice weekly (2.4) mg |
|---|------------------|------------------|-------------------------------------|
| Started | 52 | 50 | 51 |
| Completed | 36 | 33 | 45 |
| Not completed | 16 | 17 | 6 |
| Consent withdrawn by subject | 3 | 1 | - |
| Adverse event, non-fatal | 11 | 15 | 4 |
| Lost to follow-up | 1 | 1 | - |
| Other than listed | 1 | - | 2 |
| Protocol deviation | - | - | - |

| Number of subjects in period 2^[2] | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
|---|-------------------------------------|-------------|
| Started | 49 | 50 |
| Completed | 37 | 45 |
| Not completed | 12 | 5 |
| Consent withdrawn by subject | 1 | - |
| Adverse event, non-fatal | 8 | 2 |
| Lost to follow-up | - | - |
| Other than listed | 2 | 1 |
| Protocol deviation | 1 | 2 |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In total 669 subjects were enrolled in this trial. From these 669 subjects only 413 subjects were randomised.

Baseline characteristics

Reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Placebo |
| Reporting group description: This arm comprises all placebo treated patients, regardless of the dose group in which they were treated. Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered solution for subcutaneous injection of placebo matched to BI 456906 once weekly for 16 weeks or twice weekly for 16 weeks. | |
| Reporting group title | BI 456906 0.3 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1-Week 16. | |
| Reporting group title | BI 456906 0.9 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5-Week 16. | |
| Reporting group title | BI 456906 1.8 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1, 0.6 mg on Week 2, 0.9 mg on Week 3, 1.2 mg on Week 4, 1.5 mg on Week 5, and 1.8 mg on Week 6- Week 16. | |
| Reporting group title | BI 456906 2.7 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.6 milligram (mg) on Week 1 and Week 2, 1.2 mg on Week 3 and Week 4, 1.8 mg on Week 5, 2.4 mg on Week 6, 2.7 mg on Week 7- Week 16. | |
| Reporting group title | BI 456906 1.2 twice weekly (2.4) mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2 (total weekly dose=0.6 mg), 0.6 mg on Week 3 and Week 4 (total weekly dose=1.2 mg), 0.9 mg on Week 5 and Week 6 (total weekly dose=1.8 mg), 1.2 mg on Week 7- Week 16 (total weekly dose 2.4 mg). | |
| Reporting group title | BI 456906 1.8 twice weekly (3.6) mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 (total weekly dose=0.6 mg), 0.6 mg on Week 2 (total weekly dose=1.2 mg), 0.9 mg on Week 3 (total weekly dose=1.8 mg), 1.2 mg on Week 4 (total weekly dose 2.4 mg), 1.5 mg on Week 5 and on Week 6 (total weekly dose 3 mg), 1.8 mg on Week 7 -Week 16 (total weekly dose =3.6 mg). | |
| Reporting group title | Semaglutide |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of Semaglutide of 0.25 milligram (mg) on Week 1-Week 4, 0.5 mg on Week 5-Week 8, 1.0 mg on Week 9-Week 16. | |

| Reporting group values | Placebo | BI 456906 0.3 mg | BI 456906 0.9 mg |
|--|---------|------------------|------------------|
| Number of subjects | 59 | 50 | 50 |
| Age categorical | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Participants | | | |
| 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) | 44 | 40 | 38 |
| From 65-84 years | 15 | 10 | 12 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: years | | | |
| arithmetic mean | 57.5 | 56.1 | 58.2 |
| standard deviation | ± 10.5 | ± 10.2 | ± 9.6 |
| Sex: Female, Male | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Participants | | | |
| Female | 28 | 24 | 22 |
| Male | 31 | 26 | 28 |
| Race (NIH/OMB) | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 0 |
| Asian | 8 | 4 | 5 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 0 |
| Black or African American | 3 | 3 | 1 |
| White | 47 | 42 | 44 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 15 | 11 | 8 |
| Not Hispanic or Latino | 44 | 39 | 42 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Glycosylated hemoglobin A1c (HbA1c) measured in percentage units [%] | | | |
| Glycosylated hemoglobin A1c (HbA1c) measured in percentage units [%] at baseline is presented. | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: percentage of HbA1c | | | |

| | | | |
|--------------------|--------|--------|--------|
| arithmetic mean | 8.15 | 8.09 | 7.89 |
| standard deviation | ± 0.85 | ± 0.76 | ± 0.80 |

| Reporting group values | BI 456906 1.8 mg | BI 456906 2.7 mg | BI 456906 1.2 twice weekly (2.4) mg |
|--|------------------|------------------|-------------------------------------|
| Number of subjects | 52 | 50 | 51 |
| Age categorical | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Participants | | | |
| 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) | 39 | 35 | 39 |
| From 65-84 years | 13 | 15 | 12 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: years | | | |
| arithmetic mean | 55.3 | 59.6 | 58.3 |
| standard deviation | ± 10.3 | ± 8.5 | ± 8.8 |
| Sex: Female, Male | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Participants | | | |
| Female | 25 | 17 | 24 |
| Male | 27 | 33 | 27 |
| Race (NIH/OMB) | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 8 | 4 | 5 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 2 | 2 | 4 |
| White | 42 | 43 | 41 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 1 | 1 |
| Ethnicity (NIH/OMB) | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 12 | 12 | 10 |
| Not Hispanic or Latino | 40 | 38 | 41 |
| Unknown or Not Reported | 0 | 0 | 0 |

| | | | |
|--|--------|--------|--------|
| Glycosylated hemoglobin A1c (HbA1c) measured in percentage units [%] | | | |
| Glycosylated hemoglobin A1c (HbA1c) measured in percentage units [%] at baseline is presented. | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: percentage of HbA1c | | | |
| arithmetic mean | 8.14 | 8.18 | 8.11 |
| standard deviation | ± 0.86 | ± 0.97 | ± 0.94 |

| Reporting group values | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide | Total |
|--|-------------------------------------|-------------|-------|
| Number of subjects | 49 | 50 | 411 |
| Age categorical | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Participants | | | |
| 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) | 36 | 38 | 309 |
| From 65-84 years | 13 | 12 | 102 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: years | | | |
| arithmetic mean | 57.7 | 55.8 | |
| standard deviation | ± 9.4 | ± 10.5 | - |
| Sex: Female, Male | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Participants | | | |
| Female | 22 | 16 | 178 |
| Male | 27 | 34 | 233 |
| Race (NIH/OMB) | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 2 |
| Asian | 3 | 5 | 42 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 1 |
| Black or African American | 3 | 2 | 20 |
| White | 42 | 43 | 344 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 2 |
| Ethnicity (NIH/OMB) | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: Subjects | | | |

| | | | |
|--|--------|--------|-----|
| Hispanic or Latino | 9 | 14 | 91 |
| Not Hispanic or Latino | 40 | 36 | 320 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Glycosylated hemoglobin A1c (HbA1c) measured in percentage units [%] | | | |
| Glycosylated hemoglobin A1c (HbA1c) measured in percentage units [%] at baseline is presented. | | | |
| Treated set (TS): TS included all patients who were randomized and received at least one dose of study drug. | | | |
| Units: percentage of HbA1c | | | |
| arithmetic mean | 7.97 | 8.03 | |
| standard deviation | ± 0.71 | ± 0.82 | - |

End points

End points reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Placebo |
| Reporting group description: This arm comprises all placebo treated patients, regardless of the dose group in which they were treated. Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered solution for subcutaneous injection of placebo matched to BI 456906 once weekly for 16 weeks or twice weekly for 16 weeks. | |
| Reporting group title | BI 456906 0.3 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1-Week 16. | |
| Reporting group title | BI 456906 0.9 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5-Week 16. | |
| Reporting group title | BI 456906 1.8 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1, 0.6 mg on Week 2, 0.9 mg on Week 3, 1.2 mg on Week 4, 1.5 mg on Week 5, and 1.8 mg on Week 6- Week 16. | |
| Reporting group title | BI 456906 2.7 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.6 milligram (mg) on Week 1 and Week 2, 1.2 mg on Week 3 and Week 4, 1.8 mg on Week 5, 2.4 mg on Week 6, 2.7 mg on Week 7- Week 16. | |
| Reporting group title | BI 456906 1.2 twice weekly (2.4) mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2 (total weekly dose=0.6 mg), 0.6 mg on Week 3 and Week 4 (total weekly dose=1.2 mg), 0.9 mg on Week 5 and Week 6 (total weekly dose=1.8 mg), 1.2 mg on Week 7- Week 16 (total weekly dose 2.4 mg). | |
| Reporting group title | BI 456906 1.8 twice weekly (3.6) mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 (total weekly dose=0.6 mg), 0.6 mg on Week 2 (total weekly dose=1.2 mg), 0.9 mg on Week 3 (total weekly dose=1.8 mg), 1.2 mg on Week 4 (total weekly dose 2.4 mg), 1.5 mg on Week 5 and on Week 6 (total weekly dose 3 mg), 1.8 mg on Week 7 -Week 16 (total weekly dose =3.6 mg). | |
| Reporting group title | Semaglutide |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of Semaglutide of 0.25 milligram (mg) on Week 1-Week 4, 0.5 mg on Week 5-Week 8, 1.0 mg on Week 9-Week 16 | |
| Reporting group title | Placebo |
| Reporting group description: This arm comprises all placebo treated patients, regardless of the dose group in which they were treated. Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered solution for subcutaneous injection of placebo matched to BI 456906 once weekly for 16 weeks or twice weekly for 16 weeks. | |

| | |
|--|-------------------------------------|
| Reporting group title | BI 456906 0.3 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1-Week 16. | |
| Reporting group title | BI 456906 0.9 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5-Week 16. | |
| Reporting group title | BI 456906 1.8 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1, 0.6 mg on Week 2, 0.9 mg on Week 3, 1.2 mg on Week 4, 1.5 mg on Week 5, and 1.8 mg on Week 6- Week 16. | |
| Reporting group title | BI 456906 2.7 mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.6 milligram (mg) on Week 1 and Week 2, 1.2 mg on Week 3 and Week 4, 1.8 mg on Week 5, 2.4 mg on Week 6, 2.7 mg on Week 7- Week 16. | |
| Reporting group title | BI 456906 1.2 twice weekly (2.4) mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2 (total weekly dose=0.6 mg), 0.6 mg on Week 3 and Week 4 (total weekly dose=1.2 mg), 0.9 mg on Week 5 and Week 6 (total weekly dose=1.8 mg), 1.2 mg on Week 7- Week 16 (total weekly dose 2.4 mg). | |
| Reporting group title | BI 456906 1.8 twice weekly (3.6) mg |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 (total weekly dose=0.6 mg), 0.6 mg on Week 2 (total weekly dose=1.2 mg), 0.9 mg on Week 3 (total weekly dose=1.8 mg), 1.2 mg on Week 4 (total weekly dose 2.4 mg), 1.5 mg on Week 5 and on Week 6 (total weekly dose 3 mg), 1.8 mg on Week 7 -Week 16 (total weekly dose =3.6 mg). | |
| Reporting group title | Semaglutide |
| Reporting group description: Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of Semaglutide of 0.25 milligram (mg) on Week 1-Week 4, 0.5 mg on Week 5-Week 8, 1.0 mg on Week 9-Week 16. | |

Primary: Absolute change in HbA1c from baseline to 16 weeks

| | |
|---|--|
| End point title | Absolute change in HbA1c from baseline to 16 weeks |
| End point description: Absolute change in glycosylated hemoglobin A1c (HbA1c) from baseline to 16 weeks after treatment start is presented. The measurements for this outcome were performed at baseline and at Week 17. Absolute change from baseline in HbA1c to 16 weeks after treatment start was calculated by subtracting the baseline HbA1c value from the HbA1c value at Week 17. Full Analysis Set (FAS): This patient set included all patients who were randomized and received at least one dose of study drug and who had analysable data for at least one efficacy endpoint. Only patients with non-missing results are reported. | |
| End point type | Primary |

End point timeframe:

At baseline and at Week 17 (16 weeks after treatment start).

| End point values | Placebo | BI 456906 0.3 mg | BI 456906 0.9 mg | BI 456906 1.8 mg |
|--------------------------------------|-----------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 41 | 46 | 36 |
| Units: percentage (%) of HbA1c | | | | |
| arithmetic mean (standard deviation) | -0.23 (± 0.81) | -0.91 (± 0.71) | -1.37 (± 0.93) | -1.79 (± 0.92) |

| End point values | BI 456906 2.7 mg | BI 456906 1.2 twice weekly (2.4) mg | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
|--------------------------------------|------------------|-------------------------------------|-------------------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 44 | 36 | 45 |
| Units: percentage (%) of HbA1c | | | | |
| arithmetic mean (standard deviation) | -1.67 (± 0.78) | -1.68 (± 0.90) | -1.79 (± 0.76) | -1.50 (± 0.84) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | < 0.0001 |
| Method | MCP-Mod linear model fit |

Notes:

[1] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: The maximum effect is achieved at 3.6 mg dose.

| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For

the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | < 0.0001 |
| Method | MCP-Mod Exponential model fit |

Notes:

[2] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: 90% of the maximum effect is achieved at 3.6 mg dose.

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

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | < 0.0001 |
| Method | MCP-Mod Emax 1 model fit |

Notes:

[3] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: 90% of the maximum effect is achieved at 3.6 mg dose.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | < 0.0001 |
| Method | MCP-Mod Sigmoid Emax model fit |

Notes:

[4] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: 50% of the maximum effect is achieved at 1.8 mg and 90% of the maximum effect is achieved at 3.6 mg dose.

| Statistical analysis title | Statistical Analysis 4 |
|---|---|
| Statistical analysis description: | |
| A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis. | |
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 285 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | < 0.0001 |
| Method | MCP-Mod Emax 2 model fit |

Notes:

[5] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: 70% of the maximum effect is achieved at 3.6 mg dose.

| Statistical analysis title | Statistical Analysis 6 |
|--|-----------------------------------|
| Statistical analysis description: | |
| Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements. | |
| Comparison groups | Placebo v BI 456906 0.3 mg |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | < 0.0001 ^[7] |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.06 |
| upper limit | -0.46 |

Notes:

[6] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 0.3 mg - Placebo at Week 17.

[7] - P-value is considered nominal.

| Statistical analysis title | Statistical Analysis 7 |
|--|----------------------------|
| Statistical analysis description: | |
| Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements. | |
| Comparison groups | Placebo v BI 456906 0.9 mg |

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| P-value | < 0.0001 ^[9] |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | -1.01 |

Notes:

[8] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 0.9 mg - Placebo at Week 17.

[9] - P-value is considered nominal.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|-----------------------------------|
| Comparison groups | Placebo v BI 456906 1.8 mg |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| P-value | < 0.0001 ^[11] |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -1.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.87 |
| upper limit | -1.26 |

Notes:

[10] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 1.8 mg - Placebo at Week 17.

[11] - P-value is considered nominal.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v BI 456906 2.7 mg |
|-------------------|----------------------------|

| | |
|---|--|
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[12] |
| P-value | < 0.0001 ^[13] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.72 |
| upper limit | -1.1 |

Notes:

[12] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 2.7 mg - Placebo at Week 17.

[13] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 1.2 twice weekly (2.4) mg |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[14] |
| P-value | < 0.0001 ^[15] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -1.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.78 |
| upper limit | -1.19 |

Notes:

[14] - No formal hypotheses were tested.

Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 1.2 twice weekly (2.4) mg - Placebo at Week 17.

[15] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 5, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|-------------------|---|
| Comparison groups | Placebo v BI 456906 1.8 twice weekly (3.6) mg |
|-------------------|---|

| | |
|---|--|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[16] |
| P-value | < 0.0001 ^[17] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -1.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.84 |
| upper limit | -1.22 |

Notes:

[16] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 1.8 twice weekly (3.6) mg - Placebo at Week 17.

[17] - P-value is considered nominal.

Secondary: Key secondary endpoint: The relative change in body weight from baseline to 16 weeks

| | |
|-----------------|--|
| End point title | Key secondary endpoint: The relative change in body weight from baseline to 16 weeks |
|-----------------|--|

End point description:

The relative change in body weight from baseline to 16 weeks after treatment start is presented. The measurements for this outcome were performed at baseline and at Week 17.

The relative change in body weight from baseline to 16 weeks after treatment start was calculated as (body weight at Week 17 - body weight at baseline/body weight at baseline) * 100.

Full Analysis Set (FAS): This patient set included all patients who were randomized and received at least one dose of study drug and who had analysable data for at least one efficacy endpoint. Only patients with non-missing results are reported.

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

End point timeframe:

At baseline and at Week 17 (16 weeks after treatment start).

| End point values | Placebo | BI 456906 0.3 mg | BI 456906 0.9 mg | BI 456906 1.8 mg |
|---|-----------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 41 | 46 | 36 |
| Units: percentage of body weight change | | | | |
| arithmetic mean (standard deviation) | -1.20 (± 3.52) | -1.86 (± 2.91) | -4.43 (± 3.92) | -6.63 (± 5.13) |

| End point values | BI 456906 2.7 mg | BI 456906 1.2 twice weekly (2.4) mg | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
|---|------------------|-------------------------------------|-------------------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 44 | 37 | 45 |
| Units: percentage of body weight change | | | | |
| arithmetic mean (standard deviation) | -6.68 (± 4.05) | -7.16 (± 6.06) | -8.95 (± 5.33) | -5.40 (± 4.33) |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Statistical Analysis 12 |
| Statistical analysis description: A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis. | |
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[18] |
| P-value | < 0.0001 |
| Method | MCP-Mod linear model fit |

Notes:

[18] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: The maximum effect is achieved at 3.6 mg dose.

| | |
|--|---|
| Statistical analysis title | Statistical Analysis 13 |
| Statistical analysis description: A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis. | |
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[19] |
| P-value | < 0.0001 |
| Method | MCP-Mod exponential model fit |

Notes:

[19] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: 90% of the maximum effect is achieved at 3.6 mg dose.

| | |
|---|-------------------------|
| Statistical analysis title | Statistical Analysis 14 |
| Statistical analysis description: A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated | |

simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[20] |
| P-value | < 0.0001 |
| Method | MCP-Mod Emax 1 model fit |

Notes:

[20] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: 90% of the maximum effect is achieved at 3.6 mg dose.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[21] |
| P-value | < 0.0001 |
| Method | MCP-Mod Emax 2 model fit |

Notes:

[21] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: 70% of the maximum effect is achieved at 3.6 mg dose.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 6 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.025). For the twice weekly dosing schemes the total dose per week was considered for the MCP-Mod analysis.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 0.3 mg v BI 456906 0.9 mg v BI 456906 1.8 mg v BI 456906 2.7 mg v BI 456906 1.2 twice weekly (2.4) mg v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[22] |
| P-value | < 0.0001 |
| Method | MCP-Mod Sigmoid Emax model fit |

Notes:

[22] - Mixed Model Repeated Measures (MMRM) estimates were used as input for the MCP-Mod. MMRM with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

Model assumption: 50% of the maximum effect is achieved at 1.8 mg and 90% of the maximum effect is achieved at 3.6 mg dose.

| Statistical analysis title | Statistical Analysis 17 |
|--|--|
| Statistical analysis description: | |
| Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements. | |
| Comparison groups | Placebo v BI 456906 0.3 mg |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[23] |
| P-value | = 0.2228 ^[24] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.9 |
| upper limit | 0.68 |

Notes:

[23] - No formal hypotheses were tested.

Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 0.3 mg- Placebo at Week 17.

[24] - P-value is considered nominal.

| Statistical analysis title | Statistical Analysis 18 |
|--|--|
| Statistical analysis description: | |
| Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements. | |
| Comparison groups | Placebo v BI 456906 0.9 mg |
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[25] |
| P-value | < 0.0001 ^[26] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -3.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.56 |
| upper limit | -2.01 |

Notes:

[25] - No formal hypotheses were tested.

Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 0.9 mg- Placebo at Week 17.

| Statistical analysis title | Statistical Analysis 19 |
|--|--|
| Statistical analysis description: | |
| Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements. | |
| Comparison groups | Placebo v BI 456906 1.8 mg |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[27] |
| P-value | < 0.0001 ^[28] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -5.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.41 |
| upper limit | -3.81 |

Notes:

[27] - No formal hypotheses were tested.

Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 1.8 mg- Placebo at Week 17.

[28] - P-value is considered nominal.

| Statistical analysis title | Statistical Analysis 20 |
|--|--|
| Statistical analysis description: | |
| Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements. | |
| Comparison groups | Placebo v BI 456906 2.7 mg |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[29] |
| P-value | < 0.0001 ^[30] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -6.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.12 |
| upper limit | -4.38 |

Notes:

[29] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 2.7 mg - Placebo at Week 17.

[30] - P-value is considered nominal.

| Statistical analysis title | Statistical Analysis 21 |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 1.2 twice weekly (2.4) mg |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 ^[31] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -6.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.02 |
| upper limit | -4.47 |

Notes:

[31] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 22 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[32] |
| P-value | < 0.0001 ^[33] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -7.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.52 |
| upper limit | -5.83 |

Notes:

[32] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 1.8 twice weekly (3.6) mg - Placebo at Week 17.

[33] - P-value is considered nominal.

Secondary: The absolute change in body weight from baseline to 16 weeks

| | |
|-----------------|--|
| End point title | The absolute change in body weight from baseline to 16 weeks |
|-----------------|--|

End point description:

The absolute change in body weight from baseline to 16 weeks after treatment start is presented.

Measurements for this outcome were performed at baseline and at Week 17.

The absolute change in body weight from baseline to 16 weeks after treatment start was calculated as: body weight at Week 17- body weight at baseline.

Full Analysis Set (FAS): This patient set included all patients who were randomized and received at least one dose of study drug and who had analysable data for at least one efficacy endpoint. Only patients

with non-missing results are reported.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At baseline and at Week 17 (16 weeks after treatment start). | |

| End point values | Placebo | BI 456906 0.3 mg | BI 456906 0.9 mg | BI 456906 1.8 mg |
|--------------------------------------|-----------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 41 | 46 | 36 |
| Units: kilogram (kg) | | | | |
| arithmetic mean (standard deviation) | -1.28 (± 3.05) | -1.90 (± 3.12) | -4.41 (± 4.07) | -6.31 (± 4.53) |

| End point values | BI 456906 2.7 mg | BI 456906 1.2 twice weekly (2.4) mg | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
|--------------------------------------|------------------|-------------------------------------|-------------------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 44 | 37 | 45 |
| Units: kilogram (kg) | | | | |
| arithmetic mean (standard deviation) | -6.88 (± 4.41) | -6.75 (± 6.10) | -8.88 (± 4.93) | -5.18 (± 4.52) |

Statistical analyses

| | |
|----------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 23 |
|----------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|--|
| Comparison groups | Placebo v BI 456906 0.3 mg |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[34] |
| P-value | = 0.4439 ^[35] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.34 |
| upper limit | 1.03 |

Notes:

[34] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 0.3 mg - Placebo at Week 17.

[35] - P-value is considered nominal.

| | |
|--|--|
| Statistical analysis title | Statistical Analysis 25 |
| Statistical analysis description: | |
| Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements. | |
| Comparison groups | Placebo v BI 456906 1.8 mg |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[36] |
| P-value | < 0.0001 ^[37] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -4.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.62 |
| upper limit | -3.23 |

Notes:

[36] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 1.8 mg - Placebo at Week 17.

[37] - P-value is considered nominal

| | |
|--|--|
| Statistical analysis title | Statistical Analysis 24 |
| Statistical analysis description: | |
| Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements. | |
| Comparison groups | Placebo v BI 456906 0.9 mg |
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[38] |
| P-value | = 0.0001 ^[39] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -3.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.95 |
| upper limit | -1.61 |

Notes:

[38] - No formal hypotheses were tested.

Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 0.9 mg - Placebo at Week 17.

[39] - P-value is considered nominal.

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 26 |
| Statistical analysis description: | |
| Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements. | |

| | |
|---|--|
| Comparison groups | Placebo v BI 456906 2.7 mg |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[40] |
| P-value | < 0.0001 ^[41] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -5.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.53 |
| upper limit | -4 |

Notes:

[40] - No formal hypotheses were tested.

Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 2.7 mg - Placebo at Week 17.

[41] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 27 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 1.2 twice weekly (2.4) mg |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[42] |
| P-value | < 0.0001 ^[43] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -5.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.11 |
| upper limit | -3.77 |

Notes:

[42] - No formal hypotheses were tested. Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 1.2 twice weekly (2.4) mg - Placebo at Week 17.

[43] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 28 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|-------------------|---|
| Comparison groups | Placebo v BI 456906 1.8 twice weekly (3.6) mg |
|-------------------|---|

| | |
|---|--|
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[44] |
| P-value | < 0.0001 ^[45] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -7.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.79 |
| upper limit | -5.31 |

Notes:

[44] - No formal hypotheses were tested.

Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 1.8 twice weekly (3.6) mg - Placebo at Week 17.

[45] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 29 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 2, 3, 4, 5, 6, 7, 8, 12, 16 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Semaglutide |
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[46] |
| P-value | < 0.0001 ^[47] |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -3.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.52 |
| upper limit | -2.18 |

Notes:

[46] - No formal hypotheses were tested.

Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Semaglutide - Placebo at Week 17.

[47] - P-value is considered nominal.

Secondary: The absolute change in waist circumference from baseline to 16 weeks

| | |
|-----------------|--|
| End point title | The absolute change in waist circumference from baseline to 16 weeks |
|-----------------|--|

End point description:

The absolute change in waist circumference from baseline to 16 weeks after treatment start is presented. Measurements for this outcome were performed at baseline and at Week 17.

The absolute change in waist circumference from baseline to 16 weeks after treatment start was calculated as: waist circumference at Week 17- waist circumference at baseline.

Full Analysis Set (FAS): This patient set included all patients who were randomized and received at least one dose of study drug and who had analysable data for at least one efficacy endpoint. Only patients with non-missing results are reported.

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

End point timeframe:

At baseline and at Week 17 (16 weeks after treatment start).

| End point values | Placebo | BI 456906 0.3 mg | BI 456906 0.9 mg | BI 456906 1.8 mg |
|--------------------------------------|-----------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 43 | 47 | 39 |
| Units: centimeter | | | | |
| arithmetic mean (standard deviation) | -1.95 (± 9.08) | -2.73 (± 10.49) | -1.80 (± 10.55) | -3.63 (± 10.94) |

| End point values | BI 456906 2.7 mg | BI 456906 1.2 twice weekly (2.4) mg | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
|--------------------------------------|------------------|-------------------------------------|-------------------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 35 | 45 | 36 | 46 |
| Units: centimeter | | | | |
| arithmetic mean (standard deviation) | -7.47 (± 12.24) | -4.61 (± 9.73) | -12.89 (± 25.50) | -3.63 (± 5.05) |

Statistical analyses

| Statistical analysis title | Statistical Analysis 30 |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 6 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|--|
| Comparison groups | Placebo v BI 456906 0.3 mg |
| Number of subjects included in analysis | 92 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[48] |
| P-value | = 0.7708 ^[49] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -0.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.82 |
| upper limit | 3.57 |

Notes:

[48] - No formal hypotheses were tested.

Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as BI 456906 0.3 mg - Placebo at Week 17.

[49] - P-value is considered nominal.

| Statistical analysis title | Statistical Analysis 31 |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 6 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|--|
| Comparison groups | Placebo v BI 456906 0.9 mg |
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7462 ^[50] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.44 |
| upper limit | 4.79 |

Notes:

[50] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 32 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 6 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|--|
| Comparison groups | Placebo v BI 456906 1.8 mg |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1302 ^[51] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -3.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.62 |
| upper limit | 0.98 |

Notes:

[51] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 33 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 6 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v BI 456906 2.7 mg |
|-------------------|----------------------------|

| | |
|---|--|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0414 ^[52] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -4.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.03 |
| upper limit | -0.18 |

Notes:

[52] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 34 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 6 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 1.2 twice weekly (2.4) mg |
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2273 ^[53] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -2.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.71 |
| upper limit | 1.6 |

Notes:

[53] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 35 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 6 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0002 ^[54] |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -8.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.81 |
| upper limit | -3.98 |

Notes:

[54] - P-value is considered nominal.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 36 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed Model Repeated Measures (MMRM) with fixed, categorical factors of treatment at each visit, and continuous factors of baseline at each visit, using visit (Week 6 and 17) as repeated measures, subject as random effect, unstructured covariance matrix to model within subject measurements.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Semaglutide |
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1967 ^[55] |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -2.72 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.86 |
| upper limit | 1.42 |

Notes:

[55] - P-value is considered nominal.

Secondary: Percentage of patients with 5 % or greater body weight loss from baseline to 16 weeks

| | |
|-----------------|---|
| End point title | Percentage of patients with 5 % or greater body weight loss from baseline to 16 weeks |
|-----------------|---|

End point description:

The percentage of patients with 5 percent (%) or greater body weight loss from baseline to 16 weeks after treatment start is presented.

Measurements for this outcome were performed at baseline and at Week 17.

Full Analysis Set (FAS): This patient set included all patients who were randomized and received at least one dose of study drug and who had analysable data for at least one efficacy endpoint. Only patients with non-missing results are reported.

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

End point timeframe:

At baseline and at Week 17 (16 weeks after treatment start).

| End point values | Placebo | BI 456906 0.3 mg | BI 456906 0.9 mg | BI 456906 1.8 mg |
|-------------------------------|-----------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 | 50 | 50 | 52 |
| Units: percentage of patients | | | | |
| number (not applicable) | 6.8 | 8.0 | 38.0 | 42.3 |

| End point values | BI 456906 2.7 mg | BI 456906 1.2 twice weekly (2.4) mg | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
|-------------------------------|------------------|-------------------------------------|-------------------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 50 | 51 | 49 | 50 |
| Units: percentage of patients | | | | |
| number (not applicable) | 46.0 | 56.9 | 57.1 | 38.0 |

Statistical analyses

| Statistical analysis title | Statistical Analysis 37 |
|--|----------------------------|
| Statistical analysis description: | |
| Method: Logistic regression model for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 0.3 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[56] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 5.2 |

Notes:

[56] - Odds Ratio was calculated as BI 456906 / Placebo.

| Statistical analysis title | Statistical Analysis 38 |
|--|----------------------------|
| Statistical analysis description: | |
| Method: Logistic regression model for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 0.9 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[57] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 7.92 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.43 |
| upper limit | 25.74 |

Notes:

[57] - Odds Ratio was calculated as BI 456906 / Placebo.

| | |
|--|----------------------------|
| Statistical analysis title | Statistical Analysis 39 |
| Statistical analysis description: | |
| Method: Logistic regression model for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 1.8 mg |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[58] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 17.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.21 |
| upper limit | 60.03 |

Notes:

[58] - Odds Ratio was calculated as BI 456906 / Placebo.

| | |
|--|----------------------------|
| Statistical analysis title | Statistical Analysis 40 |
| Statistical analysis description: | |
| Method: Logistic regression model for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 2.7 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[59] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 25.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.31 |
| upper limit | 91.55 |

Notes:

[59] - Odds Ratio was calculated as BI 456906 / Placebo.

| | |
|--|---|
| Statistical analysis title | Statistical Analysis 41 |
| Statistical analysis description: | |
| Method: Logistic regression model for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 1.2 twice weekly (2.4) mg |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[60] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 21.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.57 |
| upper limit | 72.04 |

Notes:

[60] - Odds Ratio was calculated as BI 456906 / Placebo.

| | |
|--|---|
| Statistical analysis title | Statistical Analysis 42 |
| Statistical analysis description: | |
| Method: Logistic regression model for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.84 |
| upper limit | 124.47 |

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 43 |
| Statistical analysis description: | |
| Method: Logistic regression model for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v Semaglutide |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[61] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 8.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.52 |
| upper limit | 26.79 |

Notes:

[61] - Odds Ratio was calculated as Semaglutide / Placebo.

Secondary: Percentage of patients with 10% or greater body weight loss from baseline to 16 weeks

| | |
|-----------------|---|
| End point title | Percentage of patients with 10% or greater body weight loss |
|-----------------|---|

End point description:

The percentage of patients with 10 % or greater body weight loss from baseline to 16 weeks after treatment start is presented.

Measurements for this outcome were performed at baseline and at Week 17.

Full Analysis Set (FAS): This patient set included all patients who were randomized and received at least one dose of study drug and who had analysable data for at least one efficacy endpoint. Only patients with non-missing results are reported.

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

End point timeframe:

At baseline and at Week 17 (16 weeks after treatment start).

| End point values | Placebo | BI 456906 0.3 mg | BI 456906 0.9 mg | BI 456906 1.8 mg |
|-------------------------------|-----------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 | 50 | 50 | 52 |
| Units: percentage of patients | | | | |
| number (not applicable) | 0.0 | 2.0 | 6.0 | 13.5 |

| End point values | BI 456906 2.7 mg | BI 456906 1.2 twice weekly (2.4) mg | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
|-------------------------------|------------------|-------------------------------------|-------------------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 50 | 51 | 49 | 50 |
| Units: percentage of patients | | | | |
| number (not applicable) | 16.0 | 25.5 | 34.7 | 16.0 |

Statistical analyses

| Statistical analysis title | Statistical Analysis 44 |
|--|----------------------------|
| Statistical analysis description: | |
| Method: Logistic regression model using Firth's bias-reducing penalized maximum likelihood estimation for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 0.3 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[62] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.14 |
| upper limit | 95.73 |

Notes:

[62] - Odds Ratio was calculated as BI 456906 / Placebo.

| Statistical analysis title | Statistical Analysis 45 |
|--|----------------------------|
| Statistical analysis description: | |
| Method: Logistic regression model using Firth's bias-reducing penalized maximum likelihood estimation for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 0.9 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[63] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 7.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 163.56 |

Notes:

[63] - Odds Ratio was calculated as BI 456906 / Placebo.

| Statistical analysis title | Statistical Analysis 46 |
|--|----------------------------|
| Statistical analysis description: | |
| Method: Logistic regression model using Firth's bias-reducing penalized maximum likelihood estimation for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 1.8 mg |
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[64] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 25.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.35 |
| upper limit | 471.09 |

Notes:

[64] - Odds Ratio was calculated as BI 456906 / Placebo.

| Statistical analysis title | Statistical Analysis 47 |
|--|----------------------------|
| Statistical analysis description: | |
| Method: Logistic regression model using Firth's bias-reducing penalized maximum likelihood estimation for body weight loss with treatment as fixed effect. | |
| Comparison groups | Placebo v BI 456906 2.7 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[65] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 33.01 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.78 |
| upper limit | 613.51 |

Notes:

[65] - Odds Ratio was calculated as BI 456906 / Placebo.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 48 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Method: Logistic regression model using Firth's bias-reducing penalized maximum likelihood estimation for body weight loss with treatment as fixed effect.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 1.2 twice weekly (2.4) mg |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[66] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 42.44 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.37 |
| upper limit | 761.44 |

Notes:

[66] - Odds Ratio was calculated as BI 456906 / Placebo.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 49 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Method: Logistic regression model using Firth's bias-reducing penalized maximum likelihood estimation for body weight loss with treatment as fixed effect.

| | |
|---|---|
| Comparison groups | Placebo v BI 456906 1.8 twice weekly (3.6) mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[67] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 84.53 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.71 |
| upper limit | 999 |

Notes:

[67] - Odds Ratio was calculated as BI 456906 / Placebo.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 50 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Method: Logistic regression model using Firth's bias-reducing penalized maximum likelihood estimation for body weight loss with treatment as fixed effect.

| | |
|-------------------|-----------------------|
| Comparison groups | Placebo v Semaglutide |
|-------------------|-----------------------|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[68] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 22.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.22 |
| upper limit | 413.33 |

Notes:

[68] - Odds Ratio was calculated as Semaglutide / Placebo.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first intake of any trial drug until last intake of any trial drug (planned: 16 weeks) + residual effect period (BI 456906: 28 days, Semaglutide: 35 days), up to 159 days.

Adverse event reporting additional description:

Treated set (TS): This patient set included all patients who were randomized and received at least one dose of study drug.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

This arm comprises all placebo treated patients, regardless of the dose group in which they were treated. Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered solution for subcutaneous injection of placebo matched to BI 456906 once weekly for 16 weeks or twice weekly for 16 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | BI 456906 0.3 mg |
|-----------------------|------------------|

Reporting group description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1-Week 16.

| | |
|-----------------------|------------------|
| Reporting group title | BI 456906 2.7 mg |
|-----------------------|------------------|

Reporting group description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.6 milligram (mg) on Week 1 and Week 2, 1.2 mg on Week 3 and Week 4, 1.8 mg on Week 5, 2.4 mg on Week 6, 2.7 mg on Week 7- Week 16.

| | |
|-----------------------|-------------------------------------|
| Reporting group title | BI 456906 1.2 twice weekly (2.4) mg |
|-----------------------|-------------------------------------|

Reporting group description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2 (total weekly dose=0.6 mg), 0.6 mg on Week 3 and Week 4 (total weekly dose=1.2 mg), 0.9 mg on Week 5 and Week 6 (total weekly dose=1.8 mg), 1.2 mg on Week 7- Week 16 (total weekly dose 2.4 mg).

| | |
|-----------------------|-------------------------------------|
| Reporting group title | BI 456906 1.8 twice weekly (3.6) mg |
|-----------------------|-------------------------------------|

Reporting group description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered twice weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 (total weekly dose=0.6 mg), 0.6 mg on Week 2 (total weekly dose=1.2 mg), 0.9 mg on Week 3 (total weekly dose=1.8 mg), 1.2 mg on Week 4 (total weekly dose 2.4 mg), 1.5 mg on Week 5 and on Week 6 (total weekly dose 3 mg), 1.8 mg on Week 7 -Week 16 (total weekly dose =3.6 mg).

| | |
|-----------------------|-------------|
| Reporting group title | Semaglutide |
|-----------------------|-------------|

Reporting group description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of Semaglutide of 0.25 milligram (mg) on Week 1-Week 4, 0.5 mg on Week 5-Week 8, 1.0 mg on Week 9-Week 16.

| | |
|-----------------------|------------------|
| Reporting group title | BI 456906 0.9 mg |
|-----------------------|------------------|

Reporting group description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and

metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5-Week 16.

| | |
|-----------------------|------------------|
| Reporting group title | BI 456906 1.8 mg |
|-----------------------|------------------|

Reporting group description:

Patients with type 2 diabetes mellitus with insufficient glycaemic control despite diet, exercise and metformin treatment were administered once weekly subcutaneously a solution for injection of BI 456906 of 0.3 milligram (mg) on Week 1, 0.6 mg on Week 2, 0.9 mg on Week 3, 1.2 mg on Week 4, 1.5 mg on Week 5, and 1.8 mg on Week 6- Week 16.

| Serious adverse events | Placebo | BI 456906 0.3 mg | BI 456906 2.7 mg |
|---|----------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 1 / 50 (2.00%) | 2 / 50 (4.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 50 (0.00%) | 0 / 50 (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 | | | |
| IIIrd nerve paralysis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (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 |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (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 |
| Immune system disorders | | | |
| Autoimmune disorder | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 50 (2.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 50 (0.00%) | 0 / 50 (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 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (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 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 50 (2.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 50 (0.00%) | 0 / 50 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pharyngeal ulceration | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (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 |
| Back pain | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (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 |
| Viraemia | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (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 |

| Serious adverse events | BI 456906 1.2 twice weekly (2.4) mg | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
|---|-------------------------------------|-------------------------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 49 (0.00%) | 0 / 50 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| IIIrd nerve paralysis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Immune system disorders | | | |
| Autoimmune disorder | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Vomiting | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pharyngeal ulceration | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Back pain | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 49 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |
| Viraemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 | | | |
| Dehydration | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 49 (0.00%) | 0 / 50 (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 |

| Serious adverse events | BI 456906 0.9 mg | BI 456906 1.8 mg | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 3 / 52 (5.77%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| IIIrd nerve paralysis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Autoimmune disorder | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pharyngeal ulceration | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viraemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 52 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 52 (1.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | BI 456906 0.3 mg | BI 456906 2.7 mg |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 59 (30.51%) | 27 / 50 (54.00%) | 33 / 50 (66.00%) |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 2 / 50 (4.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 0 | 2 | 2 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 50 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |

| | | | |
|--|-----------------------|------------------------|-----------------------|
| Dizziness subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 50 (2.00%) 1 | 1 / 50 (2.00%) 2 |
| Headache subjects affected / exposed occurrences (all) | 4 / 59 (6.78%) 6 | 4 / 50 (8.00%) 9 | 1 / 50 (2.00%) 1 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 50 (2.00%) 1 | 1 / 50 (2.00%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 3 / 50 (6.00%) 4 | 2 / 50 (4.00%) 3 |
| Gastrointestinal disorders | | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 5 | 3 / 50 (6.00%) 3 | 6 / 50 (12.00%) 9 |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 0 / 50 (0.00%) 0 | 0 / 50 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 3 / 50 (6.00%) 3 | 1 / 50 (2.00%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 3 / 50 (6.00%) 3 | 7 / 50 (14.00%) 10 |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 59 (11.86%) 24 | 12 / 50 (24.00%) 17 | 7 / 50 (14.00%) 8 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 4 / 50 (8.00%) 6 | 4 / 50 (8.00%) 13 |
| Eructation subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 2 / 50 (4.00%) 2 | 3 / 50 (6.00%) 6 |
| Flatulence | | | |

| | | | |
|--|---------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 2 / 50 (4.00%) 2 | 1 / 50 (2.00%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 5 / 59 (8.47%) 5 | 10 / 50 (20.00%) 19 | 23 / 50 (46.00%) 46 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 59 (0.00%) 0 | 1 / 50 (2.00%) 1 | 2 / 50 (4.00%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 5 | 7 / 50 (14.00%) 11 | 13 / 50 (26.00%) 21 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 2 / 50 (4.00%) 2 | 2 / 50 (4.00%) 2 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 3 | 0 / 50 (0.00%) 0 | 1 / 50 (2.00%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 59 (1.69%) 1 | 0 / 50 (0.00%) 0 | 2 / 50 (4.00%) 2 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 3 | 6 / 50 (12.00%) 6 | 11 / 50 (22.00%) 12 |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 2 / 59 (3.39%) 6 | 1 / 50 (2.00%) 1 | 2 / 50 (4.00%) 2 |

| | | | |
|--|-------------------------------------|-------------------------------------|------------------|
| Non-serious adverse events | BI 456906 1.2 twice weekly (2.4) mg | BI 456906 1.8 twice weekly (3.6) mg | Semaglutide |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 33 / 51 (64.71%) | 37 / 49 (75.51%) | 20 / 50 (40.00%) |
| Investigations Lipase increased | | | |

| | | | |
|--|-----------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 2 | 0 / 49 (0.00%) 0 | 3 / 50 (6.00%) 4 |
| Weight decreased subjects affected / exposed occurrences (all) | 6 / 51 (11.76%) 6 | 4 / 49 (8.16%) 4 | 1 / 50 (2.00%) 1 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 3 / 49 (6.12%) 5 | 1 / 50 (2.00%) 1 |
| Headache subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 3 | 5 / 49 (10.20%) 5 | 0 / 50 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 2 / 49 (4.08%) 3 | 0 / 50 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 4 / 51 (7.84%) 5 | 5 / 49 (10.20%) 6 | 1 / 50 (2.00%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 4 / 49 (8.16%) 5 | 1 / 50 (2.00%) 1 |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 2 / 49 (4.08%) 2 | 0 / 50 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 5 | 2 / 49 (4.08%) 2 | 1 / 50 (2.00%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 8 / 51 (15.69%) 9 | 5 / 49 (10.20%) 7 | 3 / 50 (6.00%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 8 / 51 (15.69%) 11 | 11 / 49 (22.45%) 36 | 5 / 50 (10.00%) 8 |
| Dyspepsia | | | |

| | | | |
|---|------------------|------------------|-----------------|
| subjects affected / exposed | 4 / 51 (7.84%) | 7 / 49 (14.29%) | 1 / 50 (2.00%) |
| occurrences (all) | 4 | 7 | 1 |
| Eruption | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 49 (2.04%) | 2 / 50 (4.00%) |
| occurrences (all) | 1 | 1 | 2 |
| Flatulence | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 1 / 49 (2.04%) | 0 / 50 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 14 / 51 (27.45%) | 23 / 49 (46.94%) | 6 / 50 (12.00%) |
| occurrences (all) | 21 | 33 | 14 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 49 (2.04%) | 2 / 50 (4.00%) |
| occurrences (all) | 3 | 1 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 6 / 51 (11.76%) | 11 / 49 (22.45%) | 2 / 50 (4.00%) |
| occurrences (all) | 11 | 16 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 49 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 49 (2.04%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 49 (2.04%) | 1 / 50 (2.00%) |
| occurrences (all) | 1 | 1 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 51 (17.65%) | 15 / 49 (30.61%) | 3 / 50 (6.00%) |
| occurrences (all) | 9 | 15 | 3 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 3 / 49 (6.12%) | 4 / 50 (8.00%) |
| occurrences (all) | 0 | 3 | 18 |

| Non-serious adverse events | BI 456906 0.9 mg | BI 456906 1.8 mg | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 50 (60.00%) | 40 / 52 (76.92%) | |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 4 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 52 (3.85%) | |
| occurrences (all) | 1 | 2 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 0 / 52 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Headache | | | |
| subjects affected / exposed | 5 / 50 (10.00%) | 4 / 52 (7.69%) | |
| occurrences (all) | 5 | 7 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 3 / 52 (5.77%) | |
| occurrences (all) | 2 | 3 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 3 / 52 (5.77%) | |
| occurrences (all) | 1 | 3 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 2 | 1 | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 4 / 52 (7.69%) | |
| occurrences (all) | 0 | 4 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 1 | 1 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 7 / 52 (13.46%) | |
| occurrences (all) | 2 | 8 | |

| | | | |
|---|------------------|------------------|--|
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 50 (16.00%) | 9 / 52 (17.31%) | |
| occurrences (all) | 10 | 25 | |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 5 / 52 (9.62%) | |
| occurrences (all) | 4 | 9 | |
| Eructation | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 3 / 52 (5.77%) | |
| occurrences (all) | 3 | 3 | |
| Flatulence | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 2 / 52 (3.85%) | |
| occurrences (all) | 4 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 14 / 50 (28.00%) | 25 / 52 (48.08%) | |
| occurrences (all) | 20 | 49 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 4 / 52 (7.69%) | |
| occurrences (all) | 3 | 4 | |
| Vomiting | | | |
| subjects affected / exposed | 9 / 50 (18.00%) | 12 / 52 (23.08%) | |
| occurrences (all) | 14 | 18 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 3 / 52 (5.77%) | |
| occurrences (all) | 0 | 3 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 1 / 52 (1.92%) | |
| occurrences (all) | 4 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 4 / 52 (7.69%) | |
| occurrences (all) | 1 | 4 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 7 / 50 (14.00%) | 6 / 52 (11.54%) | |
| occurrences (all) | 7 | 10 | |

| | | | |
|---|---------------------|----------------------|--|
| Hypoglycaemia subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 3 / 52 (5.77%) 13 | |
|---|---------------------|----------------------|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 28 September 2020 | <p>Amendment 1 Part 1: Measures taken due to the Coronavirus disease 2019 (COVID-19) pandemic were added: Trial medication could be sent to patient's home when physical visits were not possible due to the COVID-19 pandemic. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) tests to be done locally. A clinic visit could be performed remotely when physical visits were not possible due to the COVID-19 pandemic. All COVID-19 related deviations were to be documented and their implications were taken into consideration for the analysis of data.</p> <p>Criteria for discontinuation of trial treatment were revised: Sustained symptomatic hypotension or hypertension was defined. " QT interval corrected for heart rate using the method of Fridericia (QTcF) change from baseline" changed from 30 ms to 60 ms. Baseline was clarified as at randomization. Trial treatment was to be terminated and patient discontinued if patient had symptoms of SARS-CoV-2 infection or diagnosed with COVID-19, patients could resume treatment if the results were negative.</p> |
| 28 September 2020 | <p>Amendment 1 Part 2: Instructions for trial drug administration were revised: Injection time "over at least 15 seconds" changed to "over 5 to 10 seconds". Instructions for medication administration from vials revised: If the volume exceeds 1.0 mL, the dose may be divided into two syringes and will be injected into two different injection sites on the same side of the abdomen. The next dose should be administered on the alternate side of the abdomen. Added the following: The placebo solution for BI 456906 is filled either into a vial or a syringe, and their composition is identical. The vials are used from weeks 1 to 6, and the pre- filled syringes are used from weeks 7 to 16.</p> <p>Procedures for monitoring of hyperglycemic and hypoglycemic events were revised: Guidance for self-monitoring of blood glucose revised. Patient should also contact the site when FBG was below 70 mg/dL (3.9 mmol/L). Hypoglycemic events classified using standard definitions as levels 1, 2, and 3. Criteria for treatment of hyperglycemia were added: Hypoglycemic events should be treated and additional glucose monitoring should be implemented per investigator discretion and medical judgement. Investigator should make a determination if a hyperglycemic or a hypoglycemic event should be reported as an adverse events (AE).</p> |
| 28 September 2020 | <p>Amendment 1 Part 3: Clarification on restrictions: Dietary supplements that potentially induce change in body weight were not permitted. Over-the-counter and prescribed weight loss products were not permitted. Assessment of skin rashes was added at request from Health Authority. More flexibility was added to let patients use their own glucometer if it was their preference. Patients did not need to return the glucometers at the end of the study, to avoid dispensing the used glucometer to another patient due to COVID-19. Analytical method for semaglutide was revised as follows: semaglutide plasma concentrations was determined by a fit-for-purpose validated liquid chromatography-tandem mass spectrometer (LC-MS/MS) assay using extended acceptance criteria of 20% (25% at lower limit of quantification (LLOQ)).</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported