Clinical trial results:
A Phase II, randomized, double blind, parallel group,46 weeks dose-finding study of BI 456906 administered once weekly subcutaneously compared with placebo in patients with obesity or overweight

Summary

EudraCT number	2020-002479-37
Trial protocol	SE IE NL BE DE
Global end of trial date	07 October 2022

Results information

Result version number	v1 (current)
This version publication date	22 October 2023
First version publication date	22 October 2023

Trial information

Trial identification

Sponsor protocol code	1404-0036

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04667377
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 Centre, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Centre, 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	22 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2022
Global end of trial reached?	Yes
Global end of trial date	07 October 2022
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, for further pivotal testing in Phase III studies.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 44
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 118
Country: Number of subjects enrolled	China: 14
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Netherlands: 29
Country: Number of subjects enrolled	New Zealand: 14
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Sweden: 40
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 183
Worldwide total number of subjects	520
EEA total number of subjects	112

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)	447
From 65 to 84 years	73
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomised, double-blinded, parallel-design, placebo-controlled, multi-national, and multi-centre study with four different BI 456906 maintenance doses (ranging from 0.6 mg/week to 4.8 mg/week) in subjects with obesity or overweight (body mass index (BMI) >=27 kg/m2), and without diabetes mellitus.

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. (Trial) participants 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	Investigator, Carer, Assessor, Subject

Blinding implementation details:

Subjects, investigators, central reviewers, and everyone involved in trial conduct or analysis, or with any other interest in this trial, remained blinded about the randomised treatment assignments until after the database lock. The data monitoring committee (DMC) was provided with unblinded data to allow them to fulfil their tasks as outlined in the DMC charter. An independent team, not otherwise involved in the conduct of the trial, provided the unblinded results to the DMC.

Arms

Are arms mutually exclusive?	Yes
Arm title	0.6 mg BI 456906 - planned maintenance treatment

Arm description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and 2, and 0.6 mg on Week 3 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 0.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events (AEs) had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subjects was randomised to.

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

Dosage and administration details:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and 2, and 0.6 mg on Week 3 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 0.6 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Arm title	2.4 mg BI 456906 - planned maintenance treatment

Arm description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 to Week 14 and 2.4 mg on Week 15 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 2.4 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

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

Dosage and administration details:

Subject with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 to Week 14 and 2.4 mg on Week 15 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 2.4 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Arm title	3.6 mg BI 456906 - planned maintenance treatment

Arm description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 and Week 12, 2.4 mg on Week 13 and Week 14, 3.0 mg on Week 15 and Week 16, and 3.6 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 3.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

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

Dosage and administration details:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 and Week 12, 2.4 mg on Week 13 and Week 14, 3.0 mg on Week 15 and Week 16, and 3.6 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 3.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Arm title	4.8 mg BI 456906 - planned maintenance treatment

Arm description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of

0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 and Week 8, 1.8 mg on Week 9 and Week 10, 2.4 mg on Week 11 and Week 12, 3.3 mg on Week 13 and Week 14, 4.2 mg on Week 15 and Week 16, and 4.8 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 4.8 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal AEs had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

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

Dosage and administration details:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 and Week 8, 1.8 mg on Week 9 and Week 10, 2.4 mg on Week 11 and Week 12, 3.3 mg on Week 13 and Week 14, 4.2 mg on Week 15 and Week 16, and 4.8 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 4.8 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal AEs had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Arm title	Placebo

Arm description:

Subjects with obesity or overweight were administered a solution for injection of Placebo, by a weekly subcutaneous injection of two syringes on the same injection day, for 46 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects with obesity or overweight were administered a solution for injection of Placebo, by a weekly subcutaneous injection of two syringes on the same injection day, for 46 weeks.

Number of subjects in period 1	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment
Started	78	78	77
Treated during dose escalation period	77	78	77
Completed	77	78	76
Not completed	1	0	1
No post-baseline efficacy data	-	-	1
Not treated	1	-	-

Number of subjects in period 1	4.8 mg BI 456906 - planned	Placebo

	maintenance treatment	
Started	77	77
Treated during dose escalation period	77	77
Completed	76	77
Not completed	1	0
No post-baseline efficacy data	1	-
Not treated	-	-

Period 2

Period 2 title	Full analysis set (FAS)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

Subjects, investigators, central reviewers, and everyone involved in trial conduct or analysis, or with any other interest in this trial, remained blinded about the randomised treatment assignments until after the database lock. The data monitoring committee (DMC) was provided with unblinded data to allow them to fulfil their tasks as outlined in the DMC charter. An independent team, not otherwise involved in the conduct of the trial, provided the unblinded results to the DMC.

Arms

Are arms mutually exclusive?	Yes
Arm title	0.6 mg BI 456906 - planned maintenance treatment

Arm description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and 2, and 0.6 mg on Week 3 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 0.6 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

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

Dosage and administration details:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and 2, and 0.6 mg on Week 3 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 0.6 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Arm title	2.4 mg BI 456906 - planned maintenance treatment

Arm description:

Subject with obesity or overweight were administered a solution for injection of BI 456906, by a weekly

subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 to Week 14 and 2.4 mg on Week 15 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 2.4 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

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

Dosage and administration details:

Subject with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 to Week 14 and 2.4 mg on Week 15 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 2.4 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Arm title	3.6 mg BI 456906 - planned maintenance treatment

Arm description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 and Week 12, 2.4 mg on Week 13 and Week 14, 3.0 mg on Week 15 and Week 16, and 3.6 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 3.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

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

Dosage and administration details:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 and Week 12, 2.4 mg on Week 13 and Week 14, 3.0 mg on Week 15 and Week 16, and 3.6 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 3.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Arm title	4.8 mg BI 456906 - planned maintenance treatment

Arm description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 and Week 8, 1.8 mg on Week 9 and Week 10, 2.4 mg on Week 11 and Week 12, 3.3 mg on Week 13 and Week 14, 4.2 mg on Week 15 and Week 16, and 4.8 mg on Week 17 to Week 20 (dose

escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 4.8 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal AEs had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

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

Dosage and administration details:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 and Week 8, 1.8 mg on Week 9 and Week 10, 2.4 mg on Week 11 and Week 12, 3.3 mg on Week 13 and Week 14, 4.2 mg on Week 15 and Week 16, and 4.8 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 4.8 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal AEs had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Arm title	Placebo

Arm description:

Subjects with obesity or overweight were administered a solution for injection of Placebo, by a weekly subcutaneous injection of two syringes on the same injection day, for 46 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects with obesity or overweight were administered a solution for injection of Placebo, by a weekly subcutaneous injection of two syringes on the same injection day, for 46 weeks.

Notes:

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

Justification: Period with number of subjects included in the full analysis set (FAS) is used as baseline period.

Number of subjects in period 2[2]	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment
Started	77	78	76
Treated during maintenance period	55	60	59
Completed	47	45	48
Not completed	30	33	28
Adverse event, non-fatal	15	20	19
Lost to Follow-up	1	1	1
Perceived lack of efficacy	-	2	1
COVID-related	-	-	1
Burden of study procedures	3	3	1

Other not specified below	5	3	5
Change of residence	-	1	-
Missing	1	-	-
Protocol deviation	3	2	-
Withdrawal by subject	2	1	-

Number of subjects in period 2[2]	4.8 mg BI 456906 - planned maintenance treatment	Placebo
Started	76	77
Treated during maintenance period	55	57
Completed	47	46
Not completed	29	31
Adverse event, non-fatal	22	4
Lost to Follow-up	-	1
Perceived lack of efficacy	-	7
COVID-related	1	-
Burden of study procedures	1	5
Other not specified below	3	9
Change of residence	-	1
Missing	-	-
Protocol deviation	2	2
Withdrawal by subject	-	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: Worldwide 520 were enrolled, whereof 387 were actually randomised in the trial and 384 were included in the baseline period (FAS).

Baseline characteristics

Reporting groups	
Reporting group title	0.6 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and 2, and 0.6 mg on Week 3 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 0.6 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	2.4 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subject with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 to Week 14 and 2.4 mg on Week 15 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 2.4 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	3.6 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 and Week 12, 2.4 mg on Week 13 and Week 14, 3.0 mg on Week 15 and Week 16, and 3.6 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 3.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	4.8 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 and Week 8, 1.8 mg on Week 9 and Week 10, 2.4 mg on Week 11 and Week 12, 3.3 mg on Week 13 and Week 14, 4.2 mg on Week 15 and Week 16, and 4.8 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 4.8 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal AEs had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	Placebo

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of Placebo, by a weekly subcutaneous injection of two syringes on the same injection day, for 46 weeks.

Reporting group values	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment
Number of subjects	77	78	76

Age categorical			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Subjects			
Adults (18-64 years)	67	68	68
Elderly (From 65-84 years)	10	10	8
Age Continuous			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: years			
arithmetic mean	48.6	49.0	50.3
standard deviation	± 12.6	± 13.1	± 11.8
Sex: Female, Male			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Participants			
Female	51	54	51
Male	26	24	25
Race (NIH/OMB)			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	8	9	9
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	10	8	3
White	59	60	63
More than one race	0	1	1
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Subjects			
Hispanic or Latino	3	1	2
Not Hispanic or Latino	74	77	74
Unknown or Not Reported	0	0	0
Body weight at baseline			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Kilogram (kg)			
arithmetic mean	106.98	106.57	104.68
standard deviation	± 18.71	± 22.97	± 19.63

Reporting group values	4.8 mg BI 456906 - planned maintenance treatment	Placebo	Total
Number of subjects	76	77	384
Age categorical			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Subjects			
Adults (18-64 years)	66	66	335
Elderly (From 65-84 years)	10	11	49

Age Continuous			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: years			
arithmetic mean	47.6	50.0	
standard deviation	± 13.5	± 13.5	-
Sex: Female, Male			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Participants			
Female	53	53	262
Male	23	24	122
Race (NIH/OMB)			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	7	7	40
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	8	8	37
White	59	60	301
More than one race	0	1	3
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Subjects			
Hispanic or Latino	6	5	17
Not Hispanic or Latino	70	72	367
Unknown or Not Reported	0	0	0
Body weight at baseline			
Full analysis set (FAS): All randomised patients who received at least one dose of trial medication and who had analysable data for at least one efficacy endpoint.			
Units: Kilogram (kg)			
arithmetic mean	105.86	104.32	
standard deviation	± 17.39	± 22.95	-

End points reporting groups

Reporting group title	0.6 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and 2, and 0.6 mg on Week 3 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 0.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events (AEs) had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subjects was randomised to.

Reporting group title	2.4 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 to Week 14 and 2.4 mg on Week 15 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 2.4 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	3.6 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 and Week 12, 2.4 mg on Week 13 and Week 14, 3.0 mg on Week 15 and Week 16, and 3.6 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 3.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	4.8 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 and Week 8, 1.8 mg on Week 9 and Week 10, 2.4 mg on Week 11 and Week 12, 3.3 mg on Week 13 and Week 14, 4.2 mg on Week 15 and Week 16, and 4.8 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 4.8 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal AEs had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	Placebo

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of Placebo, by a weekly subcutaneous injection of two syringes on the same injection day, for 46 weeks.

Reporting group title	0.6 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and 2, and 0.6 mg on Week 3 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 0.6 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the

option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	2.4 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subject with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 to Week 14 and 2.4 mg on Week 15 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 2.4 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	3.6 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 and Week 12, 2.4 mg on Week 13 and Week 14, 3.0 mg on Week 15 and Week 16, and 3.6 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 3.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	4.8 mg BI 456906 - planned maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 and Week 8, 1.8 mg on Week 9 and Week 10, 2.4 mg on Week 11 and Week 12, 3.3 mg on Week 13 and Week 14, 4.2 mg on Week 15 and Week 16, and 4.8 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 4.8 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal AEs had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	Placebo

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of Placebo, by a weekly subcutaneous injection of two syringes on the same injection day, for 46 weeks.

Primary: Percentage change in body weight from baseline to Week 46

End point title	Percentage change in body weight from baseline to Week 46

End point description:

Percentage change in body weight from baseline to Week 46 was modeled using a mixed model for repeated measures (MMRM) with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures, an unstructured covariance matrix to model within subject measurements, adjusted mean (standard error) at Week 46 is reported. For analysis, all available post-baseline body weight measurements (on- and off-treatment) were used, except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used. That is, a hypothetical strategy was used for intercurrent event (ICE) "COVID-19 pandemic-related early treatment discontinuation", a treatment policy strategy for ICE "non-pandemic-related early treatment discontinuation".
FAS, using planned maintenance treatment.

End point type	Primary

End point timeframe:

Baseline, Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 40, and 46.

End point values	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment	4.8 mg BI 456906 - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	76	76
Units: Percentage change				
least squares mean (standard error)	-6.19 (± 1.07)	-12.51 (± 1.01)	-13.22 (± 1.04)	-14.94 (± 1.01)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	77			
Units: Percentage change				
least squares mean (standard error)	-2.82 (± 1.06)			

Statistical analyses

Statistical analysis title	MCP-mod - Exponential model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different potential dose-response patterns (Linear, Exponential, Emax1, Emax2, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 2.5%).

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v 2.4 mg BI 456906 - planned maintenance treatment v 3.6 mg BI 456906 - planned maintenance treatment v 4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001 [2]
Method	MCP-Mod - Exponential model fit

Notes:

[1] - Covariate adjusted fixed effect estimates of mean percentage change in body weight at Week 46 for each treatment group with associated covariance matrix were extracted from the MMRM (including fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors) and used as input for the MCP-Mod.
Model Assumption: 50% of maximum effect achieved at dose 3.6 mg.
[2] - P-value is adjusted for multiplicity.

Statistical analysis title	MCP-mod - Linear model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different potential dose-response patterns (Linear, Exponential, Emax1, Emax2,

Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 2.5%).

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v 2.4 mg BI 456906 - planned maintenance treatment v 3.6 mg BI 456906 - planned maintenance treatment v 4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001 [4]
Method	MCP-Mod - Linear model fit

Notes:

[3] - Covariate adjusted fixed effect estimates of mean percentage change in body weight at Week 46 for each treatment group with associated covariance matrix were extracted from the MMRM (including fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors) and used as input for the MCP-Mod.
[4] - P-value is adjusted for multiplicity.

Statistical analysis title	MMRM - 4.8 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-12.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	-9.24
Variability estimate	Standard error of the mean
Dispersion value	1.46

Notes:

[5] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[6] - P-value is considered nominal.

Statistical analysis title	MMRM - 0.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v Placebo

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0257 [8]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-3.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.33
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	1.5

Notes:

[7] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[8] - P-value is considered nominal.

Statistical analysis title	MMRM - 2.4 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	2.4 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-9.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.57
upper limit	-6.81
Variability estimate	Standard error of the mean
Dispersion value	1.46

Notes:

[9] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[10] - P-value is considered nominal.

Statistical analysis title	MMRM - 3.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	3.6 mg BI 456906 - planned maintenance treatment v Placebo

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-10.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.32
upper limit	-7.49
Variability estimate	Standard error of the mean
Dispersion value	1.48

Notes:

[11] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[12] - P-value is considered nominal.

Statistical analysis title	MCP-mod - Emax2 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different potential dose-response patterns (Linear, Exponential, Emax1, Emax2, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 2.5%).

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v 2.4 mg BI 456906 - planned maintenance treatment v 3.6 mg BI 456906 - planned maintenance treatment v 4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.0001 [14]
Method	MCP-Mod - Emax2 model fit

Notes:

[13] - Covariate adjusted fixed effect estimates of mean percentage change in body weight at Week 46 for each treatment group with associated covariance matrix were extracted from the MMRM (including fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors) and used as input for the MCP-Mod.
Model Assumption: 70% of maximum effect achieved at dose 4.8 mg.
[14] - P-value is adjusted for multiplicity.

Statistical analysis title	MCP-mod - Emax1 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 456906 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different potential dose-response patterns (Linear, Exponential, Emax1, Emax2, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 2.5%).

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v 2.4 mg BI 456906 - planned maintenance treatment v 3.6 mg BI 456906 - planned maintenance treatment v 4.8 mg BI 456906 - planned maintenance treatment v Placebo

Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.0001 [16]
Method	MCP-Mod - Emax1 model fit

Notes:

[15] - Covariate adjusted fixed effect estimates of mean percentage change in body weight at Week 46 for each treatment group with associated covariance matrix were extracted from the MMRM (including fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors) and used as input for the MCP-Mod.
Model Assumption: 90% of maximum effect achieved at dose 4.8 mg.
[16] - P-value is adjusted for multiplicity.

Statistical analysis title	MCP-mod - Sigmoid Emax model fit

Statistical analysis description:

Multiple comparison procedure and Modeling (MCP-Mod) dose finding analysis to simultaneously evaluate different potential dose response patterns (Linear, Exponential, Emax1, Emax2, Sigmoid Emax), whilst protecting the overall probability of Type 1 error (one-sided, 2.5%) to identify the best-fitting model. Null hypothesis: There is a flat dose-response curve across the placebo and the BI 456906 dose groups with regard to the percentage change in body weight from baseline to Week 46.

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v 2.4 mg BI 456906 - planned maintenance treatment v 3.6 mg BI 456906 - planned maintenance treatment v 4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.0001 [18]
Method	MCP-Mod - Sigmoid Emax model fit

Notes:

[17] - Model Assumption: 50% of maximum effect achieved at dose 2.4 mg, 90% of maximum effect achieved at dose 4.8 mg.
[18] - P-value is adjusted for multiplicity.

Secondary: Weight loss of ≥ 5% of baseline weight at Week 46

End point title	Weight loss of ≥ 5% of baseline weight at Week 46

End point description:

Weight loss of greater than or equal to 5 percent (≥5%) of baseline weight at Week 46 (yes/no), reported as percentage of subjects who achieved a weight loss of ≥5% of baseline weight at Week 46. For analysis, all available post-baseline body weight measurements (on- and off-treatment) were used, except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used. Percentages were rounded to one decimal place.
Full analysis set (all randomised subjects who received at least one dose of study treatment and who have analysable data for at least one efficacy endpoint) using planned maintenance treatment.

End point type	Secondary

End point timeframe:

At baseline and at Week 46.

End point values	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment	4.8 mg BI 456906 - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	58	61	64
Units: Percentage of subjects				
number (not applicable)	60.7	81.0	82.0	82.8

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage of subjects				
number (not applicable)	25.9			

Statistical analyses

Statistical analysis title	Logistic regression - 0.6 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.0015 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.57
upper limit	6.84

Notes:

[19] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. “Percentage change in body weight from baseline to Week 46” and “Body weight loss ≥ 5% at Week 46 (yes/no)” were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin’s method.

Odds ratio is calculated as BI 456906 / Placebo.

[20] - P-value is considered nominal.

Statistical analysis title	Logistic regression - 4.8 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug)

and off-treatment), except for participants who discontinued treatment early due to COVID, only the on-treatment post-baseline body weight measurements were used.

Comparison groups	4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	< 0.0001 [22]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.77
upper limit	24.31

Notes:

[21] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 5% at Week 46 (yes/no)" were derived per participant in each of the 1000 imputed datasets.
Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.

Odds ratio is calculated as BI 456906 / Placebo.
[22] - P-value is considered nominal.

Statistical analysis title	Logistic regression - 3.6 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	3.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	< 0.0001 [24]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.41
upper limit	16.41

Notes:

[23] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 5% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.
Odds ratio is calculated as BI 456906 / Placebo.
[24] - P-value is considered nominal.

Statistical analysis title	Logistic regression - 2.4 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight

measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	2.4 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	< 0.0001 [26]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	19.46

Notes:

[25] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 5% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.

Odds ratio is calculated as BI 456906 / Placebo.
[26] - P-value is considered nominal.

Secondary: Weight loss of ≥ 10% of baseline weight at Week 46

End point title	Weight loss of ≥ 10% of baseline weight at Week 46

End point description:

Weight loss of greater than or equal to 10 percent (≥10%) of baseline weight at Week 46 (yes/no), reported as percentage of subjects who achieved a weight loss of ≥10% of baseline weight at Week 46. For analysis, all available post-baseline body weight measurements (on- and off-treatment) were used, except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used. Percentages were rounded to one decimal place.
Full analysis set (all randomised subjects who received at least one dose of study treatment and who have analysable data for at least one efficacy endpoint) using planned maintenance treatment.

End point type	Secondary

End point timeframe:

At baseline and at Week 46.

End point values	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment	4.8 mg BI 456906 - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	58	61	64
Units: Percentage of subjects				
number (not applicable)	33.9	65.5	65.6	68.8

End point values	Placebo			

Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage of subjects				
number (not applicable)	11.1			

Statistical analyses

Statistical analysis title	Logistic regression - 0.6 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.012 [28]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	8.02

Notes:

[27] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 10% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.

Odds ratio is calculated as BI 456906 / Placebo.
[28] - P-value is considered nominal.

Statistical analysis title	Logistic regression - 2.4 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	2.4 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	< 0.0001 [30]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.36
upper limit	25.86

Notes:

[29] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 10% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.

Odds ratio is calculated as BI 456906 / Placebo.
[30] - P-value is considered nominal.

Statistical analysis title	Logistic regression - 3.6 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	3.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	< 0.0001 [32]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.02
upper limit	23.79

Notes:

[31] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 10% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.

Odds ratio is calculated as BI 456906 / Placebo.
[32] - P-value is considered nominal.

Statistical analysis title	Logistic regression - 4.8 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	4.8 mg BI 456906 - planned maintenance treatment v Placebo

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	< 0.0001 [34]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	14.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.91
upper limit	35.55

Notes:

[33] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 10% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.

Odds ratio is calculated as BI 456906 / Placebo.
[34] - P-value is considered nominal.

Secondary: Weight loss of ≥ 15% of baseline weight at Week 46

End point title	Weight loss of ≥ 15% of baseline weight at Week 46

End point description:

Weight loss of greater than or equal to 15 percent (≥15%) of baseline weight at Week 46 (yes/no), reported as percentage of subjects who achieved a weight loss of ≥15% of baseline weight at Week 46. For analysis, all available post-baseline body weight measurements (on- and off-treatment) were used, except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used. Percentages were rounded to one decimal place.
Full analysis set (all randomised subjects who received at least one dose of study treatment and who have analysable data for at least one efficacy endpoint) using planned maintenance treatment.

End point type	Secondary

End point timeframe:

At baseline and at Week 46.

End point values	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment	4.8 mg BI 456906 - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	58	61	64
Units: Percentage of subjects				
number (not applicable)	12.5	37.9	45.9	54.7

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage of subjects				
number (not applicable)	5.6			

Statistical analyses

Statistical analysis title	Logistic regression - 0.6 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.2654 [36]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	8.02

Notes:

[35] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 15% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.

Odds ratio is calculated as BI 456906 / Placebo.

[36] - P-value is considered nominal.

Statistical analysis title	Logistic regression - 4.8 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.0001 [38]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	21.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.47
upper limit	68.28

Notes:

[37] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 15% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method. Odds ratio is calculated as BI 456906 / Placebo.

[38] - P-value is considered nominal.

Statistical analysis title	Logistic regression - 3.6 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	3.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	< 0.0001 [40]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.62
upper limit	38.36

Notes:

[39] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 15% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.
Odds ratio is calculated as BI 456906 / Placebo.

[40] - P-value is considered nominal.

Statistical analysis title	Logistic regression - 2.4 mg BI vs Placebo

Statistical analysis description:

Logistic regression after multiple imputation. Analysis based on all available post-baseline body weight measurements (on-treatment (first intake of study drug until 28 days after last intake of study drug) and off-treatment), except those for subjects who discontinued treatment early due to COVID-19. For these subjects only on-treatment values were used.

Comparison groups	2.4 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.0002 [42]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.89
upper limit	30.95

Notes:

[41] - Missing body weight measurements were multiply imputed using MMRM with treatment, gender, baseline body weight as factors. "Percentage change in body weight from baseline to Week 46" and "Body weight loss ≥ 15% at Week 46 (yes/no)" were derived per subject in each of the 1000 imputed datasets. Each dataset was analysed by a logistic regression. Multiple estimates from multiple imputation runs were summarised using Rubin's method.
Odds ratio is calculated as BI 456906 / Placebo.

[42] - P-value is considered nominal.

Secondary: Absolute change in body weight from baseline to Week 46

End point title	Absolute change in body weight from baseline to Week 46

End point description:

Absolute change in body weight from baseline to Week 46 was modeled using a mixed model for repeated measures (MMRM) with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 40, and 46) as repeated measures and an unstructured covariance matrix to model within subject measurements, adjusted mean (standard error) at Week 46 is reported. MMRM analysis was performed on the Full analysis set (FAS, all randomised participants who received at least one dose of study treatment and who have analysable data for at least one efficacy endpoint), using planned maintenance treatment (dose assigned at randomisation) and including only on-treatment data, regardless of whether early treatment discontinuation was COVID-19 related.

End point type	Secondary

End point timeframe:

Baseline, Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 40, and 46.

End point values	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment	4.8 mg BI 456906 - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	78	76	76
Units: Kilogram (kg)				
least squares mean (standard error)	-7.21 (± 1.06)	-14.75 (± 1.03)	-15.64 (± 1.04)	-18.47 (± 1.04)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Kilogram (kg)				
least squares mean (standard error)	-2.68 (± 1.04)			

Statistical analyses

Statistical analysis title	MMRM - 0.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.0025 [44]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-4.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.44
upper limit	-1.61
Variability estimate	Standard error of the mean
Dispersion value	1.48

Notes:

[43] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[44] - P-value is considered nominal.

Statistical analysis title	MMRM - 2.4 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	2.4 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	< 0.0001 [46]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-12.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.94
upper limit	-9.19
Variability estimate	Standard error of the mean
Dispersion value	1.46

Notes:

[45] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[46] - P-value is considered nominal.

Statistical analysis title	MMRM - 3.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	3.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	< 0.0001 [48]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-12.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.85
upper limit	-10.07
Variability estimate	Standard error of the mean
Dispersion value	1.47

Notes:

[47] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[48] - P-value is considered nominal.

Statistical analysis title	MMRM - 4.8 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline body weight as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	< 0.0001 [50]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-15.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.67
upper limit	-12.9
Variability estimate	Standard error of the mean
Dispersion value	1.47

Notes:

[49] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[50] - P-value is considered nominal.

Secondary: Absolute change in waist circumference from baseline to Week 46

End point title	Absolute change in waist circumference from baseline to Week 46

End point description:

Absolute change in waist circumference from baseline to Week 46 was modeled using a mixed model for repeated measures (MMRM) with fixed effects for baseline waist circumference as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit (Week 6, 12, 18, 24, 32, 40, and 46) as repeated measures and an unstructured covariance matrix to model within subject measurements, adjusted mean (standard error) at Week 46 is reported. MMRM analysis was performed on the full analysis set (FAS, all randomised participants who received at least one dose of study treatment and who have analysable data for at least one efficacy endpoint), using planned maintenance treatment (dose assigned at randomisation) and including only on-treatment data, regardless of whether early treatment discontinuation was COVID-19 related.

End point type	Secondary

End point timeframe:

Baseline, Week 6, 12, 18, 24, 32, 40, and 46.

End point values	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment	4.8 mg BI 456906 - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	71	74	75
Units: Centimeter (cm)				
least squares mean (standard error)	-8.32 (± 1.22)	-14.99 (± 1.21)	-14.96 (± 1.19)	-16.01 (± 1.19)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Centimeter (cm)				
least squares mean (standard error)	-3.96 (± 1.20)			

Statistical analyses

Statistical analysis title	MMRM - 0.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline waist circumference as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.0116 [52]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-4.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.74
upper limit	-0.98
Variability estimate	Standard error of the mean
Dispersion value	1.71

Notes:

[51] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[52] - P-value is considered nominal.

Statistical analysis title	MMRM - 2.4 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline waist circumference as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	2.4 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	< 0.0001 [54]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-11.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.39
upper limit	-7.66
Variability estimate	Standard error of the mean
Dispersion value	1.71

Notes:

[53] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[54] - P-value is considered nominal

Statistical analysis title	MMRM - 3.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline waist circumference as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	3.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	< 0.0001 [56]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-11

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.33
upper limit	-7.67
Variability estimate	Standard error of the mean
Dispersion value	1.69

Notes:

[55] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[56] - P-value is considered nominal.

Statistical analysis title	MMRM - 4.8 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested.
MMRM with fixed effects for baseline waist circumference as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	< 0.0001 [58]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-12.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.39
upper limit	-8.71
Variability estimate	Standard error of the mean
Dispersion value	1.69

Notes:

[57] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[58] - P-value is considered nominal.

Secondary: Absolute change in systolic blood pressure from baseline to Week 46

End point title	Absolute change in systolic blood pressure from baseline to Week 46

End point description:

Absolute change in systolic blood pressure from baseline to Week 46 was modeled using a mixed model for repeated measures (MMRM) with fixed effects for baseline systolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 40, and 46) as repeated measures and an unstructured covariance matrix to model within subject measurements, adjusted mean (standard error) at Week 46 is reported. MMRM analysis was performed on the full analysis set (FAS, all randomised participants who received at least one dose of study treatment and who have analysable data for at least one efficacy endpoint), using planned maintenance treatment (dose assigned at randomisation) and including only on-treatment data, regardless of whether early treatment discontinuation was COVID-19 related.

End point type	Secondary

End point timeframe:

Baseline, Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 40, and 46.

End point values	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment	4.8 mg BI 456906 - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	78	76	76
Units: Millimeter of mercury (mmHg)				
least squares mean (standard error)	-6.19 (± 1.47)	-8.08 (± 1.48)	-8.66 (± 1.44)	-8.62 (± 1.46)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Millimeter of mercury (mmHg)				
least squares mean (standard error)	-2.46 (± 1.46)			

Statistical analyses

Statistical analysis title	MMRM - 0.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested. MMRM with fixed effects for baseline systolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	= 0.0733 [60]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-3.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.82
upper limit	0.35
Variability estimate	Standard error of the mean
Dispersion value	2.08

Notes:

[59] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[60] - P-value is considered nominal.

Statistical analysis title	MMRM - 3.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested. MMRM with fixed effects for baseline systolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	3.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	= 0.0027 [62]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.23
upper limit	-2.17
Variability estimate	Standard error of the mean
Dispersion value	2.05

Notes:

[61] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[62] - P-value is considered nominal.

Statistical analysis title	MMRM - 4.8 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested. MMRM with fixed effects for baseline systolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	= 0.0033 [64]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-6.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.25
upper limit	-2.06
Variability estimate	Standard error of the mean
Dispersion value	2.08

Notes:

[63] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[64] - P-value is considered nominal.

Statistical analysis title	MMRM - 2.4 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested. MMRM with fixed effects for baseline systolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by

visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	2.4 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other[65]
P-value	< 0.0072 [66]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-5.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.71
upper limit	1.53
Variability estimate	Standard error of the mean
Dispersion value	2.08

Notes:

[65] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[66] - P-value is considered nominal.

Secondary: Absolute change in diastolic blood pressure from baseline to Week 46

End point title	Absolute change in diastolic blood pressure from baseline to Week 46

End point description:

Absolute change in diastolic blood pressure from baseline to Week 46 was modeled using a mixed model for repeated measures (MMRM) with fixed effects for baseline diastolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 40, and 46) as repeated measures and an unstructured covariance matrix to model within subject measurements, adjusted mean (standard error) at Week 46 is reported. MMRM analysis was performed on the full analysis set (FAS, all randomised participants who received at least one dose of study treatment and who have analysable data for at least one efficacy endpoint), using planned maintenance treatment (dose assigned at randomisation) and including only on-treatment data, regardless of whether early treatment discontinuation was COVID-19 related.

End point type	Secondary

End point timeframe:

Baseline, Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 40, and 46.

End point values	0.6 mg BI 456906 - planned maintenance treatment	2.4 mg BI 456906 - planned maintenance treatment	3.6 mg BI 456906 - planned maintenance treatment	4.8 mg BI 456906 - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	78	76	76
Units: Millimeter of mercury (mmHg)				
least squares mean (standard error)	-3.31 (± 0.90)	-4.36 (± 0.90)	-4.31 (± 0.87)	-4.80 (± 0.89)

End point values	Placebo			

Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Millimeter of mercury (mmHg)				
least squares mean (standard error)	-1.87 (± 0.89)			

Statistical analyses

Statistical analysis title	MMRM - 3.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested. MMRM with fixed effects for baseline diastolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	3.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	= 0.0506 [68]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	1.24

Notes:

[67] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[68] - P-value is considered nominal.

Statistical analysis title	MMRM - 2.4 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested. MMRM with fixed effects for baseline diastolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	2.4 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	= 0.0495 [70]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-2.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.97
upper limit	0

Variability estimate	Standard error of the mean
Dispersion value	1.26

Notes:

[69] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[70] - P-value is considered nominal.

Statistical analysis title	MMRM - 0.6 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested. MMRM with fixed effects for baseline diastolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	0.6 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	= 0.2569 [72]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.92
upper limit	1.05
Variability estimate	Standard error of the mean
Dispersion value	1.26

Notes:

[71] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.
[72] - P-value is considered nominal.

Statistical analysis title	MMRM - 4.8 mg BI vs Placebo

Statistical analysis description:

No formal hypotheses were tested. MMRM with fixed effects for baseline diastolic blood pressure as a continuous linear covariate, and treatment, gender, visit, treatment by visit interaction and baseline by visit interaction as factors, using visit as repeated measures and an unstructured covariance matrix to model within subject measurements.

Comparison groups	4.8 mg BI 456906 - planned maintenance treatment v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[73]
P-value	= 0.0202 [74]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-2.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	1.25

Notes:

[73] - Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Difference was calculated as BI 456906 - placebo.

[74] - P-value is considered nominal.

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until last drug administration, plus 28 days residual effect period (REP), up to 360 days.

Adverse event reporting additional description:

Safety analysis was performed on the treated set (TS) according to actual maintenance treatment (defined as the actual dose subjects received during the dose maintenance phase, or as the next planned maintenance dose up from the last dose taken prior to treatment discontinuation).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	0.6 mg BI 456906 - actual maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and 2, and 0.6 mg on Week 3 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 0.6 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	2.4 mg BI 456906 - actual maintenance treatment

Reporting group description:

Subject with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 to Week 10, 1.8 mg on Week 11 to Week 14 and 2.4 mg on Week 15 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 2.4 mg BI 456906. Subjects not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	Placebo

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of Placebo, by a weekly subcutaneous injection of two syringes on the same injection day, for 46 weeks.

Reporting group title	4.8 mg BI 456906 - actual maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg on Week 7 and Week 8, 1.8 mg on Week 9 and Week 10, 2.4 mg on Week 11 and Week 12, 3.3 mg on Week 13 and Week 14, 4.2 mg on Week 15 and Week 16, and 4.8 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 4.8 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal AEs had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Reporting group title	3.6 mg BI 456906 - actual maintenance treatment

Reporting group description:

Subjects with obesity or overweight were administered a solution for injection of BI 456906, by a weekly subcutaneous injection of two syringes (0.5 mL filling volume per syringe) on the same injection day, of 0.3 mg on Week 1 and Week 2, 0.6 mg on Week 3 and Week 4, 0.9 mg on Week 5 and Week 6, 1.2 mg

on Week 7 to Week 10, 1.8 mg on Week 11 and Week 12, 2.4 mg on Week 13 and Week 14, 3.0 mg on Week 15 and Week 16, and 3.6 mg on Week 17 to Week 20 (dose escalation phase, with fixed dose escalation from Week 1 to Week 10 and flexible dose escalation from Week 11 to Week 20). From Week 21 to Week 46 (maintenance dosing phase) subjects stayed on the dose of 3.6 mg BI 456906. Subject not tolerating the assigned dose escalation schedule due to gastrointestinal adverse events had the option of dose adjustment during the flexible part of the dose escalation phase (Week 11 - 20) which could lead to a maintenance dose lower than the dose the subject was randomised to.

Serious adverse events	0.6 mg BI 456906 - actual maintenance treatment	2.4 mg BI 456906 - actual maintenance treatment	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 92 (2.17%)	3 / 92 (3.26%)	5 / 77 (6.49%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	0 / 77 (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
Glioblastoma multiforme			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	0 / 77 (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
Bowen's disease			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	0 / 77 (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
Malignant melanoma in situ			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	0 / 77 (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
Wrist fracture			

subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	0 / 77 (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
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	0 / 77 (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
Endometrial hyperplasia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	0 / 77 (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
Cholelithiasis			

subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	0 / 77 (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			
Pulmonary congestion			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Tooth abscess			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	0 / 77 (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
Cellulitis			

subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	1 / 77 (1.30%)
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	1 / 92 (1.09%)	0 / 92 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	4.8 mg BI 456906 - actual maintenance treatment	3.6 mg BI 456906 - actual maintenance treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 54 (7.41%)	4 / 71 (5.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	1 / 54 (1.85%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			

subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	1 / 54 (1.85%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			

subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (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	1 / 54 (1.85%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary congestion			
subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 54 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (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			
Tooth abscess			

subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 71 (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 / 54 (0.00%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	0.6 mg BI 456906 - actual maintenance treatment	2.4 mg BI 456906 - actual maintenance treatment	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 92 (76.09%)	79 / 92 (85.87%)	48 / 77 (62.34%)
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 92 (8.70%)	7 / 92 (7.61%)	6 / 77 (7.79%)
occurrences (all)	9	8	11
Dizziness			
subjects affected / exposed	1 / 92 (1.09%)	8 / 92 (8.70%)	2 / 77 (2.60%)
occurrences (all)	1	10	3
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	6 / 92 (6.52%)	5 / 92 (5.43%)	6 / 77 (7.79%)
occurrences (all)	6	5	6
Injection site bruising			
subjects affected / exposed	3 / 92 (3.26%)	3 / 92 (3.26%)	4 / 77 (5.19%)
occurrences (all)	3	5	5
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 92 (3.26%)	5 / 92 (5.43%)	1 / 77 (1.30%)
occurrences (all)	4	8	1
Abdominal pain			
subjects affected / exposed	4 / 92 (4.35%)	10 / 92 (10.87%)	1 / 77 (1.30%)
occurrences (all)	6	12	1
Abdominal distension			
subjects affected / exposed	4 / 92 (4.35%)	4 / 92 (4.35%)	3 / 77 (3.90%)
occurrences (all)	4	6	3
Eructation			
subjects affected / exposed	4 / 92 (4.35%)	6 / 92 (6.52%)	0 / 77 (0.00%)
occurrences (all)	5	6	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 92 (2.17%)	7 / 92 (7.61%)	3 / 77 (3.90%)
occurrences (all)	2	8	3
Haemorrhoids			
subjects affected / exposed	0 / 92 (0.00%)	0 / 92 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	7 / 92 (7.61%)	9 / 92 (9.78%)	3 / 77 (3.90%)
occurrences (all)	9	11	3
Nausea			
subjects affected / exposed	36 / 92 (39.13%)	60 / 92 (65.22%)	15 / 77 (19.48%)
occurrences (all)	116	163	21
Constipation			
subjects affected / exposed	11 / 92 (11.96%)	19 / 92 (20.65%)	4 / 77 (5.19%)
occurrences (all)	12	19	6
Diarrhoea			

subjects affected / exposed	22 / 92 (23.91%)	21 / 92 (22.83%)	8 / 77 (10.39%)
occurrences (all)	31	25	10
Vomiting			
subjects affected / exposed	13 / 92 (14.13%)	28 / 92 (30.43%)	4 / 77 (5.19%)
occurrences (all)	23	56	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 92 (2.17%)	2 / 92 (2.17%)	2 / 77 (2.60%)
occurrences (all)	2	2	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 92 (3.26%)	5 / 92 (5.43%)	1 / 77 (1.30%)
occurrences (all)	3	5	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 92 (7.61%)	2 / 92 (2.17%)	3 / 77 (3.90%)
occurrences (all)	8	2	5
Arthralgia			
subjects affected / exposed	10 / 92 (10.87%)	3 / 92 (3.26%)	5 / 77 (6.49%)
occurrences (all)	11	4	7
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 92 (4.35%)	2 / 92 (2.17%)	2 / 77 (2.60%)
occurrences (all)	4	3	2
Upper respiratory tract infection			
subjects affected / exposed	2 / 92 (2.17%)	1 / 92 (1.09%)	3 / 77 (3.90%)
occurrences (all)	2	1	3
Nasopharyngitis			
subjects affected / exposed	8 / 92 (8.70%)	5 / 92 (5.43%)	7 / 77 (9.09%)
occurrences (all)	14	5	8
COVID-19			
subjects affected / exposed	18 / 92 (19.57%)	11 / 92 (11.96%)	17 / 77 (22.08%)
occurrences (all)	19	13	19
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	11 / 92 (11.96%)	10 / 92 (10.87%)	1 / 77 (1.30%)
occurrences (all)	15	12	1

Non-serious adverse events	4.8 mg BI 456906 - actual maintenance treatment	3.6 mg BI 456906 - actual maintenance treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 54 (85.19%)	64 / 71 (90.14%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 54 (9.26%)	10 / 71 (14.08%)	
occurrences (all)	12	13	
Dizziness			
subjects affected / exposed	4 / 54 (7.41%)	10 / 71 (14.08%)	
occurrences (all)	4	10	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 54 (9.26%)	13 / 71 (18.31%)	
occurrences (all)	5	19	
Injection site bruising			
subjects affected / exposed	3 / 54 (5.56%)	2 / 71 (2.82%)	
occurrences (all)	6	3	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 54 (3.70%)	8 / 71 (11.27%)	
occurrences (all)	2	13	
Abdominal pain			
subjects affected / exposed	3 / 54 (5.56%)	5 / 71 (7.04%)	
occurrences (all)	3	7	
Abdominal distension			
subjects affected / exposed	3 / 54 (5.56%)	7 / 71 (9.86%)	
occurrences (all)	6	7	
Eructation			
subjects affected / exposed	2 / 54 (3.70%)	5 / 71 (7.04%)	
occurrences (all)	4	5	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 54 (9.26%)	10 / 71 (14.08%)	
occurrences (all)	5	13	

Haemorrhoids			
subjects affected / exposed	3 / 54 (5.56%)	1 / 71 (1.41%)	
occurrences (all)	3	1	
Dyspepsia			
subjects affected / exposed	7 / 54 (12.96%)	8 / 71 (11.27%)	
occurrences (all)	16	15	
Nausea			
subjects affected / exposed	32 / 54 (59.26%)	45 / 71 (63.38%)	
occurrences (all)	98	157	
Constipation			
subjects affected / exposed	13 / 54 (24.07%)	22 / 71 (30.99%)	
occurrences (all)	18	25	
Diarrhoea			
subjects affected / exposed	9 / 54 (16.67%)	17 / 71 (23.94%)	
occurrences (all)	18	52	
Vomiting			
subjects affected / exposed	13 / 54 (24.07%)	28 / 71 (39.44%)	
occurrences (all)	28	64	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 54 (0.00%)	4 / 71 (5.63%)	
occurrences (all)	0	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 71 (1.41%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 54 (3.70%)	4 / 71 (5.63%)	
occurrences (all)	3	10	
Arthralgia			
subjects affected / exposed	2 / 54 (3.70%)	8 / 71 (11.27%)	
occurrences (all)	2	9	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	2 / 54 (3.70%)	6 / 71 (8.45%)	
occurrences (all)	2	11	
Upper respiratory tract infection			
subjects affected / exposed	4 / 54 (7.41%)	5 / 71 (7.04%)	
occurrences (all)	5	6	
Nasopharyngitis			
subjects affected / exposed	3 / 54 (5.56%)	6 / 71 (8.45%)	
occurrences (all)	3	10	
COVID-19			
subjects affected / exposed	7 / 54 (12.96%)	17 / 71 (23.94%)	
occurrences (all)	7	17	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 54 (5.56%)	16 / 71 (22.54%)	
occurrences (all)	17	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2021	Global amendment 1: Exclusion criteria were revised: Time period of stability in body weight was changed from past 3 to past 12 weeks; List of endocrinologic disorders leading to obesity was revised to include hypogonadism and growth hormone deficiency as exclusion criteria and to allow well-controlled hypothyroidism and polycystic ovarian disease; Prior surgery of the Gastrointestinal (GI) tract that could interfere with body weight was further explained; Q wave and T wave (QT)/ corrected QT interval (QTc) prolongation-related criterion was simplified; Squamous cell carcinoma added. Flow Chart was revised: Specifying that a pregnancy test is urinary; Electrocardiogram (ECG) added to visits 14,16,17,19; Insulin and C-peptide were added to efficacy parameters of fasting sample (also added to safety lab parameters); Footnote 17 was expanded to explain the procedures regarding E-diary and counselling at Visit 19 for patients who had discontinued the treatment. Inclusion criteria were revised: Reference added to criterion 5 for explanation. Criteria for discontinuation of trial treatment were revised: Criteria added: patients that require hospitalization due to drug-related gastrointestinal adverse event assessed by investigator; Exception added to which patients should stay in the trial after treatment discontinuation to exclude Glucagon-Like-Peptide 1 Receptor Agonist (GLP-1 RA) treated patients.

24 September 2021	Global amendment 1 (continued): Drug assignment and administration was revised due to authority request: Patients who cannot tolerate the study drug during Weeks 1 to 10 and Weeks 21 to 46 should be discontinued from the treatment. Restrictions regarding concomitant treatment were revised: Medications known to significantly prolong the QT or QTc interval administered for a period of >2 weeks was added. Assessment of safety was revised due to authority request: Clarification was added to encourage investigators to repeat imaging and laboratory testing in case of abnormal findings. ECG description was expanded due to authority request: Regarding the review of the ECG results by investigator; Regarding repetition of ECG recording in case of abnormalities. Explanation of process regarding cross referencing adverse events (AEs) list against Always Serious List was added due to authority request. Doses expressed in conventional units (mmol/L or nmol/L) were added to values of calcitonin, fasting serum triglyceride, fasting plasma glucose, 2-hour oral glucose tolerance test (OGTT). Clarification on who should complete PHQ-9 and C-SSRS questionnaires was added. Clarification on time points for diet/exercise counselling was added. Clarification of safety lab analysis handling if central lab cannot provide analysis due to COVID-19 restrictions. Instructions for trial drug administration were revised: To allow exceptions for visits schedule; To allow exceptions for pre-defined combination of syringes. Blood pressure measurement procedure was revised.
16 February 2022	Global amendment 2: Description of an interim analysis to be performed during the trial for sponsor planning purposes was added.
29 April 2022	Global amendment 3: It was added that discontinuation of trial treatment due to COVID-19 infection and a possibility to recommence the study treatment after skipping two consecutive doses is up to investigator’s discretion. It was added the randomisation codes will be provided during the trial to bioanalytics to exclude samples from placebo patients from the analysis of antidrug antibodies. Removal of description of Per Protocol Set and of reference to Per Protocol Set in primary endpoint analysis. Removal of the statement that important protocol deviations may lead to an exclusion from the analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported