Clinical Trial Protocol

	Document Number:	**c31754142-05**
EudraCT No. **EU Trial No.**	2020-002479-37	
BI Trial No.	1404-0036	
BI Investigational Medicinal Product(s)	BI 456906	
Title	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	
Lay Title	A study to test whether different doses of BI 456906 help people with overweight or obesity to lose weight	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Phone: Fax:	
Coordinating Investigator	[redacted] Tel	
Version and Date	**Version:** 5.0	**Date: 29 Apr 2022**

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	20 Aug 2020
Revision date	29 Apr 2022
BI trial number	1404-0036
Title of trial	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
Coordinating Investigator	[redacted] Tel [redacted]
Trial site(s)	Multi-centre trial conducted in 13 countries
Clinical phase	II
Trial rationale	The trial is designed to evaluate safety, tolerability, PK and PD of BI 456906 in male and female patients with obesity or overweight using multiple escalation schemes and doses and will support dose selection for phase 3 clinical development of BI 456906.
Trial objective(s)	The primary objective is to demonstrate proof of clinical concept 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 3 studies.
Trial endpoints	**Primary endpoint** Percentage change in body weight (%) from baseline to week 46 **Secondary endpoints** • Weight loss of ≥ 5% of baseline weight at week 46 • Weight loss of ≥ 10% of baseline weight at week 46 • Weight loss of ≥ 15% of baseline weight at week 46 • Absolute change in body weight (kg) from baseline to week 46 • Absolute change in waist circumference (cm) from baseline to week 46 • Absolute change in systolic blood pressure (mmHg) from baseline to week 46 • Absolute change in diastolic blood pressure (mmHg) from baseline to week 46
Trial design	Randomized, double blind, parallel group, placebo-controlled trial
Total number of patients randomised	350

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Number of patients on each treatment	70
Diagnosis	Obesity or Overweight defined as BMI≥27kg/m^2
Main in- and exclusion criteria	**Key inclusion criteria:** 1. Adult ≥ 18 years and < 75 years of age at screening 2. Obesity or Overweight defined as BMI ≥27 kg/m^2 at screening 3. A minimum absolute body weight of 70 kg for females and 80 kg for males at screening 4. Patients must have undergone at least one previous unsuccessful nonsurgical weight-loss attempt **Key exclusion criteria:** 1. Body weight change of +/- 5% in the past 12 weeks 2. A HbA1c ≥ 6.5% at screening or diagnosed with type 1 or type 2 diabetes mellitus 3. Screening calcitonin ≥ 20 ng/L (pg/mL) (≥5,84 pmol/L) 4. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 5. History of pancreatitis (acute or chronic) 6. Obesity induced by endocrine disorders (i.e. Cushing Syndrome, hypogonadism, growh hormone deficiency. However, well controlled hypothyroidism, polycystic ovarian disease are still allowed) 7. Treatment with medication that potentially induce a change in body weight (e.g., steroids, antipsychotics), or anti-obesity medication including over-the-counter medications, or participating in an organized weight loss program (e.g. [redacted] ® or [redacted] ®) within 3 months before screening 8. Previous irreversible surgical treatment for obesity. Previous treatment with reversible weight loss devices such as gastric banding, or intragastric balloon and removed longer than 12 months before screening should not be excluded. 9. Any suicidal behaviour in the past 2 years, any suicidal ideation of type 4 or 5 in the C-SSRS within 3 months before screening, or during screening period 10. History of major depressive disorder within 2 years before randomisation 11. Women who are pregnant, nursing, or who intend to become pregnant while in the trial
Test product(s)	BI 456906
dose	Multiple doses
mode of administration	Subcutaneous (s.c.)
Comparator product(s)	Placebo
dose	Matching

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mode of administration	Subcutaneous (s.c.)
Duration of treatment	46 weeks
Statistical methods	The analysis for PoCC and dose-finding will be performed using multiple comparison and modelling techniques (MCPMod) whereby several possible dose response models (patterns) will be evaluated, while keeping full control of the type I error at 2.5% (one-sided) to identify the best-fitting model or subset of models. A plausible and diverse range of monotone dose response patterns will be used for this purpose, with placebo mean response assumed to be zero and the mean response at the highest BI 456906 dose assumed to be -10.0 (i.e. a percentage reduction from baseline in body weight of 10%). A mixed model for repeated measures (MMRM) analysis will first be carried out. The MMRM will include fixed effects for baseline body weight and baseline by visit interaction as continuous covariates, and treatment, gender, visit and treatment-by-visit interaction as factors. Unstructured covariance will be used to model the relationship between pairs of endpoint measurements taken at different visits on the same patient. Adjusted mean percentage change in body weight at Week 46 for each treatment group and the covariance matrix will be extracted from the MMRM fit and used for the subsequent MCPMod analysis. PoCC will be established if at least one model is statistically significant, rejecting the null hypothesis of a flat dose response relationship for percentage change in body weight jointly over the candidate dose response models, with a contrast test controlled for the family–wise type I error rate at one sided $\alpha = 2.5\%$. If PoCC is established, the statistically significant (best fitting) model(s) from the above candidate set will be refitted to the data to generate new estimates for all model parameters from the data. The target dose(s) will be estimated from the best fitting model(s) by incorporating information on the minimum clinically relevant effect and accounting for safety. The primary analysis of percentage change from baseline in body weight at Week 46 will be performed using the full analysis set (FAS), defined as all randomised patients who received at least one dose of study treatment and who have analysable data for at least one efficacy endpoint. Patients will be assigned to the randomised maintenance dose. The analysis will include all available data without regard to whether patients started the maintenance period with a lower dose than the one randomised to. For patients who discontinued treatment early, a distinction will be made according to whether this is due to a COVID-19 pandemic-related reason or not. Patients who discontinued treatment early due to a pandemic-related reason will have data handled after discontinuation as if they were missing (hypothetical strategy). Patients who discontinued treatment

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	early for any other reason will have all available data included after discontinuation (treatment policy strategy).
	[redacted]

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FLOW CHART (VISIT 1 TO 11)

Trial period	**screening**	**Randomized treatment – Dose escalation phase**									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Weeks	**-12 to -1**		**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**
Days	**-84 to -7**	**1**[1]	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**
Time window for visits (days)			**+/-1**	**+/-1**	**+/-1**	**+/-1**	**+/-1**	**+/-1**	**+/-1**	**+/-1**	**+/-1**
Informed consent	X										
Informed consent for biobanking [2]	X										
Demographics	X										
Medical history	X										
Obesity clinical staging		X									
Physical examination	X	X		X		X		X		X	
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X			X			X			X
Pregnancy testing[4]	X_s	X_u		X_u		X_u		X_u		X_u	
Laboratory tests [5]	X[6]	X[7]	X	X	X	X	X[7]	X	X	X	X
12-lead ECG[8]	X	X	X	X	X	X	X	X	X	X	X
Review of in-/exclusion criteria	X	X									
Randomisation		X									
Check discontinuation criteria			X	X	X	X	X	X	X	X	X
Instructions for control of sickness		X	X	X	X	X	X	X	X	X	X
Train patients for self-injection		X		X							
Dispense trial drugs for home injections		X	X	X	X	X	X	X	X	X	X
Trial drug injection during visit		X	X	X	X	X	X	X	X	X	X
PK Sampling [9]		X	X	X	X	X	X	X	X	X	X
Blood – ADA /NAb [9]		X		X		X		X		X	
Biomarkers[10]		X					X				
HbA1c	X	X					X				
Pharmacogenomic Biomarker sample		X									
Blood sampling for biobanking[11]		X								X	
PRO completion[12] : BI-de novo eating questionnaire and PGI-S questionnaire	X	X									
PRO completion[12]: PGI-D, SF36PF10 and TFEQ		X									
Distribute and explain the patient material[13]	X	X									
3-days food diary[14]		X									
Check e-diary and paper diary		X	X	X	X	X	X	X	X	X	X

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FLOW CHART (VISIT 1 TO 11) (CONT)

Trial period	**screening**	**Randomized treatment – Dose escalation phase**									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Weeks	**-12 to -1**		**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**
Diet and physical activity counselling		X		X		X		X		X	
C-SSRS and PHQ-9	X	X	X	X	X	X	X	X	X	X	X
All AEs/SAEs/AESIs[15]	X	X	X	X	X	X	X	X	X	X	X
Assessment of breast neoplasm, colon neoplasm		X									
Compliance check			X	X	X	X	X	X	X	X	X
Concomitant therapy		X	X	X	X	X	X	X	X	X	X
Check medication change for hypertension and dyslipidaemia		X						X			

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FLOW CHART (VISIT 12 TO END OF PARTICIPATION)

Trial Periods	Randomized treatment - Maintenance phase									Follow-up [17]
Visit	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19[17]**	**EOT[17]**	**F-up**
Weeks	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**46**		**EOT+3 w**
Days	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**323**	**Last admin + 7 days**	**Last admin + 28 days**
Time window for visits	+/- 2	+/- 2	+/- 2	+/-2	+/- 2	+/- 2	+/-2	+/- 2	+/- 2	+ 7
Physical examination	X	X	X	X	X	X		X	X	X
Vital signs[3]	X	X	X	X	X	X		X	X	X
Height										
Weight	X	X	X	X	X	X		X[18]	X	
Obesity clinical staging									X	
Waist circumference		X		X		X		X	X	
Pregnancy testing [4]	X_u	X_u	X_u	X_u	X_u	X_u		X_u	X_u	X_u
Laboratory tests [5]	X[7]	X	X	X	X	X			X[7]	X
12-lead ECG[8]	X	X	X	X	X	X		X	X	X[8]
Check discontinuation criteria	X	X	X	X	X	X				
Instructions for control of sickness	X	X	X	X	X	X				
Dispense trial drugs for home injection	X	X	X	X	X	X	X[16]			
Trial drug injection during visit	X	X	X	X	X	X				
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]	X								X	
Check e-diary and paper diary	X	X	X	X	X	X		X[17]	X	
Diet and physical activity counselling	X	X	X	X	X	X		X[17]	X	
C-SSRS and PHQ-9	X	X	X	X	X	X		X	X	X
All AEs/SAEs/AESIs[15]	X	X	X	X	X	X	X[16]	X	X	X
Assessment of breast neoplasm, colon neoplasm									X	X
Compliance check	X	X	X	X	X	X			X	
Concomitant therapy	X	X	X	X	X	X		X	X	X
[redacted]	X			X					X	X

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FLOW CHART (VISIT 12 TO END OF PARTICIPATION) (CONT)

Trial Periods	Randomized treatment - Maintenance phase									Follow-up [17]
Visit	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19[17]**	**EOT[17]**	**F-up**
Weeks	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**46**		**EOT+3 w**
Completion of patient participation										X
Vital status data [18]								X		

Footnotes for Flow Charts:

1. Day of Randomisation
2. Blood sample collection for biobanking is optional and requires a separate informed consent
3. Measurements of vital signs should preceed blood sampling and be assessed at all dosing visits according to section 5.2.2. Vital signs include DBP/SBP measurement, pulse rate, respiration rate, and body temperature
4. Women of childbearing potential only. Xs =serum testing by central laboratory; Xu= onsite urine testing; Serum pregnancy testing is done at screening and as a reflex when urine testing is positive. Pregnancy testing at and after Visit 2 should be performed prior to administration of trial medication
5. Safety lab include haematology, clinical chemistry, infectious serology, lipids and urinalysis. For details refer to Table 5.2.3:1. All blood samples should be collected before the administration of trial medication.
6. PCR Test on SARS-CoV-2 to be performed at Visit 1
7. FASTING sample: on these days, blood samples will also include some efficacy parameters including fasting glucose, insulin and C-peptide, and fasting lipid battery These visits would preferably be scheduled on mornings
8. Centralized ECG. ECG should be recorded before blood samples are taken. ECG recording may be repeated by investigator for medical or quality reasons. ECG at follow up, only in case abnormal at previous visit. For ECG measurement, follow guidelines in Section 5.2.4.
9. PK and ADA/NAb sampling at trough prior to administration of next dose. In case of systemic hypersensitivity, also draw a plasma sample for IgE and ADA as detailed in the Lab Manual (ISF). Also include the evaluation of histamine, serum tryptase, and complement components
10. Blood sample for exploratory biomarkers at Visit 2 should be collected before the administration of trial medication (pre-dose value)
11. DNA biobanking requires one blood sample (preferably at Visit 2), serum and plama samples are taken at several timepoints.
12. PRO should be completed prior to assessment of vital signs and in the pre-specified order (ref to section 6.2.2) during respective visits
13. Patient's material include paper food diary distributed at screening. Once patient is randomised distribute a scale to have home weight measurements and e-diary (on their own device or on a provided smartphone).
14. 3 days food diary to be completed before the visit : includes two weekdays and one weekend day
15. After the End Of Study visit (=individual patient's end of the study) the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of and only via the BI SAE form.
16. Visit 18 is organised only for the patient to collect his medication for the remaining 2 weeks. There is no need to visit the site staff other than pharmacy, and injection can be done at home. If, due to site organisation, the patient comes to the site and reports AEs, these will be recorded. Last drug injection will be on week 45, day 316.
17. When a patient discontinues treatment, he/she has to complete a End of Treatment visit ; if he/she has reached the normal end, the EOT visit and the visit 19 (week 46) will be combined in only one visit, containing all exams due for both visits (but not in duplicate). Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EOT) visit 7 days after last drug intake, as well as a follow-up visit 3 weeks later. All efforts should be made to keep these patients in the trial, have regular weight measurements as described in section 6.2.2 and have a visit conducted at week 46. E-diary checks and patient counselling is optional at visit 19 for patients who had withdrawn drug prematurely
18. All efforts should be made at least to conduct the week 46 visit for all patients including patients who discontinue trial treatment prematurely and have agreed to be contacted. However, if this is not possible, a phone contact should be made at week 46 to obtain vital status and body weight measured at home.

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ABBREVIATIONS

ADA	Anti Drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate transaminase
AUC	Area under the curve
AUC_{0-t}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to time t
BI	Boehringer Ingelheim
BMI	Body Mass Index
BMR	Basal metabolic rate
CCS grading	Canadian Cardiovascular Society grading
CEC	Clinical event committee
CI	Confidence interval
CK	Creatinine kinase
CNS	Central Nervous system
C-SSRS	Columbia Suicide Severity Rating Scale
CTM	Clinical trial manager
C_{max}	Maximum measured concentration of the analyte in plasma
CMDS	Cardiometabolic disease staging
CRO	Contract research organization
CTR	Clinical trial report
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DMC	Data-monitoring committee
ECG	Electrocardiogram
ED	Early discontinuation
eDC	Electronic data capture
EOSS	Edmonton obesity staging system
EOT	End of treatment
ER	Extended release

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EudraCT	European clinical trials database
FAS	Full analysis set
FC	Flow chart
FFA	Free fatty acids
FPG	Fasting Plasma Glucose
GCGR	Glucagon Receptor
γ-GT	Gamma-glutamyl transferase
GI	Gastro-intestinal
GLP1R	Glucagon-Like-Peptide 1 Receptor
HA	Health Authority
HbA1C	glycosylated Hemoglobin, Type A1
HDL	High-Density lipoprotein
HR	Heart rate
ICH	International Conference on Harmonisation
IWQoL-Lite CT	Impact of Weight on Quality of Life-Lite questionnaire in Clinical Trial
IB	Investigator Brochure
IPD	Important protocol deviation
IRT	Interactive Response Technology
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine system
LDh	Lactate deshydrogenase
LDL	Low-density lipoprotein
Mar	Missing at Random
MCPMod	Multiple comparison procedure - Modelling
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed model for repeated measures
MRD	Multiple rising dose
NAb	Neutralizing antibody
NASH	Non alcoholic steato hepatitis
NYHA	New York Health Association
OTC	Over the counter
PCR	Polymerase chain reaction

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PD	Pharmacodynamics
PG	Pharmacogenomics
PGI	Patients Global Impression
PHQ	Patient Health Questionnaire
PK	Pharmacokinetics
p.o.	per os (oral)
PoCC	Proof of Clinical Concept
PPS	Per protocol set
p.r.n..	Pro re nata
PRO	Patient reported outcomes
q.d.	quaque die (once a day)
QT	Q wave and T wave
QTcF	QT interval corrected by Fredericia's formula
RA	Regulatory Authority
REP	Residual Effect Period
SAE	Serious adverse event
s.c.	subcutaneous
SC	Steering Committee
SF-36	36-Item Short Form Health Survey
SOP	Standard Operating Procedure
SR	Sustained realease
SRD	Single rising dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 diabetes mellitus
TG	Triglycerid
TIA	Transient ischemic attack
TFEQ	Three Factor Eating Questionnaire
t.i.d.	ter in die (3 times a day)
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration
TMF	Trial Master File
TS	Treated set
TSAP	Trial statistical plan

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TSH	Thyroid stimulating hormone
ULN	Upper Level of Normal
VAS	Visual Analog Scale
VLDL	Very low-density lipoprotein
WBC	White blood cells
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

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1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Obesity is a chronic, complex, heterogeneous disease caused by disruption of physiological control of overall adiposity resulting in excessive fat accumulation. Obesity substantially increases the risk of metabolic diseases (for example type 2 diabetes mellitus and fatty liver disease), cardiovascular diseases (hypertension, myocardial infarction and stroke), musculoskeletal disease (osteoarthritis), Alzheimer disease, depression and some types of cancer (for example, breast, ovarian, prostate, liver, kidney and colon). In addition, obesity can lead to reduced quality of life, employment disparities, lower productivity and social disadvantages. For example, osteoarthritis — a common consequence of obesity — is one of the leading causes of disability and early retirement. Importantly, the World Obesity Federation and other organizations, including the American and Canadian Medical Associations, have declared obesity a chronic progressive disease clearly distinct from being a risk factor for other diseases and suggest that weight loss can improve these outcomes [R20-1944].

Obesity was previosly regarded solely as a lifestyle or behavioural disorder caused by increased calorie intake or reduced physical activity; however, current evidence suggests that obesity is caused by a disruption of homeostatic control of body weight and a failure to maintain constant body fat mass. Regulation of physiological body weight set point involves numerous arrays of central nervous system circuitry and peripheral metabolic feedback signals of either energy abundance or deficit, influenced by a [redacted] of genetic, developmental, biological, environmental, behavioural and iatrogenic factors. The abnormal regulation of body weight triggers a biological resistance to weight loss and a predisposition to weight gain.

Currently, there are four major FDA-approved medications for chronic weight management: orlistat, phentermine/topiramate extended release (ER), naltrexone sustained release (SR)/bupropion SR and liraglutide, however those medications only provide modest reduction of body weight. Most of these drugs work through CNS pathways that either reduce appetite or enhance satiety, with the exception of orlistat, which decreases the absorption of fat [R20-1943]. Considering neurobiological resilience to energy homeostatic perturbations, combined with the heterogeneous pathophysiology of human metabolic disorders, targeting of multiple signalling pathways (including CNS and peripheral organs) is probably necessary. This will help patients with obesity to achive more significant improvements in weight management and might reverse the progression of these metabolic disorders and related co-morbidities. Targeting multiple pathways has become a standard treatment strategy in other diseases such as T2DM, hypertension, heart failure. It is anticipated that obesity will prove no different, with simultaneous activation of multiple target mechanisms, i.e. anorectic and thermogenic pathways, producing enhanced metabolic benefits such as improved glucose intolerance and lipid metabolism thereby producing meaningful and sustained clinical outcomes for treating obesity and related co-morbidities.

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1.2 DRUG PROFILE

Mode of action

BI 456906 is a dual agonist of GLP-1 and Glucagon receptors. Targeting both GLP-1 and Glucagon signalling pathways is expected to provide synergistic clinical benefit for chronic weight management and obesity.

Simultaneous dual activation of GLP-1R and GCGR by BI 456906 is anticipated to achieve improved glycaemic control, reduction in body weight and improvement in NASH. BI 456906 leads to full activation of the GLP-1R at the predicted therapeutic exposure, but only to a partial activation of the GCGR, which seems sufficient to achieve greater weight loss than GLP-1R activation alone, without hyperglycaemia.

In a 4-week study in mice with diet-induced obesity, BI 456906 was able to induce a body weight loss greater than liraglutide. BI 456906 dose-dependently increased energy expenditure while the pure GLP-1R agonist liraglutide had no effect even at supra-therapeutic exposure. It is expected that the increased energy expenditure will contribute to a longer lasting negative energy balance than GLP1-R agonism alone, while achieving a favourable benefit/risk profile (c14085752-05)

Key pharmacokinetic characteristics

[redacted]

Drug interactions

[redacted]

[redacted]

Data from non-clinical studies

[redacted]

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[redacted]

Data from clinical studies
GLP-1R agonists are known to be associated with GI and cardiac side effects.
Multiple studies and clinical experience from GLP-1R agonists suggest that GI side effects can be mitigated by dose escalation. Rates of nausea, vomiting, and diarrhoea appeared to be dose dependent for GLP-[redacted] agonists, and the proportion of patients reporting nausea was 20% lower in patients with dose escalation than without dose escalation [R17-4311].
Accordingly, for a number of compounds of this class it has been shown that dose escalation steps are able to significantly improve tolerability in clinical practice.
Cardiac conduction disorders were described for GLP-1R agonists in clinical trials and in the prescribing information for Saxenda [R19-1407], reported as first-degree atrioventricular block, right bundle branch block, or left bundle branch block, as well as QT-prolongation.

BI 456906 has been studied in healthy volunteers in a single rising dose trial (1404-0001). Similar to other GLP-1 agonists, nausea and vomiting were seen with increasing doses up to 1.2 mg and the study was discontinued early due to severe nausea and vomiting in a number of healthy volunteers.
BI 456906 has also been studied in otherwise healthy volunteers with obesity or overweight in a multiple rising dose trial (c21168858-06) with dose escalation to investigate the safety and tolerability of different dose escalation schemes to determine a dose escalation scheme that minimizes gastrointestinal adverse events. Data from the completed 6-week MRD trial (c21168858-06) where BI 456906 was administered in 4 different escalation schemas (one once-daily dose group and 3 once-weekly dose groups, all with weekly dose escalation) were analysed. The most frequent AEs were gastrointestinal (GI) disorders, such as nausea, vomiting, diarrhoea, in participants who received BI 456906 treatment compared to placebo. Most of the reported GI AEs were transient, mild or moderate in intensity.
Preliminary data out of the 16-week MRD trial where BI 456906 was administered in three different escalation schemas showed comparable safety profile to the 6-week data. The most frequent AEs were GI disorders, and most of the reported GI AEs were transient, mild or moderate in intensity. Severe AEs of gastrointestinal disorder were reported for 9 out of 45 patients treated with BI 456906.
No deaths, SAEs, or protocol specified AESIs, were reported in this trial to date.
For a more detailed description of the BI 456906 profile, please refer to the current Investigator's Brochure (IB).

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 456906 is a long acting dual GLP-1R and GCGR agonist being evaluated for the treatment of T2DM, chronic weight management for obesity/overweight, and NASH.
The action of dual GLP-1R and GCGR agonist likely results from a combination of central and peripheral mechanisms, at multiple target tissues.

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In addition to the known effect of GLP-1RA, [redacted]

The purpose of the study is to investigate the effect of BI 456906 at four dose levels to induce weight loss and plateau in subjects with obesity or overweight, without diabetes mellitus, compared to placebo. Safety and tolerability including the formation of anti-BI 456906 antibodies will be investigated

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see section 5.5). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

The overall benefits and safety profile of BI 456906 have been outlined in previous sections. More information on the benefits, risks, and known AEs will be presented in the Investigator's Brochure.

1.4.1 Benefits

Based on the currently available data, in otherwise healthy volunteers with obesity or overweight, dual agonism at the GLP1R and GCGR is expected to result in superior body weight loss and maintenance compared to GLP1R agonism alone, [redacted] Thus, subjects to be treated with BI 456906 are expected to achieve improved weight management results compared to prior to their trial participation.

1.4.2 Risks

There is no identified risk for BI 456906, based on the toxicology programme or any clinical trials conducted for this product to date. There are three important potential risks based on other GLP-1 receptor agonists currently approved, providing information on identified and potential risks in molecules of this class. The three important potential risks include medullary thyroid cancer (c-cell carcinogenicity), pancreatic cancer, and acute pancreatitis.

The risk for patients caused by participation in the trial, including the study procedures and exposure to the study drug, are reasonably low and do not outweigh the potential benefits. The expected side effects are known to be temporary, dose dependent, easy to monitor and manageable in clinical trials.

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Table 1.4.2:1 Overview over trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product		
Gastrointestinal disorders, or Metabolism and nutrition disorders	Well-known side effects for GLP1-R agonist-based therapies	Slow and careful dose escalation. Instructions to be given
Cardiac disorders	Well-known side effects for GLP1-R agonist-based therapies	Centralised Electrocardiogram (ECG) monitoring will be performed at screening, randomization and within predefined intervals during the trial, and criteria for heart rate, QT prolongation and cardiac conduction disorders are defined.
Acute pancreatitis	To date there is no evidence that BI456906 causes such adverse events. Well-known side effects for GLP1-R agonist-based therapies * Well-known side effects for GLP1-R agonist-based therapies, and well-known adverse event of rapid significant weight loss	An extensive safety laboratory will be performed. Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.
Medullary thyroid carcinoma (MTC), or Multiple endocrine neoplasm (MEN)Type 2		
Acute biliary disease*		
Systemic hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of adverse immune reactions which can be local (e.g redness, pruritus, and or swelling at the injection site) or systemic (e.g. anaphylactic reactions).	Patients with a history of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to interrupt and treat the condition.

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Table 1.4.2:1 Overview over trial related risks (cont.)

Trial procedures		
Insufficient weight loss	Patients who will receive placebo may not achieve sufficient weight loss during the trial.	Patients in placebo group will remain on standard of care that includes diet and exercise counselling.
Administration site conditions	Well-known side effects for injectables	Instructions to be given Injection site will be monitored during the physical exam in every visit
Other risks		
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety
Acute kidney injury (pre-renal)	Related to severe GI AEs of GLP-1RA class (severe vomiting may cause dehydration)	-In case of vomiting, nausea and diarrhea, increase fluid intake - Monitor decreased renal function
Suicide risk, depression and mood disorder	Not observed in clinical trials so far. BI456906 could potentially act on central GLP-1 receptor.	Columbia Suicide Severity Rating Scale (C-SSRS) will be applied at every visits;

These side effects can be reduced by careful dose escalation, are known to be dose dependent, are easy to monitor, and manageable in clinical trials.
In this trial the following safety measures will be applied in order to minimize the risk for trial patients:
An extensive safety laboratory will be performed.

- Patients in all groups, including placebo group will receive standard of care that includes diet and exercise counselling.
- There are no risks expected by stopping the trial medication during the trial.
- Centralised Electrocardiogram (ECG) monitoring will be performed at screening, randomization and within predefined intervals during the trial, and criteria for heart rate, QT prolongation and cardiac conduction disorders are defined.
- Instructions are to be given to the patients to help improve tolerability especially during escalation phase. In addition, patients who do not tolerate the assigned escalation schedule, can modify dose escalation schedule. Details are described in section 4.1.4.
- During the trial, patients will be under medical observation and thoroughly monitored for both expected and unexpected AEs including administration and evaluation of the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Paediatric patients (less than 18 years old) are excluded from the trial.
- Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using an adequate contraceptive method throughout the

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trial including the 4-week follow-up period are excluded from the trial (Section 4.2.2.2)
- To continue the assessment of the safety of BI 456906, adjudication of some events will be performed in that trial. The progress of the trial will also be assessed at regular intervals by an independent Data Monitoring Committee (DMC). Further details are described in Section 8.7, the adjudication charter and the DMC charter.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. Section 5.2.6.1.4 provides guidance for the investigators on how to evaluate and treat patients with suspected DILI.

Based on the pharmacological mechanism of BI 456906, the review of the non-clinical and clinical data available so far for this compound and considering the clinical and post-marketing data derived from the GLP-1 receptor agonists available on the market, there is no indication that BI 456906 could increase the risk of severe viral infections such as SARS-CoV-2.

1.4.3 Discussion

BI 456906 was well tolerated in safety pharmacology and toxicology studies and the main effects seen reflected the intended pharmacology of the compound. Single s.c. doses of 0.3 mg and 0.5 mg, but not 1.2 mg of BI 456906 were well tolerated in a single rising dose trial. In a multiple rising dose trial with weekly dose escalation up to 4.8 mg, as once weekly and twice weekly dose administrations, BI 456906 did not reveal relevant safety signals, although drug-related gastrointestinal and cardiac side effects were reported. All side effects were expected in nature, such as nausea, dyspepsia, decreased appetite, heart rate increase and cardiac conduction disorders, and are in line with other GLP-1 R agonist-based therapies. Most of the reported AEs were transient, and mild or moderate in intensity. To date, one Always serious AE from study 1404.3 occurred. It was reported as‘paroxysmal atrial fibrillation differential diagnosis ventricular tachycardia’. A 24-hour ECG (Holter Monitor) recorded from the subject at baseline (the subject had not received any dose of BI 456906) identified isolated polymorphic ventricular extrasystoles, a ventricular salve (9 beats), isolated supraventricular extrasystoles, and a supraventricular salve (4 beats). The Holter (V6/D5) used for diagnosis of the above events confirmed these findings. Initially, the investigator assessed the event as not serious. However, the event was recently upgraded to serious due to the medical significance, according to the BI Global Pharmacovigilance case processing procedure linked with the new version of the ‘Always Serious Events List’ that was implemented on 04 May 2020 and in which the event Ventricular Tachycardia was included. No deaths, or protocol specified AESIs, were reported.
Overall, the potential benefits, coupled with an acceptable safety profile and a well-controlled clinical trial environment support the initiation of the trial.

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2. TRIAL OBJECTIVES AND ENDPOINTS

The overall purpose of this trial is to assess the efficacy on weight loss and maintenance, and tolerability of four different doses of BI 456906 compared to placebo in patients with obesity or overweight (BMI ≥ 27kg/m^2), without type 1 or type 2 diabetes, in order to characterize the dose-response relationship within the therapeutic range, and to select the target dose(s) for phase III clinical development. The results of this dose-finding study will serve as Proof of Clinical Concept in patients with obesity or overweight.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

This trial will characterize the dose response curve for BI 456906 in patients with BMI ≥ 27 kg/m^2 (without diabetes) by assessing 4 doses and placebo. The response is defined as the percentage change from baseline in body weight at Week 46.

The main trial objectives are to demonstrate a non-flat dose response curve, to evaluate the size of the treatment effect (using the difference in mean percentage change between BI 456906 and placebo at Week 46), and to characterise the dose-response relationship.

The primary treatment comparison will be randomised, without regard to whether patients discontinued treatment early (and whether they subsequently received any permitted anti-obesity treatments), or whether patients started the maintenance period with a lower dose than the dose that they were randomised to.

2.1.2 Primary endpoint(s)

The primary endpoint is:
- Percentage change in body weight (%) from baseline to week 46

2.1.3 Secondary endpoint(s)

Secondary endpoints are:
- Weight loss of ≥ 5% of baseline weight at week 46
- Weight loss of ≥ 10% of baseline weight at week 46
- Weight loss of ≥ 15% of baseline weight at week 46
- Absolute change in body weight (kg) from baseline to week 46
- Absolute change in waist circumference (cm) from baseline to week 46
- Absolute change in systolic blood pressure (mmHg) from baseline to week 46
- Absolute change in diastolic blood pressure (mmHg) from baseline to week 46

[redacted]

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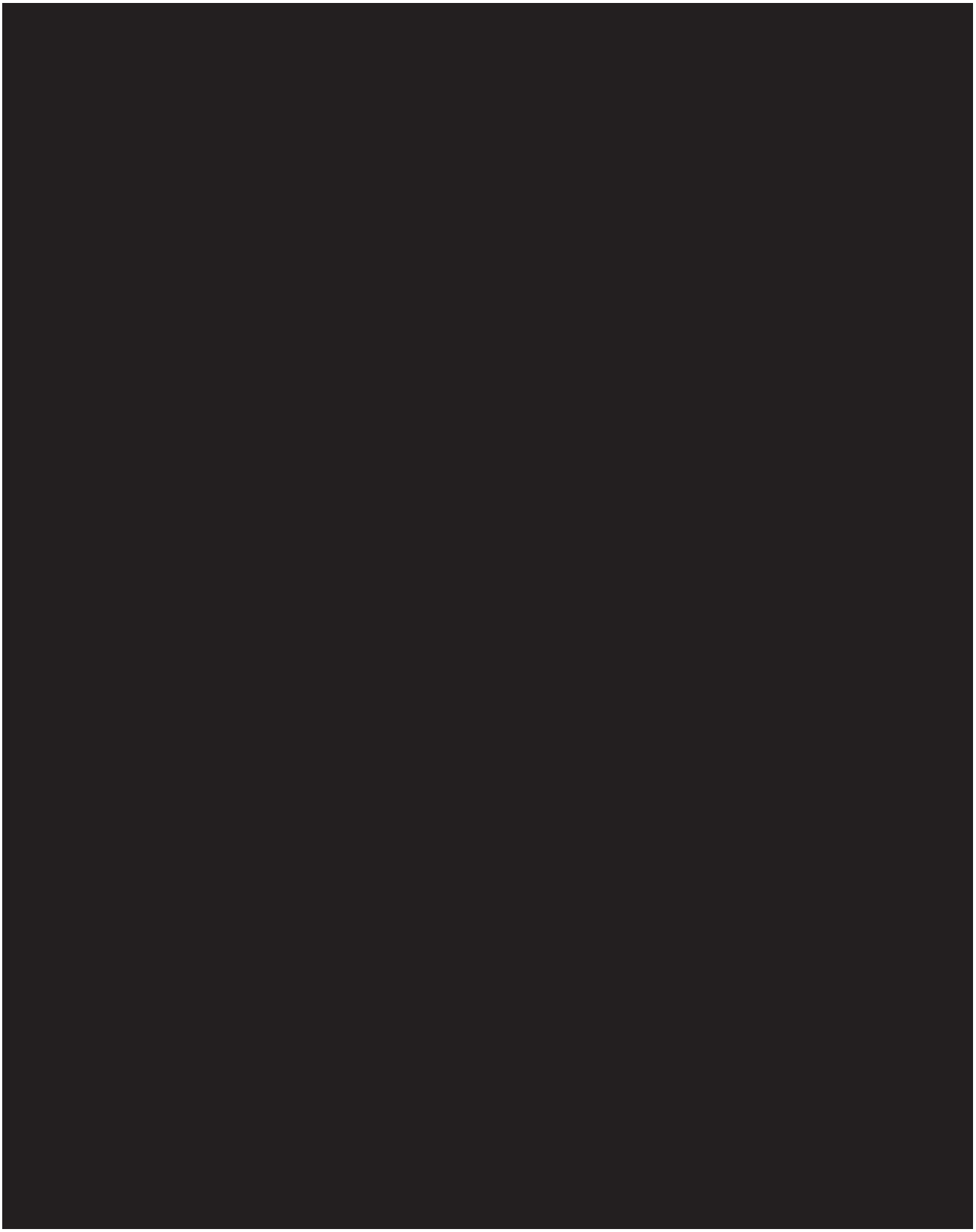

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3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a 46 week randomised, double-blind, parallel-design, placebo-controlled, multi-national and multi-centre study with 4 different maintenance doses (ranging from 0.6mg/week to 4.8mg/week) in patients with obesity or overweight (BMI ≥ 27kg/m^2), and without diabetes. Patients in all treatment arms including placebo will receive counselling for a reduced-calorie diet with an energy deficit of approximately 500 kcal/day by a dietician, as well as increased physical activity counselling (recommended minimum 150 minutes/week) by a qualified person on a monthly basis.

Participants will be randomly assigned to one of the 4 active dose arms of BI 456906 or placebo at a 1:1:1:1:1 ratio.

The different treatment arms and the dose escalation scheme are presented in Table 4.1.4:1.

There will be a screening period of minimum one week (time needed to obtain all examination results), that could be extended up to 12 weeks as needed to check eligibility criteria. The lab criteria "at screening" remain sufficient for checking lab eligibility criteria at randomisation.

The treatment duration is 46 weeks in total including a dose escalation phase of 20 weeks to minimize GI side effects of BI 456906. This is followed by a 26-week maintenance phase, and a 3-week (4 weeks after last dose) follow-up period.

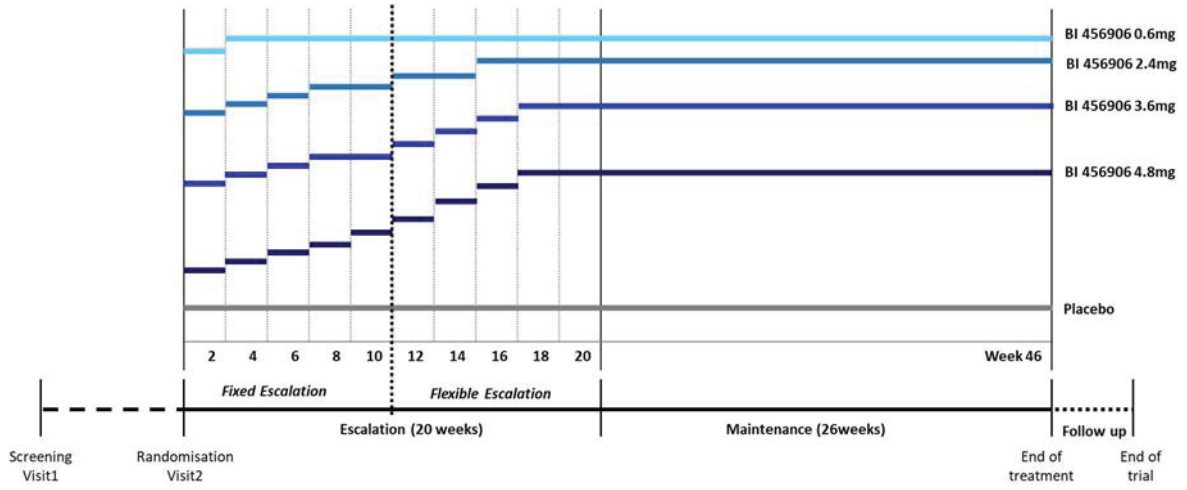

Figure 3.1:1 Dose escalation scheme

Screening period: Minimum 1 week, and up to 12 weeks maximum
Randomisation period:

- Dose escalation phase: up to 20 weeks (see section 4.1.4)
- Maintenance phase: 26 weeks

Follow up: 4 weeks after last drug injection

One interim analysis will be performed during the trial. Please refer to section 7.2.7

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3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This trial is designed to evaluate safety, tolerability and efficacy on weight reduction and maintenance of BI 456906 in patients with obesity or overweight using multiple escalation schemes and doses, and will support dose selection for phase 3 clinical development of BI 456906 in the indications of chronic weight management in patients with obesity or overweight. The inclusion of the placebo comparator helps to better characterise the nature of any dose response.
A treatment duration of 46 weeks, including at least 26 weeks with stable dose, is considered to be sufficient to assess dose response on clinically meaningful weight reduction required by regulatory authorities. Furthermore, a 46-week trial period is considered to be sufficient to characterise the safety and tolerability profile of BI 456906.

Choice of endpoints:
In patients with overweight/obesity, weight loss can be directly associated with benefits in health outcomes. The primary endpoint is a direct measure of body weight change based on the regulatory guidance. Key secondary endpoints will also look at weight loss, absolute and two different categorical responder thresholds.
It is well documented that certain thresholds of categorical weight loss (>5%, >10% >15%) are associated with improved body weight related metabolic profiles and/or related co-morbidities. [redacted]
In clinical practice, waist circumference is used as an indirect measure of visceral fat content, which when increased is associated with an elevated risk for metabolic abnormalities. Measuring waist circumference can be a means to confirm that reductions in waist circumference are associated with the expected improvements in metabolic parameters related to weight reduction.
[redacted]

Data Monitoring Committee
A Data Monitoring Committee (DMC), independent from the Sponsor, will be established to review the unblinded safety data at intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial. The tasks and responsibilities of the DMC members will be detailed in the DMC charter. See section 8.7

Clinical Event Committee
Prospective adjudication of some events will take place through an independent, blinded, external Clinical Event Committee (CEC) as described in section 5.2.6.1.5. Details on the

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composition of the committee, its procedures and interactions will be provided in a separate CEC charter.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients will be screened to ensure that an adequate number of patients will be randomized.
A total of 350 patients in approximately 45 sites, 13 countries will be randomised. More sites may be initiated depending on recruitment rate. To ensure sufficient enrolment of men, recruitment of women will be capped at 70 % and the randomisation will be stratified according to sex.
Screening of patients for this trial is generally competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. The sponsor may require some site or country to stop recruitment in case they dominate the recruitment in a way that might cause variety or quality issues. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.
A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

Re-screening is not allowed. Re-testing (of assessments) should be discussed with Clinical Trial Manager (CTM).

Re-testing:
If the investigator believes that an ineligible lab test result is the result of an error or extenuating circumstance, then that lab test can be retested once without the patient having to be re-screened. The retest should be carried out as soon as possible so the laboratory test results will be received within the next planned visit windows in order to avoid protocol window violations.

Patients must have had a stable weight for 3 months before entering the trial. If this criterion cannot be documented, it is possible to extend the screening period up to 12 weeks to allow checking the weight stability. Documentation upon patients' interview is acceptable.

3.3.1 Main diagnosis for trial entry

The main diagnosis for patients to enter the trial is BMI ≥27 kg/m^2 without diabetes at screening.

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

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3.3.2 Inclusion criteria

1. Adult ≥ 18 years and < 75 years of age at screening
2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
3. Obesity or Overweight defined as BMI ≥27 kg/m^2 at screening
4. A minimum absolute body weight of 70 kg for females and 80 kg for males at screening
5. Male or female participants. Women of childbearing potential (WOCBP)[1] must be willing and able to use two forms of effective contraception where at least one form is highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. See section 4.2.2.2.
6. Patients must have undergone at least one previous unsuccessful nonsurgical weight-loss attempt per investigator's judgement

3.3.3 Exclusion criteria

1. Body weight change of over +/- 5% or more in the past 12 weeks prior to randomization. There must be documentation of weight in the past 12 weeks before randomization.
2. Obesity induced by an endocrinologic disorder (i.e. Cushing Syndrome, hypogonadism, growh hormone deficiency. However, well controlled hypothyroidism, polycystic ovarian disease are still allowed)
3. A HbA1c ≥ 6.5% at screening or diagnosed with type 1 or type 2 diabetes mellitus
4. Exposure to GLP-1Ra based therapies within three months prior to screening
5. Any suicidal behaviour in the past 2 years, any suicidal ideation of type 4 or 5 in the C-SSRS within 3 months before screening, or during screening period
6. History of major depressive disorder within 2 years before randomization
7. Major depressive symptoms (defined as a screening Patient Health Questionnaire-9 [PHQ-9] score ≥15) at screening and/or during screening period
8. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders at screening
9. Screening calcitonin ≥20 pg/mL (≥5,84 pmol/L)
10. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, manifest hypo- or hyperthyroidism at screening

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Please note that tubal ligation is NOT accepted as a method of permanent sterilisation and therefore a woman who underwent tubal ligation is still considered as WOCBP. However tubal ligation is considered as a method of highly effective birth control.

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11. History of chronic or acute pancreatitis or elevation of serum lipase/amylase > 2x ULN, or fasting serum triglyceride levels of > 500 mg/dL (>5,65 mmol/L) at screening
12. Treatment with medication that potentially induce a change in body weight (e.g., steroids, antipsychotics) , or anti-obesity medication including over-the-counter [OTC] medications, or participating in an organized weight loss program (e.g. [redacted]® or [redacted]®) within 3 months before screening
13. Prior surgery of the GI tract that could interfere with body weight (including minimally invasive/endoscopic bariatric devices, bariatric surgery including metabolic operation that involves resection and/or reconstruction of any portion of the gastrointestinal tract) except appendectomy and simple hernia repair before randomization.However, a patient previously treated with reversible weight loss devices such as gastric banding, or intragastric balloon and removed longer than 12 months before screening should not be excluded.
14. Resting Heart Rate >100 bpm at screening or randomisation
15. Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg at screening.
16. History or currently diagnosed with congestive heart failure, New York Health Association (NYHA) class III-IV at screening
17. A marked prolongation of QT/QTc (Fridericia) interval that is greater than 450 ms at screening or at the randomisation or any other abnormal clinically significant ECG finding at screening (e.g., type 2 second-degree AV block (Type Mobitz II) or third-degree AV block) – see section 5.2.4.
18. Heart rhythm disturbances (e.g., bradycardia with baseline HR < 50 bpm, in the absence of medications that lower the heart rate), supraventricular tachycardia or tachyarrhythmia (e.g., atrial fibrillation, atrial flutter or ventricular tachycardia), considered by the investigator indicative of relevant cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals at screening. Family history of long QT Syndrome, use of prescription or over-the-counter medications known to significantly prolong the QT or QTc interval at screening.
19. Treatment with medications known to cause heart block or bradycardia, such as beta-blockers, verapamil and diltiazem, unless these drugs are indicated for heart rate control or hypertension treatment
20. Any of the following conditions or procedures within the last six months prior to screening: myocardial infarction, unstable angina (e.g. CCS grading of Angina pectoris grade III and IV), arterial bypass graft (e.g. coronary bypass, carotid bypass, peripheral vascular disease bypass), percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischaemic attack(TIA), cerebrovascular accident (stroke)
21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
22. A history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme

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major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis)

23. Chronic or relevant acute infections (including but not limited to respiratory tract infections, urinary tract infection, bladder infection, enterocolitis, abscess, tuberculosis, meningitis, influenza, Epstein-Barr virus, HIV/AIDS, and hepatitis B or C, and SARS-CoV-2(as confirmed by PCR test, see section 5.2.3)), within 2 weeks from screening or during screening.
24. Any condition which might jeopardize patient's safety or compliance with the protocol as judged by the investigator
25. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin
26. Participation in another clinical trial within 90 days before screening

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.
Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
Patients should be made aware of potential anticipated GI side effects and investigators should provide guidance on how to avoid or overcome them.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see sections 5.2.6.2.1 and 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient cannot tolerate the drug despite all efforts taken
- The patient requires hospitalization due to drug related gastrointestinal adverse event assessed by investigator
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment. Refer to section 4.2.2.1

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- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- Sustained symptomatic hypotension or hypertension: For hypotension, episode of symptoms (such as light-headedness or dizziness) associated with a systolic blood pressure <100 mmHg for > 60 minutes or for hypertension, episode of symptoms such as headaches, shortness of breath or nosebleeds associated with a systolic blood pressure > 160 mmHg in at least three consecutive measurements, each at least 30 minutes apart.
- Clinically relevant changes in ECG (QT prolongation >500 ms or an increase of 60 ms versus baseline, or Type Mobitz II, or third-degree AV block), or any symptomatic AV block, newly developed atrial fibrillation, or atrial flutter that require medical intervention.
- Sinus tachycardia (HR >120/min in two consecutive assessments 5 minutes apart) and/or tachyarrhythmia (HR >110/min) or cardiac conditions requiring medical intervention.
- Ventricular tachycardia in ECG or syncope.
- Clinically relevant coronary artery disease (e.g. CCS grading of Angina pectoris grade III and IV or congestive heart failure, NYHA class III-IV).
- The patient shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.
- The patient experiences an infection with Sars-CoV-2 (as confirmed by PCR test, see Section 5.2.3) and presents with signs or symptoms requiring discontinuation of treatment as per investigator's discretion.
- Patients newly diagnosed T2DM requires anti-diabetic treatments other than metformin
- Patients newly diagnosed acute pancreatitis
- Patients newly diagnosed medullary thyroid carcinoma
- Surgical treatment for obesity
- The patient develops suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent). The patient should immediately be referred to a mental health professional for further work-up.
- Inadequate psychotherapy and/or pharmacotherapeutic treatment of a subject's psychiatric disorder
- The subject refuses mental health professional referral and, in investigator's opinion, it is unsafe for the subject to continue
- Treatment with orlistat, zonisamide, topiramate, lorcaserin, phenteremine, bupropion, naltrexone, GLP-1 RAs alone or in combination prescribed for weight loss or any medication that could provide weight change in the opinion of the investigator
- Out of compliance with study drug (missing doses). Refer to missing dose section 4.1.4

Given the patient's agreement, a patient who discontinue drug should stay in the trial and follow procedures and visits as described in section 6.2.2 except patients taking GLP-1 RA who should be withdrawn from trial.

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For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

Pregnancy
If a patient becomes pregnant during the trial, the trial medication will be stopped, the patient will be followed up during the trial and until birth or termination of the pregnancy (see further details in section 5.2.6.2.3). The patient will be expected to attend the regularly scheduled study visits as outlined above.
There is no evidence of risk for partners of male participants, thus no need for male contraception.

Malignancies
In case of occurrence of malignant neoplasm, the Investigator should discontinue treatment with the trial medication, and notify the Sponsor. Diagnostics and treatment should be initiated according to local standard of care.

Suicidality
In case of signals of suicidal ideation or behaviour, the Investigator should discontinue treatment with the trial medication, notify the Sponsor and the patient should be referred to an appropriate psychiatric clinic.
If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:
1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

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4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1

Substance:	BI 456906
Pharmaceutical formulation:	Solution for subcutaneous injection
Source:	Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany
Unit strength:	Filling Volume: 0,5 mL Concentrations: 0,6 mg/mL, 1,8 mg/mL, 3,6 mg/mL, 4,8 mg/mL, 6,0 mg/mL
Posology:	Multiple maintenance dose (0,6 mg; 2,4 mg; 3,6 mg; 4,8 mg) obtained by injection of two syringes weekly (on same injection day). Intermediate dosages are used during titration phase. See appendix 10.1 for details on how each dose is made of 2 syringes
Method and route of administration:	s.c. injections

Table 4.1.1: 2 Reference product

Substance:	Placebo
Pharmaceutical formulation:	Solution for subcutaneous injection
Source:	Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany
Unit strength:	Filling Volume: 0,5 mL
Posology:	Multiple placebo dose to match the active maintenance doses (0,6 mg; 2,4 mg; 3,6 mg; 4,8 mg) as well as titration doses; injection of two syringes weekly
Method and route of administration:	s.c. injections

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4.1.2 Selection of doses in the trial and dose modifications

Doses from 0.6 mg to 4.8 mg once weekly were selected based on the following considerations:

Safety and tolerability of BI 456906 was evaluated in otherwise healthy volunteers with obesity or overweight up to 6 weeks for doses ranging from 0.7 to 3.15 mg/week (administered as daily dosing) and 0.3 to 3 mg /week (administered weekly dosing) and later up to 16 weeks for doses ranging from 0.6 to 4.8 mg/week (administered weekly or twice weekly dosing). The clinical experience with BI 456906 indicates that the most common GI side effects can be mitigated by a more gradual increase in exposure.

[redacted]

The lowest dose of 0.6 mg in this trial was selected to support modelling of exposure-response (MCPMod dose-response and population PK-PD modelling) and is predicted to achieve a modest weight reduction comparable to placebo. Overall, the 4 selected dose levels are anticipated to support robust dose-exposure-response analyses for multiple safety and efficacy measures to serve as a basis for selection of a suitable dose regimen for BI 456906 in patients with obesity or overweight.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups according to a randomisation plan in a 1:1:1:1:1 ratio at visit 2 via Interactive Response Technology (IRT).

4.1.4 Drug assignment and administration of doses for each patient

Table 4.1.4:1 Dose Escalation Scheme

Dose group	Weekly dose in (mg)																			
	Fixed escalation (titration is not allowed)										Flexible escalation (titration is allowed)									
Week of treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Escalation			1st		2nd		3rd		4th		5th		6th		7th		8th		9th	
BI A	0.3		0.6		0.6		0.6		0.6		0.6		0.6		0.6		0.6		0.6	
BI B	0.3		0.6		0.9		1.2		1.2		1.8		1.8		2.4		2.4		2.4	
BI C	0.3		0.6		0.9		1.2		1.2		1.8		2.4		3.0		3.6		3.6	
BI D	0.3		0.6		0.9		1.2		1.8		2.4		3.3		4.2		4.8		4.8	

Fixed dose escalation phase (week 1- week 10)
During this phase the patient will receive planned dose as described Table 4.1.4:1 and titration within the dose group will not be allowed. Patients who cannot tolerate study drug during this period despite of all the efforts taken, will be discontinued from treatment.

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Tolerability assessment after 10 weeks
Tolerability will be assessed after 10 weeks of treatment prior to dosing (visit 7). Patients who cannot tolerate medication in the week after dosing of week 10, will not continue titration to the next step, but will be moved to the next lower dosing available at week 11 and continue with this new scheme for the remaining visits

- Patients of Group D will then follow scheme of group C
- Patients of Group C and B will then follow scheme of group A
- For patients of group A, there is no lower dose possible. They will be maintained with same scheme, and if they again cannot tolerate at next visit they will be discontinued

Flexible dose escalation phase (week 11- week 20)
During this time, the investigator should make every effort to follow every two weeks dose escalation however, adjusting dosing scheme based on the patient tolerability of GI AEs will be allowed, in a blinded manner, as per the below:
Tolerability will be assessed every two weeks, at every visit (prior to week 13, week 15, week 17, and week 19) and information will be entered in IRT system accordingly.

- Patients who do not experience or who tolerate GI AEs will follow bi-weekly escalation schedule as described in the Table 4.1.4:1
- Patients who cannot tolerate GI AEs will be maintained on same dose for a third week before next escalation. If AEs remain not tolerable despite moving to escalation every 3 weeks, that will trigger discontinuation. Training materials explaining possible options for flexible escalation will be provided to the investigators with details and examples.

Maintenance dosing phase (week 21- week 46)
No dose adjustments or titrations will be allowed during the maintenance phase. No patients will start the maintenance phase at week 21 with any dose which is not one of the planned maintenance doses (0.6, 2.4, 3.6 or 4.8mg), and the dose will not be changed from week 21 until the final study visit at week 46. Patients who cannot tolerate study drug during this period despite of all the efforts taken, will be discontinued from treatment.

Injections of two syringes will occur on a weekly basis (+/- 1 day). Instructions on how to do self-injections will be given to patients. The patients will record the exact date and time of injections in their e-diary. If the patient does not feel comfortable giving a self-injection, this has to be discussed with site staff so that injections can be organised locally (depending on local rules, can be done eg by a local nurse, or additional visits to the site can be organized)

Missed dose (delayed or skipped)

- If a dose is missed on the planned dosing day, patients should take the planned dose within 48 hours. If more time has elapsed since the missed dose, then patients should wait to take the next planned dose. A minimum of 5 days between weekly doses is required. Patients should record the reason for a missed injection into their e-diary
- Total skipped doses during the trial must not exceed 4 doses (2 during escalation phase (0-20 weeks), 2 during maintenance phase (weeks 21-46)), and must not be consecutive 2 doses. Skipping more than 4 doses will be considered as non-

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compliance of trial medication and patients who missed more than 4 doses will discontinue trial medication.

- In case of consecutive 2 skipped doses, the treatment discontinuation should be considered (general rule). In some exceptional circumstances (e.g. COVID-19 like pandemic situation), sponsor must be contacted for alternative option.
  If 2 consecutive doses of study medication are missed, the patient may recommence the study treatment if considered safe as per the investigator's discretion and the patient does not meet any of the discontinuation criteria".

During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations, for more details see section 6.2.2

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators, central reviewers, and everyone involved (except as noted below) in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock.

The DMC will be provided with unblinded data in order to allow them to review safety and to fulfil their tasks as outlined in the data monitoring committee charter. An independent team, not otherwise involved in the conduct of the trial, will provide the unblinded results to the DMC.

The randomisation codes will be provided to bioanalytics during the course of the trial to allow for the exclusion from the analyses of pharmacokinetic (PK) and antidrug antibodies (ADA) samples taken from placebo patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.

One interim analysis will be performed by an independent statistics and programming team at the Sponsor for internal phase III planning purposes after approximately two thirds of randomised patients have reached Week 20. Details are given in Section 7.2.7, including how access to unblinded data and results will be controlled.

The access to the randomisation code will be kept restricted until its release for analysis.

The ECGs do not represent a risk of unblinding.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial

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participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and initials of the person who broke the code.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. Syringes will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.

Pre-filled syringes dispensed to patients at specific visits (Flow Chart) should be transported in insulated bags with cooling gel packs (or other similar cooling methods) from the site to the home. Patient should store the medication at home according to the recommended storage conditions on the medication label. Patients will not maintain a temperature log.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator, if applicable
- Availability of FDA Form 1572 for USA sites

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

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The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

4.2.1.1 Diet and physical activity counselling

During the trial, subjects in all treatment arms including placebo will receive diet and physical activity counselling every month. Patients will be given an e-diary in which they will keep tracking their level of activity everyday as well as a paper diary to track their daily dietary compliance. The subject's dietary compliance and the average daily level of physical activity will be evaluated and recorded every month by site staff into the e-CRF

Diet Counselling
At visit 2 (randomisation) subjects will receive diet counselling by a dietician or equivalent qualified delegates according to local standard with an energy deficit of approximately 500 kcal/day compared to the subject's estimated total energy expenditure (TEE).[R20-2315]

TEE = Basal metabolic rate (BMR) x Physical activity level (PAL) of 1.3

The hypocaloric diet is to be continued after randomisation and throughout the treatment period. The TEE should be re-calculated at regular intervals based on the changes in body weight and daily physical activities during the treatment period. If a BMI $\leq$ 22 kg/m^2 is reached the recommended energy intake should be recalculated with no kcal deficit (maintenance diet) for the remainder of the trial. All subjects will receive short dietary guidance materials and will be instructed by dieticians or delegates to keep a food diary. Whether or not the subject is in compliance with the prescribed diet is at the discretion of the dietician after review of the food diary

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Table 4.2.1.1:1 Equations for estimating BMR

Sex	Age: years	BMR: kcal/day
Men	18-30	15.057 x actual weight in kg + 692.2
	31-60	11.472 x actual weight in kg + 873.1
	> 60	11.711 x actual weight in kg + 587.7
Women	18-30	14.818 x actual weight in kg + 486.6
	31-60	8.126 x actual weight in kg + 845.6
	> 60	9.082 x actual weight in kg + 658.5

Table 4.2.1.1:2 Classification of lifestyles in relation to the physical activity, or PAL

Category of lifestyle	PAL value
Inactive	less than 1.4
Sedentary or light activity lifestyle	1.40-1.69
Active or moderately active lifestyle	1.70-1.99
Vigorous or vigorously active lifestyle	2.00-2.40*

* PAL values > 2.40 are difficult to maintain over a long period of time.

Physical activity counselling
An increase in physical activity, at least 150 to 300 minutes a week of moderate intensity combining aerobic and muscle strengthening exercise, will be encouraged and re-enforced.

4.2.1.2 Systemic hypersensitivity including infusion reaction and anaphylactic reaction

In case of systemic hypersensitivity including anaphylactic reaction emerging during or after injection(s) of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to

- Immediately stop further injections
- Treat with systemic anti-histamines, i.v. steroids, and in case of a severe allergic reaction (eg, anaphylactic reaction) epinephrine

Also draw a plasma sample for IgE and ADA as detailed in the Lab Manual (ISF). Also include the evaluation of histamine, serum tryptase, and complement components.

In case of systemic hypersensitivity, based on patient's clinical course and medical judgment, the injection(s) may be continued in case of mild or moderate systemic hypersensitivity.

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In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA [R11-4890] suspected to be caused by the trial medication, the investigator should permanently discontinue treatment with the BI456906

When a non-acute hypersensitivity reaction related to immune complexes (i.e., serum sickness) is suspected, please draw a sample for the laboratory assessment for circulating immune complexes.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following is not allowed during the whole trial period (including patients who discontinued study medication):

- GLP-1 RA

The following is not allowed during screening and until after 4 weeks after the last drug intake:

- Treatment with orlistat, zonisamide, topiramate/phentermine, phenteremine, bupropion/ naltrexone, alone or in combination or any medication that could provide weight change in the opinion of the investigator.

- Obesity OTC medications or supplements, or participating in an organized weight loss program (e.g. [redacted]® or [redacted]®)

- Treatment with medications known to cause heart block or bradycardia, such as beta-blockers, verapamil and diltiazem, unless these drugs are indicated for heart rate control or hypertension treatment

- Oral medications with Narrow Therapeutic Index unless dosing can be adapted according to standard of care monitoring (e.g., Levothyroxine dosing appropriately adapted to thyroid stimulating hormone levels)

- Medications known to significantly prolong the QT or QTc interval administered for a period of > 2 weeks

When discontinuing trial products, the investigator should discuss potential weight management options with the subject.

4.2.2.2 Contraception requirements

Contraception of male participants is not needed.

WOCBP (for the definition please refer to section 3.3.2) and their male sexual partner able to father a child must use two medically approved methods of birth control throughout the trial

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and for a period of at least 5 weeks after last study drug intake. Male partner of a female trial participant must use a condom if their sexual partner is a WOCBP or be vasectomised with documented absence of sperm

Female participants of childbearing potential must use highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

- Combined (oestrogen and progestogen containing) hormonal birth control that prevents ovulation (intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion

Oral contraceptives are not permitted in female participants during the study. WOCBP who use oral contraceptives at screening should change to non-oral contraceptives listed above.

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

Patients will be provided with an e-diary to record all the injections of the study drug (at home or at the clinic during on site visits).
Patients should be encouraged to be fully compliant with the medication dosing schedule.
Patients should be compliant on clinic visits within the protocol allowed time window.
Patients should be compliant on the dosing schedule when they self-administer the study drug at home with pre-filled syringes.

Compliance check of the trial medication will be performed at each clinic visit to ensure the weekly injection is being administered correctly at both the trial site and by the patient at home. In case of missed doses, the site should instruct patient as indicated in section 4.1.4.
The investigator/site staff should explain to the patient the importance of treatment compliance and discuss with the patient any tolerability issue.

Patients will be provided with a medication bag to store unused and empty cartons of trial medication and a sharp bin to store all used syringes. Patients are requested to bring all unused trial medication and empty cartons with them to their next scheduled visit for compliance check. Any discrepancies should be discussed with the investigator or the designee.

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5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Anthropometry

5.1.1.1 Weight measurement

It is important to minimise variability in body weight measurement. On site, weight measurements should be done on the same scale for one patient throughout the course of the trial (mechanical and digital scales are acceptable), and the equipment must be calibrated according to the directions for use and at a minimum once a year. Weight should be recorded with one decimal (kg)
In order to get comparable body weight values, shoes, coats/jackets, and any headgear should be taken off, and pockets should be emptied of heavy objects (i.e. keys, coins etc.). Headgear worn for religious reasons are acceptable, but this should be consistently worn for all weight measurement in the trial. Patient should empty the bladder before weight is measured.

5.1.1.2 Self-measurement of body weight at home

All patients will be provided a scale for use at home during the trial for self- measurement of body weight. Patients must use the provided scale for all home weight measurements and measure body weight on a weekly basis. The body weight should be measured with an empty bladder, without shoes and only wearing light clothing, in fasting state at the same time of the day, preferably morning fasting time, throughout the trial. The measure is then recorded in an eDiary.

5.1.1.3 Height

Height is measured at screening without shoes in centimetres (one decimal)

5.1.1.4 Body mass index (BMI)

Body mass index will be calculated within the eCRF from visit 1 (screening) data.

5.1.1.5 Waist measurement

Waist circumference measurements should be made around a patient’s bare midriff, after the patient exhales while standing without shoes and with both feet touching the ground and arms hanging freely. The measuring tape should be made of a material that is not easily stretched. The tape should be placed perpendicular to the long axis of the body and horizontal to the floor and applied with sufficient tension to conform to the measurement surface. Waist circumference should be measured against the skin, at the midpoint between the lowest rib and the iliac crest.

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5.1.2 Blood Pressure measurement

Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after approximately 5 minutes of rest in the seated position. The blood pressure measurement should be performed three times at each time point and the three values, for each of the timepoint, recorded in the CRF. Caffeine, smoking and physical activity should be avoided within 30 minutes prior to the blood pressure measurement. Further details on the procedure for blood pressure measurements are given in appendix 10.2

[redacted]

5.1.4 Efficacy laboratory parameters

Some of the lab parameters will be analysed as part of efficacy criteria (see section 2.2.2 and 5.4.1). In addition to parameters that are already collected for safety, [redacted], insulin, C-peptide and [redacted], as well as HbA1c are to be measured at the visits specified in the flow chart.

[redacted]

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[redacted]

5.2 ASSESSMENT OF SAFETY

Safety is monitored during the trial conduct as per the below procedures. Investigators are encouraged to repeat ECG and/or additional imaging, laboratory testing if any abnormal finding are observed.

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the flowchart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling.

This includes temperature, respiratory rate, systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site. At dosing visits vital signs evaluations will be performed pre-dose and within 60 min after the end of drug administration and at Visit 2 (1st dosing visit) and Visit 3 (2nd dosing visit) additional measurements will be performed approximately 15 minutes post-dose (15 min. after last injection) and approximately 60 minutes post-dose (60 min. after last injection). Further details on the procedure for blood pressure measurements are given in appendix 10.2

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling time points please see the Flow Chart.

All analyses will be performed by a central laboratory, and the respective reference ranges will be provided in the ISF. Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the laboratory manual.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as AEs (please refer to section 5.2.6).

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In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (section 5.2.6.1.4 and the DILI Checklist is provided in the electronic data capture (eDC) system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.
The central laboratory will transfer the data to the sponsor periodically.

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Table 5.2.3: 1 Safety laboratory parameters

Category	Test name	Time points
Haematology	Haematocrit Hemoglobin Reticulocyte Count (reflex test if Hb outside normal range) Red Blood Cells / Erythrocytes White blood cells / Leukocytes Platelet Count / Thrombocytes Differential Automatic (relative and absolute count): Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes	All visits
Clinical chemistry	Albumin Alkaline phosphatase Amylase ALT (alanine aminotransaminase, SGPT) AST (aspartate aminotransaminase, SGOT) Bicarbonate Bilirubin total, fractionated if increased Calcium Chloride Creatinine Creatine kinase (CK) CK-MB, troponin (reflex tests if CK is elevated) γ-GT (gamma-glutamyl transferase) Glucose (plasma) Lactate dehydrogenase (LDH) Lipase Magnesium Phosphate Potassium Protein total Sodium Urea (blood urea nitrogen) Uric acid Thyroid stimulating hormone (TSH) Calcitonin eGFR (CKD EPI Equation for adults)	All visits Except Calcitonin and eGFR not needed during follow up
	Fasting Glucose Insulin C-peptide	At visits 2,7,12 and end of treatment
	βHCG (for women only)	At screening and whenever a urine test is positive

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Table 5.2.3: 1 Safety laboratory parameters: (cont.)

Infectious serology	Hepatitis B surface antigen Hepatitis C antibodies HIV-1/2 combination	Screening only
SARS-CoV2	SARS-CoV2 PCR test	Screening only
Lipids	Cholesterol (total) HDL cholesterol LDL cholesterol (including VLDL) Triglycerides	All visits
Urinalysis	**Semi quantitative** Nitrite Protein Ketone Urine pH Leukocyte esterase (for WBC) Blood (erythrocytes) **Quantitative** Albumin Creatinine Albumin/creatinine ratio in spot urine will be calculated at the central lab.	All visits
	Pregnancy test (done on site using tests provided by central lab)	All visits except screening If positive: do a serum test
	Urine drug screen Cannabis Cocaine Benzodiazepine Amphetamines Barbiturates Methadone Opiates	Screening only

5.2.4 Electrocardiogram

A 12-lead ECGs should be collected prior to the dosing at the time points specified in the Flow Chart. Centralized ECG services will be provided by an external vendor. ECGs should be collected according to the study-specific recommendations, using the standardized equipment provided by the vendor. ECGs may be repeated for quality or safety reasons. Patients must be supine for approximately 5-10 minutes before ECG collection. Patients should remain supine, but awake, during the ECG collection process.

The investigator has the responsibility to complete an initial review as soon as the ECG recordings are obtained at the site visit. At any time during the trial, the investigator may decide to place a hold on further dosing of the patient if there is an indication of significant

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abnormalities in the ECG, and would prefer to wait until the results from the central reading are available.

The digital ECG recordings will be transmitted to the vendor for central reading. The ECG recordings will be centrally evaluated and rated as normal, abnormal, or unable to evaluate, and the results will be reported to the site. The site investigator must review the report. If the ECG is rated as abnormal, the Investigator will have to determine if the abnormal findings are clinically significant.

After the screening visit, the investigator must complete a review of the ECG results from central reading to ensure patient has met all the entry criteria for the study. Any pre-existing conditions should be recorded as baseline conditions.
At visit 2 eligibility decisions may be made based on the local reading of the screening ECG only exceptionally, if the results of the central ECG have not been received prior to randomisation visit. ECG recorded at the randomization visit should be evaluated by the investigator before the patient receives the first dose. If abnormalities are observed by the investigator in the ECG reading at randomization visit, it is strongly recommended that the investigator wait until the results from central reading are available, and the randomization visit should be rescheduled.

The site investigator will have the responsibility of following up with the patient if there are any clinically significant findings in the ECG report.It is strongly recommended to repeat 12-lead ECG recording and/ or a referral to a cardiologist and/or perform additional cardiac tests (ie. Cardiac enzymes) if there is an indication of significant abnormalities or in case of doubts.
Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

After the patient is randomized, if a clinically significant increase in the QT/QTc interval from baseline or any other clinically significant quantitative or qualitative change from baseline is identified, the investigator will assess the symptoms (e.g., palpitations, near syncope, and syncope) and decide if the patient will continue in the study. The investigator must also ensure that patient does not meet any criteria for discontinuing study treatment (see section 3.3.4.1), such as tachycardia, arrhythmia or conduction disorders. Any new findings or deterioration of previous findings observed during the trial will be recorded as AEs/SAEs and will be followed up and/or treated as medically appropriate.

All ECGs that are read in the central location will be stored in the vendor’s database, and transmitted to the sponsor periodically

5.2.5 Other safety parameters

All cases of malignancies that are detected during the trial will be reported as SAEs. Patients with a history of malignancy (except for specific cancers) will be excluded from this trial per the exclusion criteria (section 3.3.3)

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Local tolerability at the administration site of BI 456906 will be assessed by the investigator during the study drug administration visit and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. “swelling”, “induration”, “heat”, “redness” should be reported as adverse event.

5.2.5.1 Breast neoplasm

For all female subjects, information whether any new mammograms have been performed since screening must be recorded at the end of the treatment and the follow up visits. If yes, reason and diagnosis should be recorded to the extent possible.

5.2.5.2 Colon neoplasms

Information whether any new endoscopic examination(s) of the colon have been performed since screening must be recorded at the end of the treatment and the follow up visits. If yes, reason and diagnosis should be recorded to the extent possible.

5.2.5.3 Hypoglycemia

All subjects will at randomisation be instructed in symptom recognition and handling of hypoglycaemia.
Hypoglycemic events will be defined as

- The subject reported typical symptoms of hypoglycaemia or required external assistance.
- The subject’s plasma glucose concentration was <54 mg/dL (3.0 mmol/L),
- The investigator considered the event to be hypoglycaemia event.

All symptomatic hypoglycaemic events will be recorded as a hypoglycaemic event on the 'adverse event' CRF page.

5.2.5.4 Mental health questionnaires

The mental health status of subjects will be assessed by C-SSRS and PHQ-9 questionnaires.

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behaviour and suicidal ideation. It does not give a global score but provides some categorical and some severity information specifically for behaviour and ideation.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, nurse, or research coordinator with C-SSRS training. It has a typical duration of five minutes and causes only a low burden on patients. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behaviour and may be expanded to up to 17 items in case of positive responses.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the “baseline/screening” version) with the aim to exclude subjects with a lifetime history of suicidal ideation and behaviour. After the baseline visit, the assessment “since last visit” will be performed at clinic visits as specified in the Flow Chart. The investigator is to review positive and negative reports for plausibility and

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clinical relevance. Doubtful reports may be repeated, or reports may be validated by a consulting psychiatrist. If there is a positive report of suicidal behaviour or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the patient during the clinic visit and advise the patient to consult with a psychiatrist. If the positive report is confirmed, appropriate actions for the patient's safety must be initiated. Treatment with study drug should be stopped and patient should be discontinued from the trial. Additionally, all C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behaviour must be reported as separate SAEs by the investigator. For 'Self-injurious behaviour, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied. For each negative report (suicidal ideation type 1, 2 or 3) after start of the trial, the investigator is to decide based on clinical judgment whether it represents an AE as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

The PHQ-9 is the 9-item depression module of the patient health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders. The questionnaire takes approximately 10 minutes to complete

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation

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- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in section 5.2.6.2.

Adverse Event (AE) coded shall cross referenced against the Always Serious List (ASL). Non serious cases will be upgraded to serious. Cardiac related events included in the ASL, shall be fully processed as serious and expedited

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.

The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN.

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These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the eDC system
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Adverse events require additional data collection

Some pre-specified AEs critical for the assessment of safety of BI 456906 will require additional data collection with separate eCRF page, some of these events will be centrally adjudicated in a blinded fashion by an independent external Clinical Event Committee (CEC).
Definitions of the adjudicated endpoint events and the principles of standardised data collection in the centralised CEC adjudication process are outlined in the separate CEC Charter and process guideline.

Events require adjudications

- All death (CV death, non-CV death)
- Cardiovascular event (revascularization due to coronary vascular disease, myocardial infarction, hospitalization due to unstable angina)
- Cerebrovascular disease (Stoke, TIA)
- Heart failure hospitalisation.
- Pancreatitis
- Neoplasm
- Thyroid mass requires surgery

Events require additional data collection

- Acute gall bladder disease
- Acute pancreatitis
- Thyroid mass

5.2.6.1.6 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:
Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

As GI and cardiac AEs have been shown to be associated with pharmacological doses of GLP-1R agonists and glucagon, the intensity of such AEs is defined as follows for this clinical trial:

Nausea
Mild: Queasy sensation and/or the urge to vomit without decreased oral fluid or

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caloric intake

Moderate: Queasy sensation and/or urge to vomit with decreased oral intake, but able to maintain adequate fluid and caloric intake without dehydration or malnutrition; may require pharmacologic intervention

Severe: Queasy sensation and/or urge to vomit with prolonged inadequate oral fluid or caloric intake; severe or medically significant but not immediately life-threatening; requiring i.v. fluids or is resistant to anti-nausea treatment, hospitalization (different from trial site) indicated

Vomiting

Mild: Less than 3 episodes in 24 hours (individual episodes separated by at least 30 min)

Moderate: 3 to 5 episodes in 24 hours (individual episodes separated by at least 30 min).may require pharmacologic intervention

Severe: Six or more episodes in 24 hours (individual episodes separated by at least 30min); severe or medically significant but not immediately life-threatening.requiring i.v. fluids, or is resistant to antiemetic treatment, hospitalization (different from trial site) indicated

Diarrhoea

Mild: Increase of <3 stools in 24 hours over baseline

Moderate: Increase of 3 to 5 stools in 24 hours over baseline; may require pharmacologicintervention

Severe: Increase of ≥6 stools in 24 hours over baseline; severe or medically significant but not immediately life-threatening; requiring i.v. fluids, or is resistant to anti-diarrheal treatment, hospitalization (different from trial site) indicated

Mobitz (type) I atrioventricular block

Mild: Asymptomatic, intervention not indicated

Moderate: Symptomatic, medical intervention indicated

Severe: Symptomatic and incompletely controlled medically or controlled with device(e.g., pacemaker)

Mobitz (type) II atrioventricular block

Mild: Asymptomatic, intervention not indicated

Moderate: Symptomatic, medical intervention indicated

Severe: Symptomatic and incompletely controlled medically or controlled with device(e.g., pacemaker)

Sinus tachycardia

Mild: Asymptomatic, intervention not indicated

Moderate: Symptomatic, non-urgent medical intervention indicated

Severe: Urgent medical intervention indicated

Electrocardiogram QTcF corrected interval prolonged

Mild: QTcF increase from baseline of more than 30s and QTc 450-480 ms

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Moderate: QTcF increase from baseline of more than 30s and QTc 481-500 ms
Severe: QTcF increase from baseline of more than 30s and QTc >= 501 ms on at least two separate ECGs

5.2.6.1.7 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

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The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of study: all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of study:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.6.2.2), but not on the CRF.

Vital Status Data Collection
Patients who discontinue trial medication prematurely, who agree to be contacted further but do not agree to physical visits, should be followed up as described in section 3.3.4.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, and trial treatment related SAEs and trial treatment related AESIs the investigator becomes aware of.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

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5.2.6.2.4 Exemptions to SAE reporting

Not Applicable

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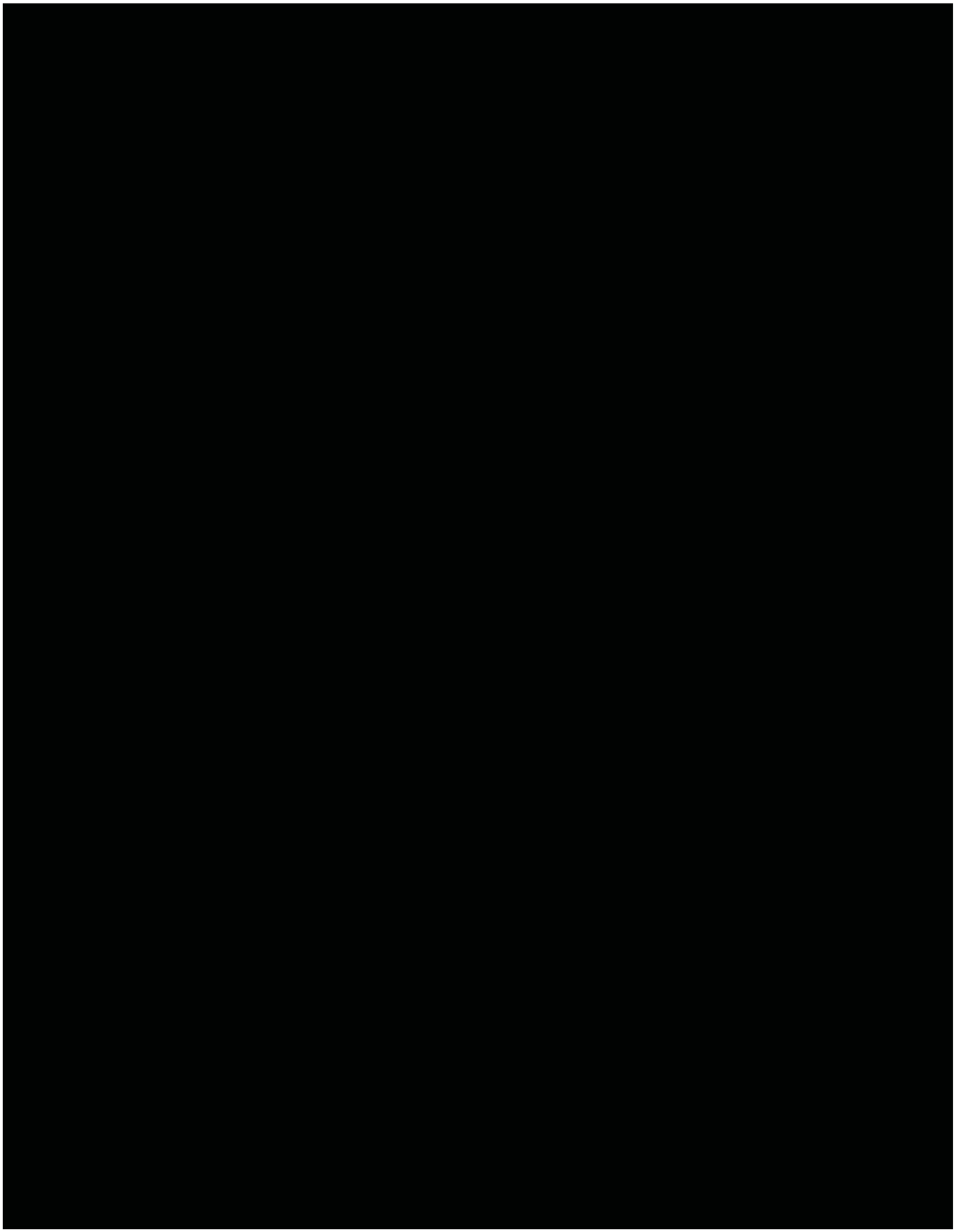

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[redacted]

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements. No samples will be taken for biobanking from patients at sites in China due to regulatory restrictions.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking. If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies. Samples will be stored for testing for a period consistent with local regulations.

5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see Flow Chart.
Approximately 48 mL blood will be drawn for DNA, Plasma, and Serum banking.

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5.8 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to evaluate efficacy and tolerability of BI456906 and to determine pharmacokinetic and pharmacodynamic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of study drug. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an s.c. administered drug and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined are generally used assessments of drug exposure.

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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

For a detailed overview of the trial procedures and time windows for visits, please refer to the Flow Chart.
The trial consists of a screening visit followed by a 46-week treatment period and a follow-up visit.
The study will last until every randomised patient has completed the last follow-up visit.

After giving his/her Informed Consent, the patient will be screened for inclusion and exclusion criteria for the study at visit 1. Visit 2 will be scheduled after visit 1, after results from central laboratory are obtained, as well as ECG central review. The minimum interval between screening and randomization is 1week. The patient will be randomized at visit 2 if all inclusion and none of the exclusion criteria are fulfilled.
During the treatment period, there will be a dose escalation period of 20 weeks followed by a dose maintenance period. Total treatment period is 46 weeks.

Windows of ±1 or ±2 days is allowed to accommodate scheduling problems. If a delay is observed for a particular visit, the original calendar schedule should be kept for subsequent visits (delays should not accumulate). If a visit is missed the patient should be instructed to reach out to the investigator as soon as possible. Handling of missed drug injections is described in section 4.1.4. Investigator should contact the BI monitor to discuss further schedule.
Follow up visits have to be organized a minimum of 28 days after last drug injection.

Patients with obesity are in general at higher risk for severe illness from COVID-19. In exceptional cases, if standard visits at the trial sites are impossible because of COVID-19 related safety risks, trial conduct may need to be adjusted, strictly consistent with local public health guidance and regulations.
If, in order to minimize the risk of exposure to COVID-19, physical visits should be avoided , the use of remote visits (via phone and/or internet-based means of communication) and local laboratory services for safety and efficacy parameters measurements should be considered if possible. However, study drug shipment to patients might not be possible in all countries to be included. In such situations, picking up trial medication could be done by patient's delegate or by patient at a sterile pharmacy (e.g. "drive -through" , "isolated" pharmacy).
Investigators should complete study procedures according to the protocol to the extent possible. The max. number of missing doses of study medication is defined in section 4.1.4 .
Considering all aspects, the investigator will decide upon each patient's (continued) participation in the planned trials. BI as the sponsor, where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the patient. All home/remote visits need to be discussed with and approved by the sponsor`s trial team. Local regulatory and legal requirements of the participating country still apply
All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

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6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period
Following informed consent, the patient will undergo visit 1/screening assessments as indicated in the Flowchart. Once the patient has consented, the patient is considered to be enrolled in the trial. The patient should be recorded on the enrolment log and be registered in the IRT.
The assessments must all fall within the acceptable screening visit window but do not need to be performed on the same day.

Re-testing for certain eligibility criteria can be performed once as outlined in section 3.3.
The screening phase can be extended up to a maximum of 12 weeks (from visit 1 to visit 2), when needed to allow proper documentation of weight stability. If the patient meets the entry criteria, visit 2 should occur as soon as possible once it has been confirmed that the patient is eligible to continue.
If the patient does not meet the entry criteria, (i.e. fail to meet one or more of the inclusion criteria, and/or meet one or more of the exclusion criteria) following Visit 1 procedures, they should be registered as a screen failure in IRT.

6.2.2 Treatment period(s)

Before visit 2, patients will have to record their food intake in a 3-days food diary (see section 5.1.5).
Patients who meet all the protocol criteria will be randomized at visit 2. After randomization, patients will start the treatment period which includes a dose escalation phase, followed by the dose maintenance phase as shown in Figure 3.1: 1.

Procedures to be completed at each visit can be found in the Flow Chart.

At visits specified in the Flow Chart, patients should be instructed to come in the fasting state after at least 10 hours without food intake. Water intake is allowed. On days when fasting is required, the clinic visit should ideally be scheduled in the mornings, if this is convenient for the patient.

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During visits, vital signs must be measured before blood sampling.
Drug injection should always take place after all assessments of the visit are done.

At each visit, patients should be advised to follow the recommended diet and exercise plan and to record their compliance daily on the provided diary. Diet and exercise counselling sessions are held at visits indicated in the Flow Chart. When necessary from a logistic point of view it is possible to have the diet/exercise counselling on a different day than the actual dosing visit, but within the timewindow of the visit.

Unscheduled visits may be arranged if necessary. Procedures completed during an unscheduled visit will depend on the circumstances under which the visit was scheduled, and at the discretion of the investigator.
Exceptionally, and after consultation with sponsor, one visit could be completed a few days in advance to accommodate for patient's imperatives. The call to IVRS and drug allocation would be made, but the injection would occur as per the initial schedule and allowed time-window.

[redacted]

After completion of the treatment period, patients will have the End of Treatment visit, one week after last drug injection. All patients will then enter the follow-up period and complete the observation period with the follow-up visit which has to be set at least 4 weeks after last drug injection.

If a patient discontinues drug during the treatment period (dose escalation phase, or maintenance phase), the patient will undergo the procedures of "end of treatment" visit, ideally 7 days after the last drug injection.

Safety lab, other laboratory tests during the treatment period (from V3 to visit 17) :
If blood sampling for central lab at the trial site is not possible, safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and proper documentation in the eCRF.
Minimum required safety lab parameters are
Haematology: Haematocrit, Hemoglobin, Red Blood Cells / Erythrocytes, White blood cells / Leukocytes, Platelet Count / Thrombocytes
Clinical chemistry: ALT (alanine aminotransaminase, SGPT), AST (aspartate aminotransaminase, SGOT), Bilirubin total, Amylase, Lipase

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6.2.3 Follow-up period and trial completion

A follow up visit has to be organized after a minimum of 4 weeks after last drug injection as outlined in the Flow Chart (FC).
Procedures to be completed at the follow-up visit can be found in the Flow Chart. The sequence of visit procedures will be the same as in the treatment period.

If a patient had withdrew drug prematurely, he should also come for that follow-up visit. In addition, the patient will be asked to return to clinic every 4 weeks to measure body weight until the end of the planned treatment period, i.e. week 46. All efforts should be made at least to conduct the week 46 visit for all patients.
However, if this is not possible, a phone contact should be made at week 46 to obtain vital status and body weight measured at home on the study scale.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary trial objective includes demonstration of PoCC with respect to a non-flat dose response curve, characterization of the dose-response relationship within the therapeutic range, and selection of the dose range for phase III development. For this purpose, the primary analysis uses methodology for dose finding employing both multiple comparison procedures and modelling techniques (MCPMod).

7.1 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis is that there is a flat dose response curve across the placebo and the BI 456906 dose groups, with regard to the primary endpoint of percentage change in body weight from baseline to Week 46. The alternative hypothesis is that there is a non-flat dose response curve indicating a benefit of BI 456906 over Placebo.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one sided 2.5%). The pre-specified models and their parameters used for this test are outlined in Section 7.2.2.

No confirmatory hypothesis testing will be performed in this trial.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Analysis Sets

Statistical analysis will be based on the following analysis sets:

The Full Analysis Set (FAS) is defined as all randomised patients who received at least one dose of study treatment and who have analysable data for at least one efficacy endpoint.

The Treated Set (TS) is defined as all randomised patients who received at least one dose of study treatment.

The Pharmacokinetic Set (PKS) is defined as all patients in the TS who provided at least one BI 456906 concentration which was not excluded due to non-evaluability or an important protocol deviation relevant for PK.

Important Protocol Deviations

Important protocol deviation (IPD) categories will be defined in the IPD specification document. IPDs will be identified no later than in the Report Planning Meeting (RPM).

IPDs may include (but not necessarily be limited to) the following:

- Violation of inclusion or exclusion criteria
- Major deviations from scheduled timing of assessments
- Non-compliance with trial medication

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- Treatment dispensing errors
- Use of prohibited or restricted concomitant medication.

Definition of baseline

In general, unless otherwise specified in the TSAP, the last non-missing measurement on or prior to the date of first dose of study treatment will be used as baseline for efficacy and safety variables.

Definition of on-treatment

For the purposes of on-treatment efficacy analyses, the definition of "on-treatment" will be given in the TSAP.

For the purposes of on-treatment safety analyses, an assessment (or AE start date) will be considered "on-treatment" if the assessment date (or AE start date) is between the date of first dose and 28 days after the date of last dose of study treatment.

7.2.2 Primary endpoint analyses

The analysis for PoCC and dose-finding will be performed using multiple comparison and modelling techniques (MCPMod) [R10-1424] whereby several possible dose response models (patterns) will be evaluated, while keeping full control of the type I error at 2.5% (one-sided) to identify the best-fitting model or subset of models.

To account for repeated body weight measurements over time and for inclusion of baseline covariates in the model, a mixed model for repeated measures (MMRM) analysis will first be carried out. The MMRM will include fixed effects for baseline body weight and baseline by visit interaction as continuous covariates, and treatment, gender, visit and treatment-by-visit interaction as factors. Unstructured covariance will be used to model the relationship between pairs of endpoint measurements taken at different visits on the same patient. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The TSAP will specify approaches to be taken to resolve possible non-convergence issues, including if necessary, the selection of a simpler covariance structure.

Covariate-adjusted fixed effect estimates of mean percentage change in body weight at Week 46 for each treatment group and the covariance matrix will be extracted from the MMRM fit. These will be used for the subsequent MCPMod analysis.

For the PoCC testing and for the sample size calculation, the basic shape of each of the models to be tested must be pre-defined. The following model assumptions and resulting graphs (Figure 7.2.2: 1) have been selected to cover a plausible and diverse range of monotone dose response patterns, with placebo mean response assumed to be zero and the mean response at the highest BI 456906 dose assumed to be -10.0 (i.e. a percentage reduction from baseline in body weight of 10%):

- Linear
- Exponential: 50% of maximum effect achieved at dose 3.6 mg
- Emax1: 90% of maximum effect achieved at dose 4.8 mg

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- Emax1: 70% of maximum effect achieved at dose 4.8 mg
- Sigmoid Emax: 50% of maximum effect achieved at dose 2.4 mg; 90% of max effect achieved at dose 4.8 mg

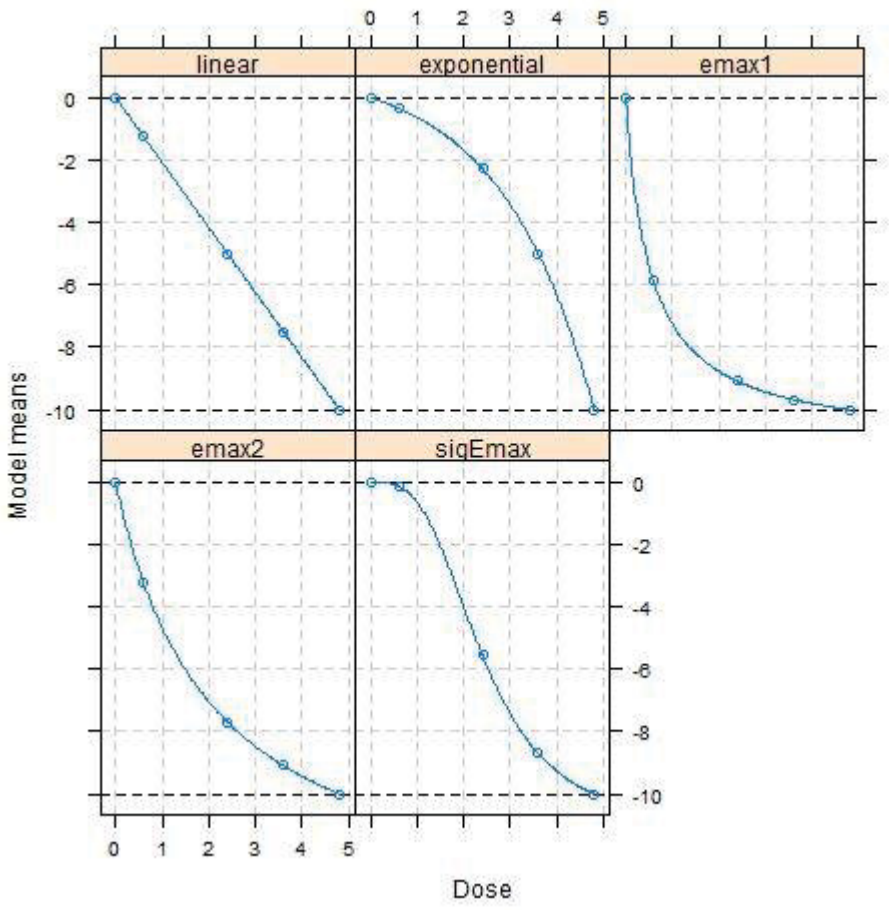

Figure 7.2.2: 1 Dose response patterns considered for the MCPMod analysis.

PoCC will be established if at least one model is statistically significant, rejecting the null hypothesis of a flat dose response relationship for percentage change in body weight jointly over the candidate dose response models, with a contrast test controlled for the family–wise type I error rate at one sided $\alpha = 2.5\%$.

If PoCC is established, the statistically significant (best fitting) model(s) from the above candidate set will be refitted to the data to generate new estimates for all model parameters from the data. The target dose(s) will be estimated from the best fitting model(s) by incorporating information on the minimum clinically relevant effect and accounting for safety.

The primary analysis of percentage change from baseline in body weight at Week 46 will be performed using the FAS and will assign patients to the randomised maintenance dose. It will include all available data without regard to whether patients started the maintenance period

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with a lower dose than the one randomised to. For patients who discontinued treatment early, a distinction will be made according to whether this is due to a COVID-19 pandemic-related reason or not. Patients who discontinued treatment early due to a pandemic-related reason (e.g. direct COVID-19 infection, drug supply issue, site closure, quarantine preventing site access) will have data handled after discontinuation as if they were missing. Patients who discontinued treatment early for any other reason will have all available data included after discontinuation, irrespective of whether such patients subsequently received any permitted anti-obesity treatments.

The above approach to the primary analysis specifies a hypothetical strategy for the intercurrent event of pandemic-related early treatment discontinuation, and a treatment policy strategy for the intercurrent event of non-pandemic-related early treatment discontinuation.

The primary endpoint will be summarised descriptively overall, and by pre-specified subgroups (to be specified in the TSAP, but which may include e.g. subgroups based on gender, baseline BMI and age at screening).

7.2.3 Secondary endpoint analyses

The responder secondary endpoints (percentage change from baseline < -5.0% and < -10.0% in body weight at Week 46, respectively) will be summarised descriptively.

Logistic regression with treatment group and gender as factors and baseline body weight as a continuous linear covariate will be used to estimate the odds ratio for each active BI 456906 dose compared with placebo, and to provide covariate-adjusted estimates of the proportion of responders at each BI 456906 dose.

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The analyses of the responder endpoints will be aligned with the treatment policy and hypothetical strategy approaches respectively in Section 7.2.2 for handing early treatment discontinuation and missing data. As a first step, multiple imputation will be performed on the underlying continuous endpoint to generate multiple imputed datasets, each one containing complete data for every patient. A minimum of 100 imputed datasets will be used for this purpose. The imputation model will assume that a patient with missing data follows a similar trajectory to a patient without missing data in the same treatment group (with similar baseline covariates and observed values). The responder endpoints will be derived from the complete data in each of the imputed datasets, and then analysed using the logistic regression model specified above. Finally, the estimates from the logistic regression model will be combined across the imputed datasets in a way which correctly accounts for the within and between imputation variance. Further technical details of the multiple imputation will be provided in the TSAP.

Continuous secondary endpoints measured repeatedly over time will be summarised descriptively and analysed using an MMRM similar to the one specified in Section 7.2.2, except that baseline body weight will be replaced in the model by the baseline value of the relevant endpoint. The model will be used to obtain covariate-adjusted mean estimates of differences between active BI 456906 doses and placebo at the relevant time point.

MCPMod dose finding analyses will not be performed for any secondary endpoints.

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7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 28 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

Safety analyses will be performed on the Treated Set (TS), using the actual maintenance treatment received. Key safety analyses will also be performed using the randomised maintenance treatment (if this is different for any patient).

In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

The adjudicated events specified in Section 5.2.6.1.5 will be summarised descriptively for each treatment group.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations and 12-lead ECG observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.2.6 Other Analyses

Not applicable.

7.2.7 Interim Analyses

Data Monitoring Committee

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A Data Monitoring Committee (DMC) will be implemented, with tasks as described in Section 8.7.

Interim Analysis

One interim analysis will be performed after approximately two-thirds of randomised patients have reached Week 20.

[redacted]

The interim analysis will be performed for Sponsor internal phase III planning purposes. The interim analysis results are not intended to be used to stop the trial, nor to make confirmatory claims. No statistical adjustments to Type I error are therefore considered necessary.

The interim analysis will be performed by the Sponsor, using the steps below to protect the integrity of the trial. The external DMC will be informed of the results of the interim analysis and will be given opportunity to review them at the scheduled DMC meeting following their availability.

The interim analysis will be performed by an independent statistics and programming team within BI. Personnel involved with trial conduct at study sites will not have access to unblinded data from the interim analysis. Secure folders with restricted access will be used for the storage of unblinded interim data and results. Further operational details of who will perform the interim analysis, and the steps to be taken to protect the integrity of the ongoing trial, will be specified in a Logistics Plan. Details of the BI personnel who will have access to unblinded interim data or results, and how interim results will be communicated within BI, will be specified in an Access Plan. These documents will be finalised prior to unblinding treatments at interim database lock.

7.3 HANDLING OF MISSING DATA

Every effort will be made to keep the patient in the trial and taking study treatment, where possible. If the patient discontinues from treatment early, every effort will also be made to capture body weight post-discontinuation up to and including Week 46. These data will be used in the treatment policy strategy for handling early treatment discontinuation in the analysis (see Section 7.2.2 for details, including regarding the reason for early treatment discontinuation). Nevertheless, there may still be some missing data, even using such a treatment policy strategy for analysis. In the hypothetical strategy for handling early treatment discontinuation, body weight values recorded after early discontinuation of treatment will not be used and will be handled as if these data were missing.

In both cases, missing data will be handled implicitly by the statistical model (MMRM). This makes the assumption that the data are missing at random (MAR). Patients who do not have a

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Week 46 body weight value, but who have earlier post-baseline values, still contribute to this analysis.

For the responder endpoints (percentage change from baseline < -5.0% and < -10.0% at Week 46, respectively), analyses will be performed in which the handling of data after early treatment discontinuation and missing data are aligned with the treatment policy and hypothetical strategy approaches for the underlying continuous endpoint of percentage change from baseline at Week 46. This will be done by performing the multiple imputation analysis which was specified in Section 7.2.3. Since the imputation model assumes that a patient who discontinues treatment early behaves in the same way as a similar patient who completed treatment in the same treatment group, this also makes the MAR assumption.

[redacted]

Handling of missing data for other secondary and further endpoints will be specified in the TSAP. In general, unless specified otherwise, MMRM will be used to analyse continuous endpoints, and therefore the MAR assumption is made.

7.4 RANDOMISATION

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list(s) will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report (CTR). Access to the codes will be controlled and documented.

Patients will be randomised in blocks using equal allocations to one of 5 double-blind treatment groups. Randomisation will be performed at the start of the dose escalation period at Day 1, Visit 2 (starting dose and timing of dose escalation as outlined in Table 4.1.4: 1), with allocation to one of the following target maintenance period treatments:

- Placebo once weekly
- BI 456906 0.6 mg once weekly
- BI 456906 2.4 mg once weekly
- BI 456906 3.6 mg once weekly
- BI 456906 4.8 mg once weekly

Randomisation will be stratified by gender. It is anticipated that no more than 70% women will be randomised.

7.5 DETERMINATION OF SAMPLE SIZE

Sample size evaluation was performed using simulation in R software (version 3.6.1), with 10000 simulations performed for each scenario summarised below.

The sample size calculation was based on the following assumptions:

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- An overall significance level of 2.5% (one-sided) for the contrast test of the null hypothesis of flat dose response
- The (monotone) dose response shapes specified in Section 7.2.2
- A placebo effect size (mean percentage change from baseline in body weight at Week 46) of zero
- A maximum effect size (mean percentage change from baseline in body weight at Week 46) in the highest dose group of -10.0%
- A standard deviation of 7.0% [R20-0479].

Simulations were also performed to investigate departures from the assumed true maximum effect stated above, as well as for different scenarios for the true nature of the dose response relationship. The probability of success for each of these scenarios is summarised in Table 7.5: 1 below.

A success was defined as meeting all 3 of the following criteria:

1. Null hypothesis of flat dose response was rejected in favour of at least one of the alternative candidate models, and
2. A target dose was selected within the dose range using the following criterion: difference in mean between selected dose and placebo < -9.0%, and
3. Proportion of patients in the highest dose group meeting the responder definition (percentage change in body weight from baseline < -10.0%) was greater than 35%.

Table 7.5: 1 Probability of success with N=70 patients in each treatment group and SD = 7.0%.

	Probability of success (%)						
		Linear	**Exponential**	**Emax1**	**Emax2**	**SigEmax**	**AVERAGE**
True maximum effect (%)	-9.0	48.9	48.9	48.8	49.0	65.3	52.2
	-9.5	67.8	68.3	69.1	67.9	79.2	70.5
	-10.0	**82.8**	**83.3**	**83.8**	**83.3**	**89.0**	**84.4**
	-10.5	92.4	92.6	93.2	92.2	95.6	93.2
	-11.0	97.1	97.3	97.8	96.5	98.4	97.4

A sample size of 70 patients per treatment group gives a probability of success of greater than 80% for all assumed dose response shapes, with the assumed maximum dose effect and standard deviation as stated earlier.

Further simulations were performed to investigate the sensitivity of the probability of a successful trial outcome (as presented in Table 7.5: 1) to different possible allocation ratios which might be observed in practice in an analysis which uses actual maintenance dose. It is possible that some patients may not be able to reach the BI 456906 maintenance dose they

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were randomised to according to the planned titration steps in Section 4.1.4, and will receive a lower maintenance dose instead. The scenarios investigated consider the possibility of tolerability issues for patients randomized to the highest BI 456906 dose only, and tolerability issues for patients randomized to one of the top two BI 456906 doses.

All other assumptions other than the allocation ratio are unchanged from what is presented in Table 7.5: 1. For each scenario, 10000 simulations were again used. For simplicity, only the average probability of a successful outcome across the different assumptions on functional form (linear, exponential etc.) is presented in Table 7.5: 2 below. The notation "X-X-X-X-X" is used to refer (from left to right) to the number of patients who received maintenance doses of 0 mg (Placebo), 0.6 mg, 2.4 mg, 3.6 mg and 4.8 mg respectively.

Table 7.5: 2 Probability of success for unequal allocation scenarios in an analysis of actual maintenance dose

Average probability of successful trial outcome (%)						
	True maximum effect (%)					
		-9.0	**-9.5**	**-10.0**	**-10.5**	**-11.0**
Unequal Allocation ratio	**70-70-70-80-60**	52.0	69.4	83.5	92.4	97.2
	70-70-70-90-50	51.7	68.7	82.7	91.8	96.6
	70-70-80-80-50	51.5	68.6	82.4	91.6	96.7
	70-70-90-60-60	51.6	69.7	83.7	92.4	97.0
	70-70-100-60-50	52.0	68.6	82.2	91.3	96.6

The average probability of success remained above 80% for the assumed maximum dose effect for all unequal allocation scenarios investigated.

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8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."
The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

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The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source documents necessary for adjudication of events and ECG central reading will be provided to the corresponding vendors. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents. The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the participant's medical file.

For eDiary, the electronic record is the source document.

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If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history. Weight stability in previous 12 weeks can be obtained by investigator during the interview led at screening visit. The investigator should document this in the patient file.
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

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8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.
The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

An independent external committee (Clinical Event Committee, [CEC]) will be established to adjudicate some events, as specified in section 5, jointly with trial 1404-0043 (BI 456906 dose finding trial in patients with non-alcoholic steatohepatitis (NASH)).

Events will be adjudicated by external independent event adjudication committee; both in a blinded fashion. Events to be reviewed will be defined in a charter.

Events may either be defined by abnormal laboratory values and/or relevant adverse events or both.

For qualifying events, relevant source documents generated from any medical evaluations of these events will be requested including for example laboratory values, histological analysis, reports from ultrasound, CT, MRI, scintigraphy, hospital discharge letters, and medical reports from other physicians. All evaluations will be performed in a blinded fashion.

A Data Monitoring Committee (DMC) will be established, jointly with trial 1404.43. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician. The DMC will evaluate safety data. The DMC will receive urgent significant safety concerns, and cases of DILI, for immediate evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

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The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service, a centralized ECG service, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 AVAILABLE DOSING BY COMBINATION OF SYRINGES

Five concentrations of BI 456906 are available, all available in syringes of 0,5 mL. The below combination of two syringes at every injection day will be used to obtain the various dosages used during the trial, in a blinded manner. Exceptionnally, and when possible, a different combination may be used to avoid missing supplies.

Dose to be achieved per injection (mg)	Syringe 1		Syringe 2	
	syringe concentration	dose dispensed by syringe	syringe concentration	dose dispensed by syringe
0,3	0,6 mg/mL	0,3 mg	Placebo	0 mg
0,6	0,6 mg/mL	0,3 mg	0,6 mg/mL	0,3 mg
0,9	1,8 mg/mL	0,9 mg	Placebo	0 mg
1,2	0,6 mg/mL	0,3 mg	1,8 mg/mL	0,9 mg
1,8	3,6 mg/mL	1,8 mg	Placebo	0 mg
2,4	4,8 mg/mL	2,4 mg	Placebo	0 mg
3	6,0 mg/mL	3,0 mg	Placebo	0 mg
3,3	4,8 mg/mL	2,4 mg	1,8 mg/mL	0,9 mg
3,6	3,6 mg/mL	1,8 mg	3,6 mg/mL	1,8 mg
4,2	3,6 mg/mL	1,8 mg	4,8 mg/mL	2,4 mg
4,8	4,8 mg/mL	2,4 mg	4,8 mg/mL	2,4 mg

10.2 BLOOD PRESSURE MEASUREMENT PROCEDURE

Initially, blood pressure should be taken in both arms. If the pressures differ by more than 10 mmHg (as in the presence of a subclavian steal syndrome), obtain readings in both arms. The arm with the highest pressure (either systolic or diastolic) should be used for all subsequent measurements.
Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The same method and device must be used throughout the trial for a patient.
After patients have rested quietly, in the seated position for five minutes, three blood pressure measurements will be taken two minutes apart and all three results will have to be entered in the CRF. The seated pulse rate will be taken during the two-minute interval between the second and third blood pressure reading.

Blood pressure measurements should be recorded to the nearest 2 mmHg when applicable

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10.3 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

PK samples will be taken together with safety samples, before drug injection on the days of the visits

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of Version		22 Oct 2020
EudraCT number **EU number**		2020-002479-37
BI Trial number		1404-0036
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		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
Version 2.0 of this Clinical trial Protocol is considered initial version of the CTP and includes some modifications shortly after the version 1.0 was archived. Version 1.0 dated 20 Aug 2020 has not been submitted to any IRB or HA.		

11.2 GLOBAL AMENDMENT 2

Date of Version		24 Sep 2021
EudraCT number **EU number**		2020-002479-37
BI Trial number		1404-0036
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		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
Global Amendment due to urgent safety reasonsl		
Global Amendment		X

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Section to be changed		Synopsis key exclusion criteria
Description of change		1.Body weight change of +/- 5% in the past 3 months *Was changed to* 1. Body weight change of +/- 5% in the past 12 weeks
Rationale for change		Harmonized wording with section 3.3.3 exclusion criteria
Section to be changed		Synopsis key exclusion criteria
Description of change		2.Screening calcitonin ≥ 20 ng/L (pg/mL) *Was changed to* 2.Screening calcitonin ≥ 20 ng/L (pg/mL) (≥5,84 pmol/L)
Rationale for change		Harmonized respective changes in the section 3.3.3 exclusion criteria
Section to be changed		Synopsis key exclusion criteria
Description of change		6.Obesity induced by an endocrinologic disorder (e.g. Cushing Syndrome) *Was changed to* 6.Obesity induced by an endocrinologic disorder (i.e. Cushing Syndrome, **hypogonadism, growh hormone deficiency. However, well controlled hypothyroidism, polycystic ovarian disease are still allowed**)
Rationale for change		Harmonized respective changes in the section 3.3.3 exclusion criteria
Section to be changed		Synopsis key exclusion criteria
Description of change		8.Previous surgical treatment for obesity *Was changed to* 8.Previous **irreversible** surgical treatment for obesity. **Previous treatment with reversible weight loss devices such as gastric banding, or intragastric balloon and removed longer than 12 months before screening should not be excluded.**
Rationale for change		Harmonized respective changes in the section 3.3.3 exclusion criteria
Section to be changed		Flow Chart

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Description of change		It is specified that pregnancy test at End of Treatment visit is a urinary test
Rationale for change		Specification was missing
Section to be changed		Flow Chart
Description of change		12-lead ECG is added to visits 14, 16, 17, 19
Rationale for change		ECG will be done at every visit (except visit 18 which is only to collect medication) during treatment phase as requested by Authorities
Section to be changed		Flow Chart
Description of change		Foot note 7 : FASTING sample: on these days, blood samples will also include some efficacy parameters including fasting glucose and fasting lipid battery These visits would preferably be scheduled on mornings *Was changed to* FASTING sample: on these days, blood samples will also include some efficacy parameters including fasting glucose**, insulin and C-peptide,** and fasting lipid battery These visits would preferably be scheduled on mornings
Rationale for change		The insulin and C-peptide are mentioned in section 5.4.1 but were not repeated here in flow chart
Section to be changed		Flow Chart foot note 17
Description of change		The following is added to foot note 17 : E-diary checks and patient counselling is optional at visit 19 for patients who had withdrawn drug prematurely
Rationale for change		After drug discontinuation patients are encouraged to stay in the trial until its planned end. In order to minimize the number of trial withdrawals, focus is made on primary endpoint and safety. Thus, records in e-diary are made optional to relief the daily burden.
Section to be changed		1.4.3 Discussion

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Description of change		However, the event was recently upgraded to serious due to the medical significance, according to the BI GPV case processing procedure *Was changed to* However, the event was recently upgraded to serious due to the medical significance, according to the BI **Global Pharmacovigilance** case processing procedure
Rationale for change		Replace abbreviation
Section to be changed		3.3.2. Inclusion criteria
Description of change		Reference to section 4.2.2.2 is added to inclusion criterion 5 (contraception)
Rationale for change		Refer to the corresponding paragraph of protocol where details are given
Section to be changed		3.3.3. Exclusion criteria and flow chart
Description of change		2.Obesity induced by an endocrinologic disorder (e.g. Cushing Syndrome) *Was changed to* 2.Obesity induced by an endocrinologic disorder (i.e. Cushing Syndrome, **hypogonadism, growh hormone deficiency. However, well controlled hypothyroidism, polycystic ovarian disease are still allowed**)
Rationale for change		Clarification and examples given
Section to be changed		3.3.3. Exclusion criteria
Description of change		9. Screening calcitonin ≥20 pg/mL 11. History of chronic or acute pancreatitis or elevation of serum lipase/amylase > 2x ULN, or fasting serum triglyceride levels of > 500 mg/dL at screening *Were changed to* 9. Screening calcitonin ≥20 pg/mL **(≥5,84 pmol/L)** 11. History of chronic or acute pancreatitis or elevation of serum lipase/amylase > 2x ULN, or fasting serum triglyceride levels of > 500 mg/dL **(>5,65 mmol/L**) at screening

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Rationale for change		Provide both SI and Conventional units
Section to be changed		3.3.3 Exclusion criteria
Description of change		13. Prior surgery of the GI tract that could interfere with body weight (including minimally invasive/endoscopic bariatric devices, bariatric surgery) except appendectomy and simple hernia repair before randomization. *Was changed to* 13. Prior surgery of the GI tract that could interfere with body weight (including minimally invasive/endoscopic bariatric devices, bariatric surgery **including metabolic operation that involves resection and/or reconstruction of any portion of the gastrointestinal trac**t) except appendectomy and simple hernia repair before randomization. **However, a patient previously treated with reversible weight loss devices such as gastric banding, or intragastric balloon and removed longer than 12 months before screening should not be excluded**.
Rationale for change		Clarifications and details to answer queries from sites
Section to be changed		3.3.3 Exclusion criteria
Description of change		17. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are greater than 450 ms at screening or an increase of 30 ms versus screening) or any other abnormal or clinically significant ECG finding at screening (e.g., type 2 second-degree AV block (Type Mobitz II) or third-degree AV block) *Was changed to* 17. A marked prolongation of QT/QTc **(Fridericia)** interval that is greater than 450 ms at screening ~~or an increase of 30 ms versus screening~~ **or at the randomisation** or any other abnormal or clinically significant ECG finding at screening (e.g., type 2 second-degree AV block (Type Mobitz II) or third-degree AV block) **see section 5.2.4**
Rationale for change		Specify what correction of QT is used and simplify the criterion
Rationale for change		Simplification of reading

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Section to be changed		3.3.3 Exclusion criteria
Description of change		25.Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin *Was changed to* 25.Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal **or squamous** cell carcinoma of the skin.
Rationale for change		Clarification
Section to be changed		3.3.4.1. discontinuation of trial treatment
Description of change		Addition of one criterion • **The patient requires hospitalization due to drug related gastrointestinal adverse event assessed by investigator**
Rationale for change		Authority request
Section to be changed		3.3.4.1. discontinuation of trial treatment
Description of change		Given the patient's agreement, a patient who discontinue drug should stay in the trial and follow procedures and visits as described in section 6.2.2. *Was changed to* Given the patient's agreement, a patient who discontinue drug should stay in the trial and follow procedures and visits as described in section 6.2.2 **except patients taking GLP-1 RA who should be withdrawn from trial**.
Rationale for change		To aligned with section 4.2.2.1
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient

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Description of change		Fixed dose escalation phase (week 1- week 10) During this phase the patient will receive planned dose as described Table 4.1.4:1 and titration within the dose group will not be allowed. *Was changed to* Fixed dose escalation phase (week 1- week 10) During this phase the patient will receive planned dose as described Table 4.1.4:1 and titration within the dose group will not be allowed. **Patients who cannot tolerate study drug during this period despite of all efforts taken, will be discontinued from treatment**
Rationale for change		Authority request
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Maintenance dosing phase (week 21- week 46) No dose adjustments or titrations will be allowed during the maintenance phase. No patients will start the maintenance phase at week 21 with any dose which is not one of the planned maintenance doses (0.6, 2.4, 3.6 or 4.8mg), and the dose will not be changed from week 21 until the final study visit at week 46 *Was changed to* Maintenance dosing phase (week 21- week 46) No dose adjustments or titrations will be allowed during the maintenance phase. No patients will start the maintenance phase at week 21 with any dose which is not one of the planned maintenance doses (0.6, 2.4, 3.6 or 4.8mg), and the dose will not be changed from week 21 until the final study visit at week 46. **Patients who cannot tolerate study drug during this period despite of all the efforts taken, will be discontinued from treatment**.
Rationale for change		Authority request
Section to be changed		4.2.2.1. Restrictions regarding concomitant treatment

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		The following is not allowed during screening and treatment phase: • Treatment with orlistat, zonisamide, topiramate/phentermine, phenteremine, bupropion/ naltrexone, GLP-1 RAs alone or in combination or any medication that could provide weight change in the opinion of the investigator. *Was changed to :* The following is not allowed during **the whole trial period (including patients who discontinued study medication) :** • **GLP-1 RAs** The following is not allowed during screening and **until after 4 weeks after the last drug intake** ~~treatment phase~~: • Treatment with orlistat, zonisamide, topiramate/phentermine, phenteremine, bupropion/ naltrexone, ~~GLP-1 RAs~~ alone or in combination or any medication that could provide weight change in the opinion of the investigator.
Rationale for change		To precisely assess dose response relationship of BI456906 on body weight without an interference of the medication that poses the same mode of action
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		The following bullet point was added in the list of restricted drugs : • **Medications known to significantly prolong the QT or QTc interval administered for a period of > 2 weeks**
Rationale for change		To align with exclusion criteria
Section to be changed		5.1.4 efficacy laboratory parameters

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Description of change		Some of the lab parameters will be analysed as part of efficacy criteria (see section 2.2.2 and 5.4.1). In addition to parameters that are already collected for safety, fasting glucose and lipid battery, as well as HbA1c are to be measured at the visits specified in the flow chart. *Was changed to* Some of the lab parameters will be analysed as part of efficacy criteria (see section 2.2.2 and 5.4.1). In addition to parameters that are already collected for safety, fasting glucose, **insulin, C-peptide** and lipid battery, as well as HbA1c are to be measured at the visits specified in the flow chart.
Rationale for change		Clarifications : these parameters were already mentioned in section 5.4.1 and are added here for clarity
Section to be changed		5.2 Assessment of safety
Description of change		The following text is added : **Safety is monitored during the trial conduct as per the below procedures.** **Investigators are encouraged to repeat ECG and/or additional imaging, laboratory testing if any abnormal finding are observed**
Rationale for change		Clarification requested by Authorities
Section to be changed		5.2.3 safety lab parameters
Description of change		Addition of C-peptide and Insulin in the table
Rationale for change		Clarifications : these parameters were already mentioned in section 5.4.1 and are added here for clarity
Section to be changed		5.2.4 Electrocardiogram

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Description of change		A 12-lead ECGs should be collected at the time points specified in the Flow Chart. Centralized ECG services will be provided by an external vendor. ECGs should be collected according to the study-specific recommendations, using the standardized equipment provided by the vendor. ECGs may be repeated for quality or safety reasons. Patients must be supine for approximately 5-10 minutes before ECG collection. Patients should remain supine, but awake, during the ECG collection process. The investigator has the responsibility to complete an initial review as soon as the ECG recordings are obtained at the site visit. At any time during the trial, the investigator may decide to place a hold on further dosing of the patient if there is an indication of significant abnormalities in the ECG, and would prefer to wait until the results from the central reading are available. The digital ECG recordings will be transmitted to the vendor for central reading. The ECG recordings will be centrally evaluated and rated as normal, abnormal, or unable to evaluate, and the results will be reported to the site. The site investigator must review the report. If the ECG is rated as abnormal, the Investigator will have to determine if the abnormal findings areclinically significant. The site investigator will have the responsibility of following up with the patient if there are any clinically significant findings in the ECG report. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate. After the screening visit, the investigator must review the ECG results to ensure patient has met all the inclusion criteria and does not meet any of the exclusion criteria. Any pre-existing

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		conditions should be recorded as baseline conditions. *Was changed to :* A 12-lead ECGs should be collected **prior to the dosing** at the time points specified in the Flow Chart. Centralized ECG services will be provided by an external vendor. ECGs should be collected according to the study-specific recommendations, using the standardized equipment provided by the vendor. ECGs may be repeated for quality or safety reasons. Patients must be supine for approximately 5-10 minutes before ECG collection. Patients should remain supine, but awake, during the ECG collection process. The investigator has the responsibility to complete an initial review as soon as the ECG recordings are obtained at the site visit. At any time during the trial, the investigator may decide to place a hold on further dosing of the patient if there is an indication of significant abnormalities in the ECG, and would prefer to wait until the results from the central reading are available. The digital ECG recordings will be transmitted to the vendor for central reading. The ECG recordings will be centrally evaluated and rated as normal, abnormal, or unable to evaluate, and the results will be reported to the site. The site investigator must review the report. If the ECG is rated as abnormal, the Investigator will have to determine if the abnormal findings are clinically significant. **After the screening visit, the investigator must complete a review of the ECG results from central reading to ensure patient has met all the entry criteria for the study. Any pre-existing conditions should be recorded as baseline conditions. At visit 2 eligibility decisions may be made based on the local reading of the screening ECG only exceptionally if the results of the central ECG have not been received, prior to randomisation visit. ECG recorded at the**

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		randomization visit should be evaluated by the investigator before the patient receives the first dose. If abnormalities are observed by the investigator in the ECG reading at randomization visit, it is strongly recommended that the investigator wait until the results from central reading are available, and the randomization visit should be rescheduled. The site investigator will have the responsibility of following up with the patient if there are any clinically significant findings in the ECG report. **It is strongly recommended to repeat 12-lead ECG recording and/ or a referral to a cardiologist and/or perform additional cardiac tests (e.g. cardiac enzymes) if there is an indication of significant abnormalities or in case of doubts.** ~~After the screening visit, the investigator must review the ECG results to ensure patient has met all the inclusion criteria and does not meet any of the exclusion criteria. Any pre-existing conditions should be recorded as baseline conditions~~.

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Rationale for change		Clarification on the role of investigator review and central review, as requested by some local authorities
Section to be changed		5.2.6.1.3 AEs considered as "Always serious"
Description of change		The following text was added : **Adverse Event (AE) coded shall cross referenced against the Always Serious List (ASL). Non serious cases will be upgraded to serious. Cardiac related events included in the ASL, shall be fully processed as serious and expedited**
Rationale for change		Clarification of process as requested by Authority
Section to be changed		5.2.6.1.6 Intensity (severity) of AEs
Description of change		<u>Electrocardiogram QT corrected interval prolonged</u> Mild: QTc increase from baseline of more than 30s and QTc 450-480 ms Moderate: QTc increase from baseline of more than 30s and QTc 481-500 ms Severe: QTc increase from baseline of more than 30s and QTc >= 501 ms on at least two separate ECGs *Was changed to* <u>Electrocardiogram QT**cF** corrected interval prolonged</u> Mild: QTc**F** increase from baseline of more than 30s and QTc 450-480 ms Moderate: QTc**F** increase from baseline of more than 30s and QTc 481-500 ms Severe: QTc**F** increase from baseline of more than 30s and QTc >= 501 ms on at least two separate ECGs
Rationale for change		To be more specific on what QT correction is applied

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Section to be changed		Foot note of table in section 5.7.1 (CMDS)
Description of change		Low HDL: high-density lipoprotein (HDL) cholesterol <40 mg/dL in men, <50 mg/dL in women High TG Fasting triglycerides ≥150 mg/dL or on antihyperlipidemia medication High BP : SBP ≥130mmHg and/or DBP ≥85 mmHg or on antihypertensive medication Prediabetes: fasting plasma glucose ≥100 mg/dl, and/or 2-hour OGTT ≥140 mg/dl. *Was changed to* Low HDL: high-density lipoprotein (HDL) cholesterol <40 mg/dL(1,04mmol/L) in men, <50 mg/dL **(1,30 mmol/L)** in women High TG Fasting triglycerides ≥150 mg/dL**(1,69 mmol/L)** or on antihyperlipidemia medication High BP : SBP ≥130mmHg and/or DBP ≥85 mmHg or on antihypertensive medication Prediabetes: fasting plasma glucose ≥100 mg/dL **(5,55 mmol/L)**, and/or 2-hour OGTT ≥140 mg/dL**.(7,77 mmol/L)**
Rationale for change		Provide both SI and Conventional units
Section to be changed		6.2.2 treatment period
Description of change		At the visits where PRO questionnaires are completed by the patient, the C-SSRS questionnaire should be administered only after receiving the completed PRO questionnaires *Was changed to* At the visits where PRO questionnaires are completed by the patient, **the PHQ-9 (completed by the patient) and** the C-SSRS questionnaire **(completed by qualified site staff)** should be administered only after receiving the completed PRO questionnaires.
Rationale for change		Clarification on the completion of questionnaires
Section to be changed		6.2.2 treatment period

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Description of change		At each visit, patients should be advised to follow the recommended diet and exercise plan and to record their compliance daily on the provided diary. Diet and exercise counselling sessions are held at visits indicated in the Flow Chart. *Was changed to* At each visit, patients should be advised to follow the recommended diet and exercise plan and to record their compliance daily on the provided diary. Diet and exercise counselling sessions are held at visits indicated in the Flow Chart. **When necessary from a logistical point of view it is possible to have the diet/exercise counselling on a different day than the actual dosing visit, but within the time window of the visit.**
Rationale for change		Give flexibility
Section to be changed		6.2.2 treatment period
Description of change		The following text was added : **Safety lab, other laboratory tests during the treatment period (from V3 to visit 17) :** **If blood sampling for central lab at the trial site is not possible, safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and proper documentation in the eCRF.** **<u>Minimum</u> required safety lab parameters are** **Haematology: Haematocrit, Hemoglobin, Red Blood Cells / Erythrocytes, White blood cells / Leukocytes, Platelet Count / Thrombocytes** **Clinical chemistry: ALT (alanine aminotransaminase, SGPT), AST (aspartate aminotransaminase, SGOT), Bilirubin total, Amylase, Lipase**
Rationale for change		Due to COVID-19sanitary crisis it may happen that central lab cannot provide tubes or results
Section to be changed		6.2.2 treatment period

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		The following text was added : **Exceptionally, and after consultation with sponsor, one visit could be completed a few days in advance to accommodate for patient's imperatives. The call to IVRS and drug allocation would be made, but the injection would occur as per the initial schedule and allowed time-window.**
Rationale for change		Avoid too many withdrawals due to patients missing a visit and therefore would miss 2 consecutive doses
Section to be changed		10.1 Available dosing by Combination of syringes
Description of change		Five concentrations of BI 456906 are available, all available in syringes of 0,5 mL. The below combination of two syringes at every injection day will be used to obtain the various dosages used during the trial, in a blinded manner. *Was changed to* Five concentrations of BI 456906 are available, all available in syringes of 0,5 mL. The below combination of two syringes at every injection day will be used to obtain the various dosages used during the trial, in a blinded manner. **Exceptionnally, and when possible, a different combination may be used to avoid missing supplies**
Rationale for change		Give flexibility to the IRT system
Section to be changed		10.2 Blood pressure measurement procedures
Description of change		The following text is deleted : ~~The preferred method of blood pressure measurement is by a standard mercury sphygmomanometer. If a standard mercury sphygmomanometer is not available, alternative devices according to homepage:dableducational.org may be used after consultation with the Clinical Trial Leader~~
Rationale for change		Sphygmomanometer is not widely used anymore and this requirement is obsolete

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11.3 GLOBAL AMENDMENT 3

Date of Version		16 Feb 2022
EudraCT number **EU number**		2020-002479-37
BI Trial number		1404-0036
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		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
Global Amendment due to urgent safety reasons		
Global Amendment		X

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Section to be changed		Synopsis statistical methods
Description of change		The following text was added : **One interim analysis will be performed by the Sponsor for internal planning purposes after approximately two-thirds of randomised patients have reached Week 20. The interim analysis will include body weight reduction at Week 20 and descriptive summaries of safety and tolerability. In addition, exploratory model based longitudinal population PKPD analyses of 1404.0036 interim data, pooled with data from other studies with BI 456906, will be conducted for weight reduction and incidence of nausea and vomiting AEs** **The interim analysis results are not intended to be used to stop the trial, nor to make confirmatory claims.**
Rationale for change		An interim analysis will be performed for sponsor planning purposes only.
Section to be changed		3.1 Overall Trial Design
Description of change		The following text was added : **One interim analysis will be performed during the trial. Please refer to section 7.2.7**
Rationale for change		An interim analysis will be performed for sponsor planning purposes only
Section to be changed		4.1.5.1 Blinding
Description of change		The following text was added : **One interim analysis will be performed by an independent statistics and programming team at the Sponsor for internal phase III planning purposes after approximately two thirds of randomised patients have reached Week 20. Details are given in Section 7.2.7, including how access to unblinded data and results will be controlled.**
Rationale for change		An interim analysis will be performed for sponsor planning purposes only.
Section to be changed		7.2.7 Interim Analysis

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Description of change		No interim analysis is planned in this trial. A Data Monitoring Committee (DMC) will be implemented, with tasks as described in Section 8.7. *was changed to* **<u>Data Monitoring Committee</u>** A Data Monitoring Committee (DMC) will be implemented, with tasks as described in Section 8.7. **<u>Interim Analysis</u>** **One interim analysis will be performed after approximately two-thirds of randomised patients have reached Week 20.** **The interim analysis will include body weight reduction at Week 20 and descriptive summaries of safety and tolerability. Details of the proposed analyses will be specified in an interim TSAP. In addition, exploratory model based longitudinal population PKPD analyses of 1404.0036 interim data, pooled with data from other studies with BI 456906, will be conducted for weight reduction and incidence of nausea and vomiting AEs.** **The interim analysis will be performed for Sponsor internal phase III planning purposes. The interim analysis results are not intended to be used to stop the trial, nor to make confirmatory claims. No statistical adjustments to Type I error are therefore considered necessary.** **The interim analysis will be performed by the Sponsor, using the steps below to protect the integrity of the trial. The external DMC will be informed of the results of the interim analysis and will be given opportunity to review them at the scheduled DMC meeting following their availability.**

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		The interim analysis will be performed by an independent statistics and programming team within BI. Personnel involved with trial conduct at study sites will not have access to unblinded data from the interim analysis. Secure folders with restricted access will be used for the storage of unblinded interim data and results. Further operational details of who will perform the interim analysis, and the steps to be taken to protect the integrity of the ongoing trial, will be specified in a Logistics Plan. Details of the BI personnel who will have access to unblinded interim data or results, and how interim results will be communicated within BI, will be specified in an Access Plan. These documents will be finalised prior to unblinding treatments at interim database lock
Rationale for change		An interim analysis will be performed for sponsor planning purposes only.

11.4 GLOBAL AMENDMENT 4

Date of Version		29 Apr 2022
EudraCT number **EU number**		2020-002479-37
BI Trial number		1404-0036
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		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
Global Amendment due to urgent safety reasons		
Global Amendment		X

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Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		The patient experiences an infection with Sars-CoV-2 (as confirmed by PCR test, see Section 5.2.3). *Was changed to:* The patient experiences an infection with Sars-CoV-2 (as confirmed by PCR test) **and presents with signs or symptoms requiring discontinuation of treatment as per investigator's discretion.**
Rationale for change		Provide further clarification about whether trial treatment should be discontinued in the event a subject experiences an infection with Sars-CoV-2. In line with the COVID-19 benefit-risk assessment for BI 456906, the investigator will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will determine whether each individual patient should continue trial treatment. In the event trial treatment was stopped due to an infection with Sars-CoV-2, the investigator may decide to continue the trial treatment based on a thorough risk assessment.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient

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Description of change		• In case of consecutive 2 skipped doses, the treatment discontinuation should be considered (general rule). In some exceptional circumstances (e.g. COVID-19 like pandemic situation), sponsor must be contacted for alternative option. *Was changed to* • In case of consecutive 2 skipped doses, the treatment discontinuation should be considered (general rule). In some exceptional circumstances (e.g. COVID-19 like pandemic situation), sponsor must be contacted for alternative option. **If 2 consecutive doses of study medication are missed, the patient may recommence the study treatment if considered safe as per the investigator's discretion and the patient does not meet any of the discontinuation criteria"**.
Rationale for change		In the event that trial treatment was stopped two consecutive weeks, in circumstances that do not meet discontinuation criteria, give the investigator the possibility to decide to continue the trial treatment based on a thorough risk assessment
Section to be changed		4.1.5.1.Blinding

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Description of change		The randomisation codes will be provided to bioanalytics during the course of the trial to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded. *Was changed to :* The randomisation codes will be provided to bioanalytics during the course of the trial to allow for the exclusion from the analyses of pharmacokinetic (PK) **and antidrug antibodies (ADA)** samples taken from placebo patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.
Rationale for change		ADA analyses are run in parallel to PK analyses
Section to be changed		7.2.1 General considerations
Description of change		The following text is deleted : In "Analysis set" : ~~The Per Protocol Set (PPS) is defined as all patients in the FAS who were without an important protocol deviation relevant for efficacy.~~ In "Important protocol deviations" ~~IPD categories which lead to exclusion form analysis sets will also be specified in the TSAP~~
Rationale for change		Removal of description of Per Protocol Set (PPS) and removal of statement that important protocol deviations (IPDs) may lead to exclusion from analysis sets. Expected to be covered by analyses using other estimands and sensitivity analyses (details to be specified in trial statistical analysis plan).
Section to be changed		7.2.2 Primary endpoint analyses

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Description of change		[redacted] *Was changed to :* [redacted]
Rationale for change		[redacted]

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine	[redacted]	02 May 2022 14:28 CEST
Author-Clinical Trial Leader		02 May 2022 15:30 CEST
Author-Trial Statistician		03 May 2022 11:34 CEST
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