



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
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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
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No investigational medicinal product assigned in this arm

Arm title	BI 456906 2.7 mg
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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
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No investigational medicinal product assigned in this arm

Arm title	BI 456906 1.2 twice weekly (2.4) mg
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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
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No investigational medicinal product assigned in this arm

Arm title	BI 456906 1.8 twice weekly (3.6) mg
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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
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No investigational medicinal product assigned in this arm

Arm title	Semaglutide
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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
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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	-	-	-
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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
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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
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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
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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
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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
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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
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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
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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 standard deviation	8.14 ± 0.86	8.18 ± 0.97	8.11 ± 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 standard deviation	57.7 ± 9.4	55.8 ± 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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Placebo
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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
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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
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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
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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
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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
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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
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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
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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
Eructation			
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
Gastrooesophageal 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	
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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:</p> <p>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:</p> <p>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:</p> <p>Injection time "over at least 15 seconds" changed to "over 5 to 10 seconds".</p> <p>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.</p> <p>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:</p> <p>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.</p> <p>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:</p> <p>Dietary supplements that potentially induce change in body weight were not permitted. Over-the-counter and prescribed weight loss products were not permitted.</p> <p>Assessment of skin rashes was added at request from Health Authority.</p> <p>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.</p> <p>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