Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c31412745-10**
EudraCT No.	2020-002600-38	
BI Trial No.	1466-0001	
BI Investigational Medicinal Product	BI 3006337	
Title	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)	
Lay Title	A study to test how well men tolerate different doses of BI 3006337	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: Fax:	
Coordinating Investigator	[redacted] Phone: Mobile Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment No. 9))	
Version and Date	Version: 10.0	Date: 24 Nov 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	27 Aug 2020
Revision date	24 Nov 2022
BI trial number	1466-0001
Title of trial	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)
Coordinating Investigator	[redacted]
Trial site (s)	Multi-centre trial
Clinical phase	I
Trial rationale	BI 3006337 is a dual GLP-1/FGF21 receptor agonist designed for the treatment of nonalcoholic steatohepatitis (NASH). The complementary activities of GLP-1 and FGF21 on insulin resistance, obesity, hepatic fat metabolism, and fibrosis biomarkers provide the rationale to combine GLP-1 and FGF21 in one molecule with the expectation to improve multiple NASH-associated pathologies.
Trial objectives	To investigate safety, tolerability and pharmacokinetics of single doses of BI 3006337 in healthy male subjects
Trial endpoints	Primary endpoint: Percentage of subjects with drug-related adverse events (AEs) after single dose of BI 3006337 Secondary endpoints: $AUC_{0-\infty}$, C_{max}, and t_{max} of BI 3006337
Trial design	Single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design

Number of subjects	
total entered	92
each treatment	8 per dose group 1 - 10 (6 on BI 3006337 and 2 on placebo) 12 per dose group 11 (9 on BI 3006337 and 3 on placebo) due to exploratory investigation of gastric emptying rate (paracetamol absorption test). * Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 92, but is not to exceed 108.
Diagnosis	Not applicable
Main criteria for inclusion	Healthy, male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) ≥20 to <32 kg/m^2
Test product	BI 3006337 solution for injection 50 mg/mL
dose	0.2 mg, 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg, 15 mg, 30 mg, 50 mg, 100 mg, 150 mg
mode of admin.	SC
Reference product	Placebo of BI 3006337
dose	Not applicable
mode of admin.	SC
Duration of treatment	Single dose
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHART (DG 1-10)

Visit	Day	Planned time (relative to trial activities[10]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	BI 3006337 in serum[8]	Anti-Drug Antibodies[9]	[redacted]	Holter ECG (24-hour HR)	Glucose bedside test	12-lead ECG	Vital signs (Temperature, BP, PR)	Neurological Examination	Questioning for AEs and concomitant therapy[6]
1	-33 to -5			Screening (SCR)[1,16]	x[5]				▲ |		x	x	x	
2	-2	-41:00	16:00	Admission to trial site[5,15]					▼					
	-1	-26:00	07:00	Randomization[14,]	x				▲	x	x	x		x
		-25:00	08:00	Breakfast					|					
		-21:00	12:00	Lunch					|					
		-17:00	16:00	Snack (voluntary)					|					
		-14:00	19:00	Dinner					|					
	1	-2:00[2]	07:00	Body weight (BW)	x	x	x		▼ ▲	x	x[7, 11]	x		x
		0:00	**09:00**	**s.c. injection of BI 3006337 or placebo**					|		x[7, 17]	x[17]		x[17]
		1:00	10:00						|		x[7]	x		x
		1:30	10:30	Light breakfast					|					
		2:00	11:00	Local tolerability at injection site					|		x[7]	x		x
		3:00	12:00	Lunch[12]		x			|	x	x[7]	x		x
		7:00	16:00	Snack (voluntary)[12]		x			|	x	x[7]	x		x
		10:00	19:00	Dinner					|					
		11:00	20:00			x			|		x[7]	x		x
		15:00	24:00			x			|		x[7]			
	2	22:00	07:00	Local tolerability at injection site	x				▼ ▲					
		23:00	08:00	Breakfast[12]		x			|	x	x[7]	x		x
		24:00	09:00						|			x		x
		25:00	10:00						|			x		x
		27:00	12:00	Lunch[12]		x			|	x	x[7]	x		x
		31:00	16:00	Snack (voluntary)[12]		x			|	x	x[7]	x		x
		34:00	19:00	Dinner					|					
		35:00	20:00			x			|		x[7]	x		x
		39:00	24:00			x			|		x[7]			
	3	46:00	07:00	Local tolerability at injection site	x				▼ ▲					
		47:00	08:00	Breakfast[12]		x			|	x	x[7]	x		x
		51:00	12:00	Lunch					|					
		55:00	16:00	Snack (voluntary)					|					
		58:00	19:00	Dinner[12]		x			|			x		x
	4	70:00	7:00	Local tolerability at injection site	x				▼					
		72:00	09:00	Breakfast[12] (voluntary)		x				x	x[7]	x	x	x
		73:00	10:00	Discharge from trial site										
	5	96:00[3]	09:00	Ambulatory visit	x	x					x[7]	x		x

Visit	Day	Planned time (relative to trial activities[10]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	BI 3006337 in serum[8]	[redacted]	[redacted]	Holter ECG (24-hour HR)	Glucose bedside test	12-lead ECG	Vital signs (Temperature, BP, PR)	Neurological Examination	Questioning for AEs and concomitant therapy[6]
	6	120:00[3]	09:00	Ambulatory visit, body weight	x[13]	x					x[7]	x		x
	8	168:00[3]	09:00	Ambulatory visit, local tolerability at injection site	x	x					x[7]	x		x
	11	240:00[3]	09:00	Ambulatory visit, body weight		x					x[7]	x		x
	15	336:00[3]	09:00	Ambulatory visit	x	x					x[7]	x	x	x
	22	504:00[3]	09:00	Ambulatory visit, body weight	x	x						x		x
	29	672:00[3]	09:00	Ambulatory visit	x	x						x		x
3	32 to 40			End of trial (EOT) examination[4]	x	x					x	x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any SCR procedures. SCR procedures include physical examination, check of vital signs, ECG, Holter monitoring of HR, safety laboratory, demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the respective procedures are to be performed and completed within 2 h prior to drug administration on Day 1 of Visit 2.
3. On Days 5-29, a deviation from the scheduled time of ±120 min is acceptable for all the planned trial activities.
4. End of trial examination includes physical examination (potential injection site reactions), BW, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. In addition, a drug SCR and alcohol breath or urine test will be done at this time point.
6. AEs and concomitant therapies will be recorded throughout the trial but will be specifically asked for at the time points indicated in the Flow Chart (DG 1-10) above.
7. The ECG recording has to be performed as triplicate at this time point.
8. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 375 mL per subject. A front and a back-up sample will be collected.
9. Blood sample for anti-drug antibody (ADA) analysis (front and a back-up sample).
10. Planned time relative to administration of BI 3006337 or placebo in Visit 2.
11. 3 ECG triplicate series, each approximately 15 minutes apart, will be taken at this time period for calculating baseline value. Only the first triplicate ECG (i.e. 3 single ECGs) will be evaluated for baseline.
12. If several actions are indicated at the same time point, the intake of meals or liquids will be the last action.

[redacted]

14. Randomization will be done following enrolment and possibly before 24 h Holter ECG at Visit 2 Day -1, the latest prior to administration of trial medication (BI 3006337 or placebo) at Visit 2 Day 1.
15. Polymerase chain reaction (PCR) Test on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) will be performed at Visit 2 and according to internal requirements of the site.
16. The Holter ECG devices will be brought back by the subjects the day after installation for analysis by the central ECG reader.
17. Following BI 3006337 / placebo administration

FLOW CHART (DG-11)

Visit	Day	Planned time (relative to trial activities [10]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	[redacted]	BI 3006337 in serum[8]	Anti-Drug Antibodies [9]	[redacted]	[redacted]	Holter ECG (24-hour HR)	Glucose bedside test	12-lead ECG	Vital signs (Temperature, BP, PR)	Neurological Examination	Questioning for AEs and concomitant therapy[6]
1	-33 to -5			Screening (SCR)[1,16]	x[5]						▲		x	x	x	
2	-2	-41:00	16:00	Admission to trial site[5,15]							▼					
	-1	-26:00	07:00	Randomization[14,]	x						▲	x	x	x		x
		-25:10	07:50													
		-25:00	08:00	[redacted]												
		-24:45	08:15													
		-24:30	08:30													
		-24:15	08:45													
		-24.00	09:00													
		-23:30	09:30													
		-23.00	10:00	240 mL fluid intake[12]												
		-22.00	11:00													
		-21:00	12:00	Lunch[12]												
		-20.00	13:00													
		-19.00	14:00													
		-17:00	16:00	Snack (voluntary)[12]												
		-15.00	18:00													
		-14:00	19:00	Dinner												
	1	-2:00[2]	07:00	Body weight (BW)	x		x	x			▼	x	x[7, 11]	x		x

Visit	Day	Planned time (relative to trial activities[10]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Paracetamol in plasma	BI 3006337 in serum[8]	[redacted]	Serum adiponectin, serum bone biomarker	Glucose, insulin, C-peptide in plasma	Holter ECG (24-hour HR)	Glucose bedside test	12-lead ECG	Vital signs (Temperature, BP, PR)	Neurological Examination	Questioning for AEs and concomitant therapy[6]
		0:00	**09:00**	**s.c. injection of BI 3006337 or placebo**							▲		x[7, 17]	x[17]		x[17]
		1:00	10:00										x[7]	x		x
		1:30	10:30	Light breakfast												
		2:00	11:00	Local tolerability at injection site									x[7]	x		x
		3:00	12:00	Lunch[12]			x					x	x[7]	x		x
		7:00	16:00	Snack (voluntary)[12]			x					x	x[7]	x		x
		10:00	19:00	Dinner												
		11:00	20:00				x						x[7]	x		x
		15:00	24:00				x						x[7]			
	2	22:00	07:00	Local tolerability at injection site	x						▼▲					
		23:50	07:50			x				x						
		23:00	08:00	[redacted]												
		23:15	08:15			x				x						
		23:30	08:30			x				x						
		23:45	08:45			x				x						
		24:00	09:00			x				x				x		x
		24:30	09:30			x				x						
		25:00	10:00	240 mL fluid intake[12]		x				x				x		x
		26.00	11:00			x				x						
		27:00	12:00	Lunch[12]		x	x			x		x	x[7]	x		x
		28.00	13:00			x										
		29.00	14:00			x										

Visit	Day	Planned time (relative to trial activities[10]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Paracetamol in plasma	BI 3006337 in serum[8]			Glucose, insulin, C-peptide in plasma	Holter ECG (24-hour HR)	Glucose bedside test	12-lead ECG	Vital signs (Temperature, BP, PR)	Neurological Examination	Questioning for AEs and concomitant therapy[6]
		31:00	16:00	Snack (voluntary)[12]		x	x					x	x[7]	x		x
		33.00	18:00			x										
		34:00	19:00	Dinner												
		35:00	20:00				x						x[7]	x		x
		36:00	21:00	Snack (voluntary)[12]												
		39:00	24:00				x						x[7]			
	3	46:00	07:00	Local tolerability at injection site	x						▼▲					
		47:00	08:00	Breakfast[12]			x					x	x[7]	x		x
		51:00	12:00	Lunch												
		55:00	16:00	Snack (voluntary)												
		58:00	19:00	Dinner[12]			x							x		x
		60:00	21:00	Snack (voluntary)[12]												
	4	70:00	7:00	Local tolerability at injection site	x						▼					
		72:00	09:00	Breakfast[12] (voluntary)			x					x	x[7]	x	x	x
		73:00	10:00	Discharge from trial site												
	5	96:00[3]	09:00	Ambulatory visit	x		x						x[7]	x		x
	6	120:00[3]	09:00	Ambulatory visit, body weight	x[13]		x						x[7]	x		x
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	11	240:00[3]	09:00	Ambulatory visit, body weight			x						x[7]	x		x
	15	336:00[3]	09:00	Ambulatory visit	x		x						x[7]	x	x	x

Visit	Day	Planned time (relative to trial activities[10]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Paracetamol in plasma	BI 3006337 in serum[8]	[redacted]	[redacted]	Glucose, insulin, C-peptide in plasma	Holter ECG (24-hour HR)	Glucose bedside test	12-lead ECG	Vital signs (Temperature, BP, PR)	Neurological Examination	Questioning for AEs and concomitant therapy[6]
	22	504:00[3]	09:00	Ambulatory visit, body weight	x		x							x		x
	29	672:00[3]	09:00	Ambulatory visit	x		x							x		x
3	32 to 40			End of trial (EOT) examination[4]	x		x						x	x	x	x

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12. If several actions are indicated at the same time point, the intake of meals or liquids will be the last action.
13. [redacted]
14. Randomization will be done following enrolment and possibly before 24 h Holter ECG at Visit 2 Day -1, the latest prior to administration of trial medication (BI 3006337 or placebo) at Visit 2 Day 1.
15. Polymerase chain reaction (PCR) Test on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) will be performed at Visit 2 and according to internal requirements of the site.

16. The Holter ECG devices will be brought back by the subjects the day after installation for analysis by the central ECG reader.
17. Following BI 3006337 / placebo administration

TABLE OF CONTENTS

[redacted]

[redacted]	[redacted]
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
API	Active Pharmaceutical Ingredient
AST	Aspartate Transaminase
[redacted]	[redacted]
AUC	Area under the Curve
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity
[redacted]	[redacted]
[redacted]	[redacted]
β	Slope parameter associated with the power model used to evaluate dose proportionality
[redacted]	[redacted]
BI	Boehringer Ingelheim
BMI	Body Mass Index (weight divided by height squared)
BP	Blood Pressure
BW	Body Weight
CA	Competent Authority
[redacted]	[redacted]
CI	Confidence Interval
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in serum
$C_{max,SS}$	Maximum measured concentration of the analyte in serum during steady state
C_{min}	Minimum measured concentration of the analyte in serum
$C_{min,SS}$	Minimum measured concentration of the analyte in serum during steady state
COVID-19	Corona Virus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CRO	Contract Research Organization
CT	Computer Tomography

CTL	Clinical Trial Leader
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
[redacted]	[redacted]
DEXA	Dual-Energy X-Ray Absorptiometry
DG	Dose Group
DILI	Drug Induced Liver Injury
DIO	Diet-induced
ECG	Electrocardiogram
[redacted]	[redacted]
EDTA	Ethylenediaminetetraacetic acid
EOT	End of Trial
ES	Enrolled set
EudraCT	European Clinical Trials Database
FC	Fragment Crystallizable
FGF21	Fibroblast Growth Factor 21
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP-1	Glucagon-like Peptide 1
GLP1R	Glucagon-like Peptide 1 Receptor
HMW	High Molecular Weight
HR	Heart Rate
IB	Investigator's Brochure
ICH-GCP	International Conference of Harmonization - Good Clinical Practice
IEC	Independent Ethics Committee
iPD	Important Protocol Deviation
IRB	Institutional Review Board
ISF	Investigator Site File
ka	Absorption rate constant
λ_z	Terminal rate constant of the analyte in serum
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
micro-CT	Micro-Computer Tomography
MRT_{SC}	Mean residence time of the analyte in the body after subcutaneous administration
MTC	Medullary Thyroid Carcinoma
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
NOAEL	No Observed Adverse Effect Level
[redacted]	[redacted]
PCR	Polymerase chain reaction
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PKS	PK parameter analysis set

PP	Polypropylene
PR	Pulse Rate
q2d	Every second day
QRS	Time between start of the Q-wave and the end of the S-wave in an electrocardiogram
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
qw	Weekly (once a week)
R	Reference treatment
REP	Residual Effect Period
RPM	Report Planning Meeting
RR	Time between two R-waves in an electrocardiogram
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
s.c.	Subcutaneous
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRD	Single-Rising Dose
[redacted]	[redacted]
TAA	Thioacetamide
T-BIL	Total Bilirubin
TC	Total Cholesterol
TG	Triglycerides
TGFß	Transforming Growth Factor beta
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in serum
TMF	Trial Master File
TS	Treated set
TSAP	Trial Statistical Analysis Plan
TSTAT	Trial Statistician
t_z	Time of last measurable concentration of the analyte in serum
ULN	Upper Limit of Normal
[redacted]	[redacted]
XTC	Ecstasy
WOCBP	Woman of Childbearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) has a prevalence of about 20 to 30% in the general population of Western countries and is rapidly becoming the most common liver disease worldwide [R15-5365]. While simple hepatic steatosis can have a benign non-progressive course, about 10% of patients with NAFLD progress to non-alcoholic steatohepatitis (NASH). As the disease progresses, significant fibrosis develops in 37 to 41% of patients within 15 years. According to the National Institute of Health, NASH is believed to be the most common cause of liver cirrhosis [R15-6070], and the 12th leading cause of death in the United States [R15-6057]. Patients with NASH are also at increased risk of hepatocellular carcinoma, even in the absence of cirrhosis [R15-5365]. By 2023, about 13 million patients are projected to have NASH with advanced stages of fibrosis. The risk of liver-related death in Western patients with NASH ranges from 10% over 13.7 years to 18% over 18.5 years [P13-02280].

Neither approved NASH-targeted therapy nor effective disease modifying regimens are currently available. Treatment is focused on addressing comorbidities from metabolic syndrome. Moreover, while lifestyle modifications – including weight loss and exercise – are recommended across different phenotypes and considered the mainstay initial treatment for NASH, they are difficult to achieve and maintain.

The test product BI 3006337 is a long-acting dual glucagon-like peptide 1 (GLP-1) and fibroblast growth factor 21 (FGF21) receptor agonist. By combining activities of GLP-1 and FGF21 in one molecule (dual GLP-1/FGF21 receptor agonist), BI 3006337 is expected to address multiple disease-related components of NASH by:

- reducing liver cell injury (steatosis, oxidative stress) and hepatic inflammation
- reducing fibrosis and
- improving glucose metabolism and insulin resistance

GLP-1 is a gut-derived incretin hormone that possesses glucose-lowering features by inducing insulin secretion and reducing the production of glucagon. It also suppresses appetite and retards gastric emptying.

GLP-1 receptor (GLP1R) agonists are one of the newer classes of medications for the treatment of adults with type 2 diabetes and/or obesity. The GLP1R agonist class first became available in 2005 in the United States with the approval of short-acting exenatide by the FDA. There are now several GLP1R agonists (all for s.c. application) available for the treatment of type 2 diabetes and obesity. In clinical studies in patients with NASH, liraglutide, a long-acting GLP-1 agonist, achieved resolution of NASH without worsening of fibrosis in 39% (9/23) of patients compared with 9% (2/22) in the placebo group after 48 weeks of treatment. Improvements in steatosis and hepatocyte ballooning were greater in the liraglutide group, but no differences were seen in lobular inflammation and overall NAFLD activity score [R16-3177]. The fibroblast growth factor (FGF) family of hormones mediate metabolic functions and tissue repair and regeneration. FGF21, a non-mitogenic hormone, is a key regulator of energy metabolism. It increases energy expenditure, reduces hepatic triglyceride, and improves insulin sensitivity [R19-2360].

Several FGF21-class molecules have been tested in humans, and several are still in different stages of clinical development for the treatment of type 2 diabetes or NASH. In clinical studies involving patients with NASH, pegbelfermin s.c. showed beneficial effects of FGF21 on steatosis, injury, and fibrosis markers. Pegbelfermin significantly reduced the absolute hepatic fat fraction in the groups receiving either 10 mg daily (-6.8% vs -1.3%) or 20 mg once a week (qw) (-5.2% vs -1.3%), compared with the placebo group. It also decreased Alanine transaminase (ALT) and Aspartate transaminase (AST), and reduced the serum fibrosis biomarker Pro-C3 in both treatment groups (-30%, 10 mg qd; -19%, 20 mg qw) relative to the placebo group [R20-0507].

Dual GLP-1/FGF21 receptor agonism is therefore expected to reduce liver cell injury (steatosis, oxidative stress, release of aminotransferases) and hepatic inflammation. While sustained resolution of steatohepatitis could result in subsequent reduction of fibrosis, a dual agonist is also expected to have direct anti-fibrotic effects via FGF21 mediated attenuation of Transforming Growth Factor beta (TGFß) signaling and hepatic stellate cell activation as recently described [R20-0498]. In addition, a dual GLP-1/FGF21 receptor agonist should improve insulin resistance as a root cause of liver steatosis and inflammation.

Overall, the clinical data available from literature on the separate components (GLP-1 and FGF21 agonists) are supportive for the development of BI 3006337 in patients with NASH. To date, there is no clinical data available for this compound.

1.2 DRUG PROFILE

The test product BI 3006337 is a [redacted] receptor agonist designed for the treatment of NASH. It is a [redacted] and [redacted] antibody fragment crystallizable (FC) fusion protein of the IgD/IgG4 subclass, that binds to and activates the function of GLP-1 and FGF21 receptors.

1.2.1 Nonclinical pharmacology

For the test product BI 3006337, the core safety pharmacology (neurological, cardiovascular and respiratory functions) was evaluated as part of the 4-week GLP repeat dose toxicity study in monkeys. No adverse findings were associated with BI 3006337 administration in the neurological or respiratory function. There was a trend of BI 3006337 treatment-related decreases in the systolic, diastolic, and mean arterial blood pressures (BPs) at doses [redacted], where supra exposures are anticipated. However, this trend was considered non-adverse since individual animal values were within the range of control values, and the combined mean systolic, diastolic, and mean arterial BP values remained within the 95% confidence limits from the background data range for restrained BPs in monkeys. The minimal effect on BPs did not progress further during the dosing period and was shown to be reversible. There were no effects on the heart rate (HR) or electrocardiography of the heart. The effects on gastrointestinal function (decreased food consumption, body weight (BW) loss, and decreased BW gain) were observed in all animal species and are the expected Pharmacodynamic (PD) effects of BI 3006337. The mouse was the most sensitive species with continuous BW loss throughout the dosing period while the effects were subsided in the rat and monkey starting the second week after the initial loss of BW during the first week of treatment. These PDs effects did not produce adverse outcome with regard to overall animal health. There were no microscopic findings in the kidney at dose levels up to [redacted]

[redacted] in mice, [redacted] in rats or [redacted] in monkeys; thus, a potential adverse effect on the kidney function is also unlikely.

BI 3006337 was tested for efficacy in a diet-induced (DIO)-NASH mouse model. The (DIO)-NASH mouse model (AMLN diet) exhibits many features common to human NASH including the development of hepatic steatosis, lobular inflammation, and injury [n00275086].

[redacted]

[redacted]

1.2.2 Toxicology

Sprague-Dawley rat and Cynomolgus monkey were selected as the appropriate rodent and non-rodent species for nonclinical toxicology studies. The rat was the preferred rodent species compared to the mouse due to the exaggerated pharmacological effect (marked BW loss with no recovery) observed in a 6-week (once every two day) and a 2-week (once daily) dose range finding studies in the mouse. The marked BW loss in mice limited the evaluation of potential toxicities at dose levels that provide adequate safety margins to the predicted human therapeutic dose [redacted]. Thus, the mouse was not considered an appropriate species for subsequent repeat dose toxicity studies with longer durations.

1.2.2.1 Genotoxicity

Genetic toxicology studies are generally not applicable to therapeutic proteins as they are not expected to directly interact with DNA. Therefore, genetic toxicology studies were not conducted per ICH S6 R1 [R12-0027].

1.2.2.2 Single dose toxicity

No stand-alone single dose toxicity assessments have been conducted with BI 3006337.

1.2.2.3 Repeated dose toxicity

A series of repeat dose toxicity studies were conducted in mice, rats, and monkeys with BI 3006337. Ante mortem parameters evaluated included toxicokinetics, anti-drug antibodies (ADAs), mortality, clinical observation, BW, food consumption, hematology, blood chemistry, urinalysis, and ophthalmic examination. Post mortem parameters included organ weights, and macroscopic and microscopic evaluations. Cardiovascular evaluations (electrocardiography, BP, HR, and body temperature) and bone safety assessments [serum biomarkers and bone mineral density measurements using Dual Energy X-Ray Absorptiometry (DEXA) and micro-computed tomography (micro-CT)] were conducted in the 6-week non-GLP toxicity study in monkeys. The comprehensive core safety pharmacology endpoints (central nervous, cardiovascular, and respiratory functions) were evaluated as part of the 4-week GLP toxicity study in monkeys.

<u>4-Week Subcutaneous Toxicity and Toxicokinetics Study in Sprague-Dawley Rats with a 4-Week Recovery Period (Once Daily)</u>

Groups (10/sex) of male and female rats were given [redacted] of BI 3006337 once daily by [redacted] at a target dose volume of [redacted]. Control animals received the vehicle [redacted]. Additional 5 rats/sex in the control and [redacted] groups were designated for recovery period, during which time the rats were not dosed.

Once daily s.c. administration of BI 3006337 at doses up to [redacted] to Sprague-Dawley rats for 4 weeks was well tolerated. BI 3006337 treatment-related findings were directly or indirectly (secondary responses due to the effect on BW) attributable to the expected pharmacological effects of BI 3006337. All of these findings were either completely or partially reversed after the 4-week recovery period. These on-target related findings were considered non-adverse because these effects did not produce adverse outcome with regard to overall animal health. There was no evidence for any off-target toxicity in this study. Under the conditions of this study, the No observed adverse effect level (NOAEL) is determined to be [redacted]. At [redacted], for GLP-1, [redacted].

4-Week Subcutaneous Toxicity and Toxicokinetics Study in Cynomolgus Monkeys with a 4-Week Recovery Period

Groups (up to 5/sex) of male and female monkeys were given [redacted] of BI 3006337 once daily by [redacted] at a target dose volume of 2 mL/kg. Control animals received the vehicle [redacted].

[redacted] administration of BI 3006337 at dose levels up to [redacted] to Cynomolgus monkeys for at least 4 weeks was well tolerated. BI 3006337 treatment-related findings were directly or indirectly (secondary responses due to the effect on BW) attributable to the expected pharmacological effects of BI 3006337. All of these findings were either completely or partially reversed after the 4-week recovery period. These on-target related findings were considered non-adverse because these effects did not produce adverse outcome with regard to overall animal health. There was no evidence for any off-target toxicity in this study. Under the conditions of this study, [redacted].

1.2.2.4 Special studies

As recommended in ICH M3(R2) [R09-1400], local tolerance of the clinical formulation of BI 3006337 [redacted] was evaluated as part of repeat dose toxicology studies in the mouse, rat, and monkey [n00276740, n00276741, n00276743, n00276744, n00276745, n00276746]. No suppurative inflammation or adverse histopathology findings were identified at the s.c. injection site, indicating that the risk of injection site local irritation due to BI 3006337 formulation is low.

1.2.2.5 Reproductive and developmental toxicity

Developmental and reproductive toxicity studies have not been conducted with BI 3006337.

1.2.3 Nonclinical pharmacokinetics

Two ELISA assays were designed to measure full length and therefore active components of the molecule (GLP-1 and FGF21). The pharmacokinetics (PKs) of BI 3006337 were dose linear after i.v. and s.c. dosing in mice, rats, cynomolgus monkeys and minipigs. The absorption rate constant (ka) and bioavailability (F) in preclinical animals were species dependent during the single dose PK studies. BI 3006337 is expected to be primarily distributed to blood and interstitial fluid. Dedicated metabolism studies have not been performed. BI 3006337 is expected to undergo protein catabolism in animals and humans to peptides and amino acids. The molecular weight of BI 3006337 is [redacted], which is above the renal filtration cut-off threshold (around 60 kDa). BI 3006337 is not expected to have significant renal filtration. Differential PK profiles were observed in mice and cynomolgus monkeys only. Mice showed exposure to active GLP-1 slightly higher than the exposure to active FGF21. Monkeys showed a PK profile for active GLP-1 substantially shorter than the profile for active FGF21. The cause of the discrepancies in the exposure between GLP-1 and FGF21 is unknown.

[redacted]

[redacted]

1.2.5 Clinical experience in humans

To date, humans have not been exposed to BI 3006337. This will be the first clinical trial in man. Experience with the single pharmacologically active components of BI 3006337 are available.

The GLP1R agonist class first became available in 2005 in the United States with the approval of short-acting exenatide by the FDA. There are now several GLP1R agonists (all for s.c. application) available for the treatment of type 2 diabetes and/or obesity. In healthy volunteers, GLP1R agonists do not increase the risk of hypoglycemia, even after prolonged fasting. Among the most common adverse effects for the GLP-1 class are nausea, vomiting, diarrhea, headache, and HR increases, which did not impact the cardiac safety of the class. Several GLP1R agonists even demonstrated cardiac benefits in long-term cardiac outcome studies. Cardiac conduction disorders were described for GLP1R agonists in clinical trials as well as in the prescribing information for Saxenda® [R19-1407]. These were reported as first degree atrioventricular block, right bundle branch block, or left bundle branch block as well as QT-prolongation up to 10 ms. In clinical trials, there were more cases of pancreatitis among GLP1R-treated patients than among comparator-treated patients. If pancreatitis is suspected, GLP-1 agonists should be discontinued. They should be used with caution in patients with a history of pancreatitis. GLP1R agonists are contraindicated in patients with a personal or family history of Medullary Thyroid Carcinoma (MTC) and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Several FGF21-class molecules have been tested in humans, and several are still in different stages of clinical development for the treatment of type 2 diabetes or NASH. The most frequently reported adverse events (AEs) in studies with FGF21 agonists were gastrointestinal (diarrhea and nausea), which were generally mild and did not require treatment. Effects of FGF21 agonists on HR or BP are conflicting, with studies from pegbelfermin, a PEGylated FGF21 agonist, showing no obvious changes, while a 2017 study of an intravenously administered, long-acting FGF21 analogue showed increases in BP and HR [R20-0507, R20-0509].

1.2.6 Residual Effect Period

The Residual Effect Period (REP) of BI 3006337 in humans is not known to date. This is the period after the last dose with measurable drug levels and/or PD effects still likely to be present. Based on the PK half-life of about [redacted] days for the GLP-1 component and 6 days for the FGF21 component, it could be determined with about 30 days.

[redacted] This is the period after this dose with measurable drug levels and/or PD effects still likely to be present.

In summary the overall residual effect period of 30 days was based on the longest IMP half-life, in this case from the BI 3006337.

1.2.7 Drug product

For a more detailed description of the BI 3006337 profile, please refer to the current Investigator's Brochure (IB) [c30782091].

1.3 RATIONALE FOR PERFORMING THE TRIAL

Healthy male subjects, aged 18-55 years will be recruited for this study. They are expected to provide a relatively stable physiological, biochemical and hormonal basis (steady state) for studying drug effects, they may not show disease-related variation and they will be selected not taking concomitant medication.

Within each dose group (DG), all actively treated individuals will receive the same BI 3006337 dose. The next higher dose will only be administered (to the next DG) if the treatment in the preceding DG was safe and showed acceptable tolerability.

BI 3006337 is a dual GLP-1/FGF21 receptor agonist showing in preclinical models, that BI 3006337 has superior efficacy to GLP1R analogues alone. Thus, these complementary activities on GLP-1 and FGF21 receptors have the potential to provide improved efficacy in metabolic disease states.

A high-unmet medical need is evident in this indication, since neither approved NASH-targeted therapy nor effective disease modifying regimens are currently available.

As a transition from preclinical investigations to clinical development, the present first-in-man trial is designed to assess safety, tolerability, PK and PDs of BI 3006337 in healthy male volunteers. The present trial provides the basis for a continued ongoing clinical development of BI 3006337 in the indication NASH.

It is intended to investigate the following dose levels of BI 3006337 in this trial: 0.2 mg, 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg, 15 mg, 30 mg, 50 mg, 100 mg and 150 mg. For this trial, s.c. doses in the range of 0.2 mg to 150 mg have been selected in order to assess the safety and tolerability of BI 3006337 in healthy male subjects, and to investigate the PK of this novel dual GLP-1 and FGF21 receptor agonist. The background for this dose selection is described in the following paragraphs.

The predicted human dose for BI 3006337 is [redacted]. The selected doses cover a safe starting dose in the sub-therapeutic range, the estimated therapeutic range and potentially supra-therapeutic doses within the levels that are determined by toxicological investigations.

A starting dose based on the NOAELs from the 4-week rat and monkey toxicity studies would by far exceed the predicted human therapeutic dose of 50 mg. Thus, the starting dose was estimated based on in vitro and in vivo pharmacological data rather than the NOAEL.

The agonistic activities of BI 3006337 for hGLP-1R and hFGFR1/hβKlotho were calculated using respective EC_{50} values determined in in vitro assays. By using in vitro EC_{50} values and Hill slopes, target % attainment was predicted. At the predicted single dose C_{max} of 0.2 mg, approximately 10% and an average 20% (range = 8 - 32%) target attainments are anticipated for hGLP-1R and hFGFR1/hβKlotho, respectively (i.e., ~10 - 20% of the anticipated E_{max}), and which is considered appropriate to be at or below the minimal anticipated biological effect level given a combined agonistic effect at both receptors. Further, the estimated GLP-1 and FGF21 exposures at the starting dose of 0.2 mg are well below those at the efficacious dose of 1 mg/kg in the TAA-induced rat fibrosis model [800x (C_{max}) and 632x (AUC_{0-168h}) for GLP-1 and 688x (C_{max}) and 660x (AUC_{0-168h}) for FGF21].

The maximum dose is planned to be [redacted]. The human exposures of the planned maximum dose of [redacted] are substantially lower than the NOAELs determined from the 4-week rat toxicity study [609x (C_{max}) and 580x (AUC_{0-168h}) for GLP-1 and 371x (C_{max}) and 351x (AUC_{0-168h}) for FGF21] and the 4-week monkey toxicity study [689x (C_{max}) and 740x (AUC_{0-168h}) for GLP-1 and 414x (C_{max}) and 431x (AUC_{0-168h}) for FGF21].

The dose escalation factors show a maximum of 2 (except from DG 1 to DG 2 with the factor of 2.5) in order to avoid the risk of abrupt safety or tolerability issue while switching from the lower dose level to the next DG.

[redacted]

1.4 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for the healthy subjects. Their participation in the study, however, is of major importance for the development of BI 3006337 as a s.c. drug, which might improve the therapy in patients with NASH. Prevention of liver-related complications and reduction of overall mortality are the ultimate treatment goals for patients with NASH and advanced fibrosis.

The subjects are exposed to the risks of the study procedures and the risks related to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

The total volume of blood withdrawn during the entire study per subject will not exceed the volume of a normal blood donation (375 mL DG 1-10 and 500 mL DG-11). No health-related risk to healthy subjects is expected from this blood withdrawal.

In the usual phase I settings, subjects stay in house in small groups for several days and there is a potential risk for spreading the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) across the subject group or site staff. Some trial procedures, e.g. collecting blood samples, recording of Electrocardiogram (ECG), or assessing vital signs, may not allow keeping the recommended distance of 1.5 to 2 meters to prevent the transmission of SARS-CoV-2. A risk management procedure has been set up at the site detailing specific cautionary measures (e.g. hygiene rules, wearing of face masks and physical distance), which is filed in the ISF. The local requirements may be subject to change and the trial procedures will be adapted accordingly, if applicable.

Drug-related risks and safety measures

The test product BI 3006337 did not demonstrate any adverse effects on the core safety pharmacology function (central nervous, cardiovascular, respiratory, renal systems) evaluated as part of the 4-week GLP repeat dose toxicity study in monkeys. The effects on the gastrointestinal function including decreased food consumption, BW loss, and decreased BW gain were observed in all animal species (mice, rats, monkeys) and are the expected pharmacological effects of BI 3006337, attributable to GLP-1 and FGF21 agonism. Anticipated with the possible role of FGF21-signalling in skeletal homeostasis, there was a trend of slight decreases in bone formation markers [Bone-specific alkaline phosphatase (BALP) and Osteocalcin (OC)] in monkeys, but no changes in bone resorption marker [Carboxy-terminal collagen crosslinks (CTX-1)], bone density (DEXA and micro-CT or microscopic correlates. The nonclinical toxicology package did not indicate any adverse toxicities at doses providing high safety margins and the predicted exposures at the proposed dose levels in this Single-Rising Dose (SRD) trial in humans are far below those at the NOAELs achieved in the repeat dose toxicity studies. The risk of immunogenicity for BI 3006337 and its consequences in humans are currently unknown. BI 3006377 is judged to be a medium risk molecule with regard to the antigenicity risk assessment. Due to the s.c. administration local intolerabilities may occur. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

Preclinical safety pharmacology studies with BI 3006337 have neither identified adverse effects on respiratory nor cardiovascular function that would imply an increased risk in context of the Corona Virus Disease 2019 (COVID-19) pandemic. Based on the mechanism of action, BI 3006337 is not expected to promote malfunction of the immune system resulting in an increased risk of progression of COVID-19 infection.

It is unlikely that there will be an additional risk to overweight (Body Mass Index (BMI) <32.0 kg/m^2), healthy subjects by the application of BI 3006337. These healthy subjects do not belong to the population at higher risk for severe illness from COVID-19 (e.g. older age, serious underlying medical conditions or obesity).

The following safety measures will be applied in this study in order to minimize the risk for healthy volunteers:

- Careful dose selection (refer to Section 1.3)
- Preliminary measurement of BI 3006337 serum concentrations and preliminary determination of PK parameters
- For precautionary reasons, drug plasma concentrations of healthy male volunteers in this trial should not exceed the mean C_{max} of 395 µg/mL (BI 3006331 GLP-1 assay)

and 362 µg/mL (BI 3006331 FGF21 assay) or mean $AUC_{0\text{-}168h}$ of 52080 µg*h/mL (BI 3006331 GLP-1 assay) and 46340 µg*h/mL (BI 3006331 FGF21 assay)

- An extensive safety laboratory will be performed with special focus on full blood exam also including bone turnover biomarkers (see Flow Chart (DG 1-10) and Flow Chart (DG-11))
- For safety reasons, each DG of 8 subjects (6 on active, 2 on placebo) will be divided into two cohorts of 2 subjects each (cohort 1 and 2) and one cohort of 4 subjects (cohort 3). The drug administrations of these three cohorts will be separated by at least 72 hours (between 1st subject of each cohort) to cover the period of highest risk/peak effect
- A thorough ECG monitoring to cover the anticipated period of highest drug exposure and additional repeated single 12-lead ECGs over 336 hours following s.c. drug administration
- Although the risk of hypoglycaemic episodes is considered to be low for BI 3006337 because of its mode of action (induction of glucose-dependent insulin-secretion), blood glucose will be monitored within predefined intervals after administration of the trial medication (see Flow Chart (DG 1-10) and Flow Chart (DG-11))
- The subjects will stay at the trial site for at least 72 hours after s.c. study drug administration at each dose level and will be monitored for vital signs and local tolerability at injection site
- During in house-confinement the subjects will be under medical observation and thoroughly monitored for both expected and unexpected AEs
- Only if the respective dose of BI 3006337 was safe and showed acceptable tolerability and if no stopping criterion was met, the next higher dose will be given
- As reproductive toxicity studies have not yet been conducted, women will not be enrolled in this study.
- A risk management plan has been set up at the site detailing specific cautionary measures, e.g. hygiene rules, wearing of face masks and physical distance which is filed in the Investigator Site File (ISF).
- In addition, a screening (SCR) of SARS-CoV-2 has been implemented to be performed as part of the safety assessments on Day -1 at visit 2. Subjects positive in the results for these virus are not eligible to the trial in accordance to exclusion criterion 29 and will be excluded from the trial. During the ambulatory visits, subjects are allowed to enter the site only after it was confirmed that subjects do not have any signs or symptoms of infection (e.g. fever).

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 subjects´ safety; see also Section 5.2.6.1.4, AEs of special interest.

In summary, although not tested in humans to date, BI 3006337 has the potential to become a s.c. treatment for NASH. Based on the mode of action, the pharmacological targets, the clinical experience of the separate components and the nonclinical toxicology data as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of this compound. Healthy volunteers are not expected to have

any direct benefit from participation in this first in man clinical trial with BI 3006337, as is the usual case in such Phase I trials. The benefit/risk assessment for the administration of BI 3006337 to healthy subjects remains unaltered despite the COVID-19 pandemic. As of today, no pharmacological treatment has been approved for the treatment of NASH, particularly also for the more advanced fibrosis stages of NASH, which constitute a population with high unmet medical need. Therefore, the Sponsor considers that the benefit outweighs the potential risks and justifies exposure to healthy human volunteers.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate safety, tolerability and PK of BI 3006337 in healthy male subjects following s.c. administration of SRDs.

2.1.2 Primary endpoint

The primary endpoint for assessment of safety and tolerability of BI 3006337 is the percentage of subjects with drug-related AEs occurring between first administration of trial medication (BI 3006337 or placebo) and end of trial (EOT).

2.1.3 Secondary endpoints

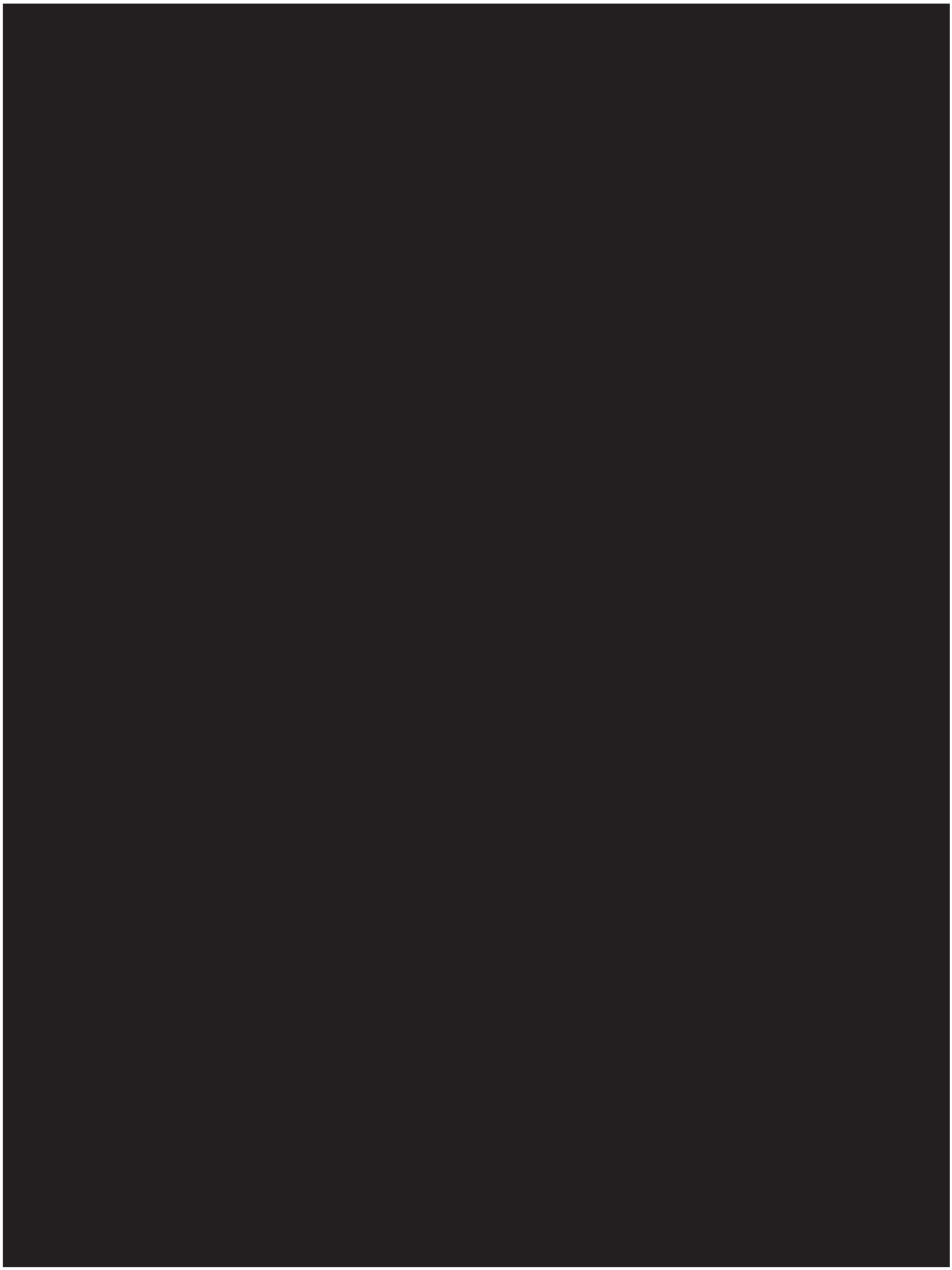
The following PK parameters of BI 3006337 will be determined if feasible:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in serum)
- t_{max} (time from dosing to the maximum measured concentration of the analyte in serum)

2.2.2.1 Safety and tolerability

Safety and tolerability of BI 3006337 will be assessed during the on-treatment period, i.e. occurring between first administration of trial medication (BI 3006337 or placebo) and EOT based on:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Continuous (24 h) ECG monitoring
- Vital signs (Temperature, BP, pulse rate (PR))



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This SRD trial is designed as single-blind, partially randomised, and placebo-controlled within sequential DGs parallel trial.

It is planned to include a total of 92 healthy male subjects in the trial. The subjects will be assigned to 10 groups consisting of 8 subjects per group and 1 group consisting of 12 subjects. The groups will be dosed sequentially (see Table 3.1: 1). The investigator (after consultation with the sponsor) is allowed to alter the scheduled DGs (e.g., add low and/or intermediate DGs, as a maximum 2 DGs) on the basis of experience gained during the study (for instance, based on preliminary PK data), provided the planned and approved highest dose is not exceeded. Thus, the actual number of subjects entered may be more than 92 but is not to exceed 108. Such changes may be implemented via substantial Clinical Trial Protocol (CTP) Amendments.

Within DG 1 - 10, 6 subjects will receive BI 3006337 and 2 will receive placebo. Only one dose is tested within each DG. For safety reasons, each DG will consist of 3 cohorts. The trial medication will be administered in the following order:

- Cohort 1 (fixed order: ‘active – placebo’): 1 subject on active treatment and 1 subject on placebo (in total 2 subjects)
- Cohort 2 (fixed order: ‘active – active’): 2 subjects on active treatment (in total 2 subjects)
- Cohort 3 (randomised): 3 subjects on active treatment and 1 subject on placebo (in total 4 subjects)

In cohort 1 both subjects will be dosed sequentially. Dosing of each subject in cohort 2 will be separated by a minimum of 10min (72 hours between last subject of cohort 1 and first subject of cohort 2, which is based on an anticipated time of approximately 39 h (FGF21) and 42 h (GLP-1) to reach peak concentration of BI 3006337 and is expected to cover the period of highest risk/peak effect). The first 2 cohorts will be dosed in a single-blinded, fixed sequence fashion ‘active – placebo’ (cohort 1) and ‘active – active’ (cohort 2). First dosing in cohort 3 can only start after all subjects on the previous cohorts have completed 72 hours. Dosing within cohort 3 will be separated by a minimum of 10 minutes. Every effort should be made to recruit a complete DG with 8 subjects. In case of dropouts prior to randomization, minimum data from 4 subjects on active drug need to be available for escalation to a higher dose.

Within DG-11, 9 subjects will receive BI 3006337 and 3 will receive placebo. The trial medication will be administered in the following order:

- Cohort 1 (fixed order: ‘active – placebo’): 1 subject on active treatment and 1 subject on placebo (in total 2 subjects)
- Cohort 2 (fixed order: ‘active – active’): 2 subjects on active treatment (in total 2 subjects)
- Cohort 3 (randomised): 6 subjects on active treatment and 2 subjects on placebo (in total 8 subjects)

The DGs to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Planned dose groups

Dose Group	1	2	3	4	5	6	7	8	9	10	11
Dose (mg)	0.2	0.5	1	2	4	8	15	30	50	100	150
Number of subjects	8	8	8	8	8	8	8	8	8	8	12
Subjects receiving placebo	2	2	2	2	2	2	2	2	2	2	3
Subjects receiving BI 3006337	6	6	6	6	6	6	6	6	6	6	9

The groups will be dosed consecutively in ascending order, and a time interval of at least 72 hours will be maintained between the last drug administration to subjects in the previous DG and the first drug administration to subjects in the subsequent DG. The decision to proceed to the next DG will be based upon the safety and tolerability of the preceding DGs. The next DG will only be treated if no safety concerns have arisen in the preceding DGs (i.e. no dose-limiting events occurred), and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.2). In addition to safety and tolerability as well as PK parameters, the trial will be performed to investigate PDs like metabolic parameters and BW.

3.1.1 Data Safety Monitoring Board – Operations and Safety Review

A documented Safety Review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the Sponsor of the study, e.g. because of any unforeseen AEs, etc. Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy), the Clinical Trial Leader (CTL) (or an authorised deputy) and a medical expert representative from the therapeutic area. Changes to the planned dosing schedule (i.e. addition of new DGs that are not predefined) will be implemented through a substantial amendment. In summary, the implementation of Data Safety Monitoring Board and safety monitoring measures as described in current protocol are considered adequate to ensure subject safety in this phase I trial.

Every effort should be done to recruit complete DG 1-10 with 8 subjects and DG-11 with 12 subjects. In case of dropouts prior to randomization, for DG 1-10 a minimum data from 4 subjects on active drug need to be available for escalation to a higher dose. For DG-11 data from all subjects on active drug need to be available. For the minimum dataset with regards to preliminary PK data, see Section 7.4. The minimum data set for review consists of the following:

- AEs in the current and preceding DGs up to at least 72 h post dosing, including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)

- Results from 12-lead ECG and continuous ECG monitoring in the current and preceding DGs up to at least 72 h post dosing
- Vital signs in the current and preceding DGs up to at least 72 h post dosing
- Clinical laboratory tests in the current and preceding DGs up to at least 72 h post dosing
- Assessment of local tolerability
- Preliminary PK data as described in Section 7.4
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy), the CTL (or an authorised deputy) and a medical expert representative from the therapeutic area after in-depth analysis of all available safety data, especially Serious Adverse Events (SAEs) (if occurred), AEs, and out-of-range laboratory results (if considered clinically significant). For the purpose of safety evaluation and decision taking at completion of each dose level in this trial, the Principal Investigator will provide [redacted] assessment based on [redacted] direct clinical experience in the use of the investigational compound; because decisions in this phase I dose escalation trial are taken based on safety observations of the participant subject cohorts, the view of the investigator on individual subjects is considered essential for the overall safety assessment. In addition and depending on the results and findings, suitable experts from the sponsor (e.g. trial statistician) or external institutions may be consulted on an as needed basis. In these cases expert recommendations will be documented in the minutes of the Safety Review and considered for the decision making. Dose escalation will only be permitted if no safety concerns exist. Decision of the Drug Safety Monitoring Board must be unanimously.

Safety Reviews can be conducted face-to-face or by video/telephone conference. The CTL is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and CTL (or an authorised deputy) and will be filed in the ISF and Trial Master File (TMF).

An overview of all relevant trial activities is provided in the Flow Chart (DG 1-10) and Flow Chart (DG-11). For visit schedules and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

3.1.2 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, Germany.

BI has appointed a CTL, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial
- ensure appropriate training and information of local Clinical Trial Manager, Clinical Research Associates (CRAs), and the participating trial site.

The BI investigational product BI 3006337 (test product) and the placebo (reference product) will be provided by the [redacted]

The trial will be conducted on two sites: [redacted] and [redacted] under the supervision of the

Principal Investigators. Both trial sites manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs).

Safety laboratory tests will be performed by the local laboratory of the trial sites:

[redacted]

In both labs, also glucose, insulin, C-peptide in serum will be measured.

The analyses of BI 3006337 concentrations and ADA in serum will be performed at [redacted].

[redacted] in a central laboratory and/ or a dedicated Contract Research Organisation (CRO) appointed by BI using validated assays.

The digitally recorded 2-channel Holter HRs and 12-lead ECGs will be sent to a specialised CRO ([redacted]) for evaluation.

On-site monitoring will be performed by a CRO appointed by BI or staff from BI.

Data management will be done by BI according to BI SOPs. Statistical tasks and programming will be performed by BI or a CRO appointed 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. Trial Statistician (TSTAT) responsibilities will be filed in the TMF.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

For SRD trials, the sequential rising dose design described in Section 3.1 is viewed favorably under the provision not to expose the subjects involved to undue risks. For safety reasons the first four subjects of each dose level will be treated in a fixed treatment sequence (active-placebo-active-active). Single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each DG. However, subjects and investigators will be aware of the dose of drug administered. The disadvantage of the trial design is a possible observer bias with regard to the dose-dependent effects; in addition, the sequential dosing of groups could potentially result in time-related effects. However, as such effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected. It is standard in SRD trials involving healthy volunteers to include a placebo group to control for safety, tolerability. Each DG 1-10 consists of 8 subjects, with 6 on active treatment, and 2 on placebo. DG-11 consists of 12 subjects, with 9 on active treatment, and 3 on placebo. For data analysis purposes, the placebo control group will include all subjects of all DGs treated with placebo. For DG 1-10, 6 subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of the main objectives. For DG-11, 9 subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of the main objectives.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 92 healthy male subjects will enter the study. The actual number of subjects entered may exceed the total of 92 if additional intermediate doses are tested (see Section 3.1) but will not exceed108 subjects entered. Subjects will be recruited from the volunteers' pool of the trial site.

The trial involves overweight subjects because overweight or even obesity is a risk factor for the development of NAFLD and NASH, which is an indication the current study medication is developed for. In addition, medications with a GLP-1-component are better tolerated by subjects with higher BW.

Only male subjects will be included in the trial because no data on reproductive toxicology are available at this time. With respect to the embryo-fetal risk coming from the treatment of male subjects with BI 3006337, where it is theoretically possible that relevant exposure to BI 3006337 may be achieved in women of childbearing potential (WOCBP) from exposure to seminal fluid, male contraception (condom or abstinence) should be used in order to avoid exposure of an existing embryo/fetus [R16-0373] (see Section 3.3.3, exclusion criterion 24).

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

Subjects will only be included in the trial if they meet the following criteria:

(1) Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (Temperature, BP, PR), 12-lead ECG, neurological examination, and clinical laboratory tests

(2) Age of ≥18 to ≤55 years at SCR

(3) BMI of ≥20.0 to <32.0 kg/m^2 at SCR

(4) A minimum absolute BW of 70 kg at SCR

(5) Male subjects who meet any of the following criteria from the administration of trial medication until 30 days after administration of trial medication:

- Use of adequate contraception, e.g. any of the following methods (of female partners) *plus* condom or sexually abstinence (if lifestyle-related): implants, injectables, vaginal contraceptives, intrauterine device, oral contraception (failure rate <1%). In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Surgically sterilised/vasectomised (including hysterectomy with or without bilateral salpingectomy or bilateral oophorectomy of female partner. In case of salpingectomy or oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment).

- Postmenopausal female partner, defined as at least 1 year of spontaneous amenorrhea.

(6) Signed and dated written informed consent prior to admission to the study, in accordance with Good Clinical Practice (GCP) and local legislation

3.3.3 Exclusion criteria

Subjects will not be allowed to participate, if any of the following general criteria apply:

(1) Female gender

(2) Any finding in the medical examination (including BP, PR or ECG) or neurological examination deviating from normal and assessed as clinically relevant by the investigator

(3) 3 times repeated measurements of systolic BP outside the range of 90 to 150 mmHg, diastolic BP outside the range of 50 to 90 mmHg, or PR outside the range of 40 to 100 bpm. In case of documented white coat hypertension the decision for eligibility is left to the investigator.

(4) Any laboratory value outside the reference range that the investigator considers to be of clinical relevance, in particular, hepatic parameters ALT (1.25xULN), AST (1.25xULN) and T-BIL (1.5xULN) or renal parameters (creatinine 1.25xULN) exceeding the Upper Limit of Normal (ULN) as specified: after 2 times repeated measurements

(5) Any evidence of a concomitant disease assessed as clinically relevant by the investigator

(6) Clinically relevant gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders

(7) Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders

(8) History of relevant orthostatic hypotension, fainting spells, or blackouts

(9) Chronic or relevant acute infections, including positive tests for Hep B antigen/ Hep C antibodies, HIV-1/2 antibodies and SARS-CoV-2

(10) History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)

(11) Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)

(12) Participation in another trial where an investigational drug has been administered within 30 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug

(13) Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)

(14) Inability to refrain from smoking on specified trial days

(15) Alcohol intake (from signing of ICF to EOT)

(16) Drug abuse or positive drug at SCR and visit 2 (D-2)

(17) Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial

(18) Intention to perform excessive physical activities within 5 days prior to the administration of trial medication or during the trial

(19) Inability to comply with the dietary regimen of the trial site

(20) A marked prolongation of QT/QTcF interval (such as QTcF intervals that are 3 times repeatedly greater than 450 ms) or any other relevant ECG finding at SCR

(21) A history of additional risk factors for Torsade de Pointes (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)

(22) Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, the subject has a condition that would not allow safe participation in the study, or excessive dietary behaviour

In addition, the following trial-specific exclusion criteria apply:

(23) Male subjects with sperm donation from the administration of trial medication until 30 days after administration of trial medication

(24) Personal or family history of medullary thyroid carcinoma or history of multiple endocrine neoplasia syndrome type 2

(25) Delayed gastric emptying (gastroparesis) or history of pancreatitis or bone disorders, bone trauma, fracture, and previous bone surgery in the last 2 months as well as subjects with risk for osteoporosis

(26) Findings from SCR Holter ECG of HR judged to be clinically relevant by the investigator or the cardiologist of the ECG core lab

(27) GLP-1-agonist or FGF21-agonist treatment in the last 6 months prior to SCR

(28) A positive Polymerase chain reaction (PCR) test for SARS-CoV-2 on visit 2 at day -2

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects 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.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication (BI 3006337 or placebo), the data of this subject will not be entered in the case report form (CRF) and will not be reported in the Clinical Trial Report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR.

At the time of discontinuation, a complete EOT examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end

of the REP (see Section 1.2.4), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

(1) The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision

(2) Findings from continuous ECG (or the 12 lead ECGs) judged to be clinically relevant by the investigator

(3) The subject 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

(4) The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment

(5) The subject is no longer able to participate for medical reasons (such as surgery, AEs, or diseases)

(6) An AE or clinically significant laboratory change or abnormality occurs that the investigator assesses as warranting discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg), clinically relevant changes in ECG requiring intervention, or unexplained hepatic enzyme elevations at any time during the trial

(7) The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of T-BIL ≥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

(8) The patient experiences an infection with SARS-CoV-2 (as confirmed by PCR Test)

In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in Flow Chart (DG 1-10) and Flow Chart (DG-11) and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject 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

BI reserves the right to discontinue the trial at any time for any of the following reasons:

(1) Failure to meet expected enrolment goals overall or at a particular trial site

(2) New toxicological findings, SAEs, or any safety information invalidating the earlier positive benefit-risk assessment. More specifically, the dose escalation will be terminated if more than 50% of the subjects at one dose level show unexpected drug-related and clinically relevant AEs of moderate or severe intensity, or if at least one drug-related SAE is reported.

(3) The dose escalation will be terminated if unexpected severe non-SAEs considered as drug-related by the investigator in 2 subjects of the same DG (8 subjects) occure.

(4) Violation of GCP, or the CTP by a trial site or investigator, or the contract with BI impairing the appropriate conduct of the trial.

(5) The sponsor decides to discontinue the further development of the investigational product.

The investigator/trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

3.3.5 Replacement of subjects

If a subject is considered as non-evaluable for the minimum data set (see Section 3.1.1), enrolment of a new subject to the current cohort will be considered in order to support the benefit-risk assessment and to achieve the required number of evaluable subjects before dose-escalation. Required evaluable subjects per cohort and dosing group are defined in Section 3.1.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products BI 3006337 (test product) & placebo (reference product) have been manufactured by BI Pharma GmbH & Co. KG. BI 3006337 solution for injection is a sterile, buffered, isotonic, preservative-free, clear and slightly brown liquid solution at pH of [redacted] BI 3006337 solution for injection is formulated at a protein concentration of 50 mg/mL of active pharmaceutical ingredient (API) and contains the excipients L-Histidine-HCl, Trometamol, Trehalose, Polysorbate 20 and water for injection. The placebo and the solvent for dilution of BI 3006337 composites of the same components without API.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 3006337
Pharmaceutical formulation:	Solution for injection
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg/mL (100 mg per vial)
Posology:	Single dosing
Route of administration:	s.c.
Duration of use:	Single dose

The characteristics of the reference product (placebo) are given below:

Substance:	Placebo of BI 3006337
Pharmaceutical formulation:	Solution for injection
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	Not applicable
Posology:	Single dosing
Route of administration:	s.c.
Duration of use:	Single dose

Placebo of BI 3006337 solution for injection also serves as solvent for dilution of BI 3006337.

4.1.2 Identity of non-investigational medicinal product

Not applicable.

4.1.3 Selection of doses in the trial

For this trial, s.c. doses in the range of 0.2 mg to 150 mg have been selected in order to assess the safety and tolerability of BI 3006337 in healthy male volunteers, and to investigate the PK of this novel dual GLP-1 and FGF21 receptor agonist. The selected doses cover a safe starting dose in the sub-therapeutic range, the estimated therapeutic range and potentially supra-therapeutic doses within the levels determined by toxicological investigations (see Section 1.2).

4.1.4 Method of assigning subjects to treatment groups

Prior to the SCR visit, subjects will be contacted and informed about the planned visit dates. The subjects willing to participate will be recruited to DGs (3 cohorts per DG) according to their temporal availability. As soon as enough subjects have been allocated to one of the planned dose cohorts (3 cohorts per DG), the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the DGs are not expected.

In Cohorts 3 of each DG, subjects will be randomly assigned to treatments (active or placebo) prior to the first administration of trial medication, while treatments in Cohorts 1 and 2 will be assigned in a fixed order for safety reasons, as described in Section 3.1.
For the purpose of random assignment, the randomization list will be provided to the Clinical Trail Leader in advance. Numbers of the randomization list will be allocated to subjects by the method 'first come - first served' according to Flow Chart (DG 1-10) and Flow Chart (DG-11). The sites will receive the randomization number from the Clinical Trial Leader to assign the subjects to the treatment according to the randomization list. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomization procedure is described in Section 7.6.

4.1.5 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.5: 1 below. The dose volume for placebo corresponds to dose volume of the respective dose level.

Table 4.1.5: 1 BI 3006337 and placebo treatments, s.c. administration

Dose group	Substance	Pharmaceutical form	Unit strength	Total dose
1	BI 3006337	Solution for injection	50 mg/mL	0.2 mg
2	BI 3006337	Solution for injection	50 mg/mL	0.5 mg
3	BI 3006337	Solution for injection	50 mg/mL	1 mg
4	BI 3006337	Solution for injection	50 mg/mL	2 mg
5	BI 3006337	Solution for injection	50 mg/mL	4 mg
6	BI 3006337	Solution for injection	50 mg/mL	8 mg
7	BI 3006337	Solution for injection	50 mg/mL	15 mg
8	BI 3006337	Solution for injection	50 mg/mL	30 mg
9	BI 3006337	Solution for injection	50 mg/mL	50 mg
10	BI 3006337	Solution for injection	50 mg/mL	100 mg
11	BI 3006337	Solution for injection	50 mg/ml	150 mg
1-11	Placebo*	Solution for injection	--	--

* Subjects receiving placebo are equally distributed across dose groups

The syringes containing the s.c. solutions for administration (BI 3006337 or placebo) will be prepared by qualified medical study personnel at the trial site under the responsibility of the investigator according to the Medication Handling Instruction provided by the sponsor. The investigator can decide at any time to discontinue dosing in case of intolerability or safety concerns.

On Day 1 of Visit 2 (time-point 0:00), BI 3006337 or placebo will be administered by the investigating physician or authorised designee to the subject by s.c. injection into a lifted skin fold of the abdominal wall while lying in supine position. The injection needle has to be placed at a 45 degree angle and injected into the skin fold over at least 15 seconds. Skin is sanitized before injection. For administration, syringe sizes dependent on administered volume (e.g. Inject®-F/Inject®, [redacted], will be used. If the volume exceeds 2 mL the dose will be divided into two syringes and will be injected into two different injection sites of the abdominal wall. Following s.c. injection, the subject should remain in a supine position for at least 30 minutes. Injection sites will be specified by naming the quadrant of the abdomen in which the injection will be done (upper right quadrant; upper left quadrant; lower left quadrant; lower right quadrant).

For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Administration of BI 3006337 or placebo will be performed by the investigator or authorised designee following an overnight fast, which is to start no later than 10 h before the scheduled dosing until at least 1,5h after dosing. Water may be consumed ad libitum except for 1 hour before and 1.5 hours after drug administration. Predefined meals will be served as outlined in Flow Chart (DG 1-10) and Flow Chart (DG-11). For restrictions with regard to diet see Section 4.2.2.2.

Subjects will be kept under close medical surveillance until 72 h after drug administration. Thereafter, the trial will be performed in an ambulatory fashion.

4.1.6 Blinding and procedures for unblinding

4.1.6.1 Blinding

The trial is designed single-blind. The treatments administered (BI 3006337 or placebo) will be blinded to subjects but will be known to the investigators (outcome assessors). Only the current dose level will be known to the subjects due to the rising dose design.

A single–blind design is considered acceptable because the potential bias in this type of study seems to be low and according to study procedures it is assured that the investigator's knowledge of the next treatment does not influence the decision to enter a subject.

All trial data will be handled open label. This means that trial functions of the sponsor are unblinded (including clinical monitor, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated personnel of the trial site). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Within the central ECG lab, the staff involved with interval measurements and morphological analyses will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician.

Access to the randomization schedule will be controlled and documented.

4.1.6.2 Unblinding and breaking the code

As this trial will be conducted single-blind, subjects' treatment assignments will be known to investigators. Therefore, no emergency envelopes will be provided.

4.1.7 Packaging, labelling, and re-supply

4.1.7.1 BI 3006337 and placebo

The investigational medicinal product BI 3006337 and placebo will be provided by BI. It will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

For details of packing and the description of the label, refer to the ISF.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The European Clinical Trials Database (EudraCT) number is indicated on the title page of this protocol as well as on the subject information and informed consent forms. Examples of the labels will be available in the ISF. A re-supply can be triggered when needed.

[redacted]

4.1.8 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be contacted immediately.

4.1.9 Drug accountability

The investigator or designee will receive the investigational drug BI 3006337 from the sponsor when the following requirements are fulfilled:

- Approval of the CTP by the Institutional Review Board (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 (CA)
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated CTP

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

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 subject, and the disposal of unused products. 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 subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused trial medication will be disposed of locally by the trial site upon written authorisation of the CTL. Receipt, usage, and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

No additional treatment is planned. However, in case of AEs in need of treatment, the investigator can authorize symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

There are no special emergency procedures to be followed. Most frequent AEs of dual GLP-1/FGF21 receptor agonists are nausea and vomiting. In case of prolonged or severe vomiting, the investigator will monitor serum creatinine, if deemed necessary. If nausea or vomiting are not amenable to conservative management, anti-emetics (e.g. dimenhydrinate, metoclopramide, granisetron or ondansetron) may be administered at the investigator's discretion.

Symptoms of mild to moderate hypoglycaemia, or blood glucose levels below 49 mg/dL (measured using bedside glucose test) can be treated by ingestion of carbohydrates (e.g. stepwise in defined amounts of 10 g). Typical clinical signs of mild or moderate hypoglycemia include cold sweats, cool pale skin, nervousness or tremor, anxious feeling, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, temporary vision changes, headache, nausea, and palpitations. Severe hypoglycemia may lead to unconsciousness. Subjects experiencing hypoglycemia should remain confined until the symptoms have improved and resolved, blood glucose is within or above the normal range and the investigating investigator deems the subject safe for discharge.

Hypoglycemic events will be recorded as AEs if symptomatic, or if serum glucose levels (local safety laboratory) are below 54 mg/dL or blood glucose levels (bedside test) are below 49 mg/dL (see Section 5.2.6.2.5).

Approved SARS-CoV-2 vaccination has been administered at least 14 days prior to planned administration of trial medication and complete vaccination protection is available.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed, except mentioned in Section 4.2.1. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Predefined meals will be served at the times indicated in Flow Chart (DG 1-10) and Flow Chart (DG-11).

For s.c. administration of the trial medication (BI 3006337 or placebo), the subject will be fasting within at least 10 hours before and 1.5 h after dosing. During this fasting period, liquid intake will be limited to water, which may be consumed ad libitum apart from 1 hour before and 1.5 h after drug administration. On other days (Day 2 – 3) subjects are allowed to have an evening Snack (voluntary).

Total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 5 days before the BI 3006337 application until the EOT examination.

Alcoholic beverages must not be consumed from signing the ICF until end of treatment (EOT). Smoking is not allowed during in-house confinement at the trial site.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks and chocolate) are not allowed from 12 h before until 8 h after administration of trial medication (BI 3006337 or placebo).

Excessive physical activity (such as competitive sport) should be avoided starting 5 days before the BI 3006337 application until the EOT examination.

Subjects will be instructed not to perform any tasks or physical activity that may influence the 24-hour ECG Holter recordings of HR in Visits 1 and 2.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured serum concentrations of trial medication will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable. No efficacy endpoints will be evaluated in this trial.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At SCR, the medical examination will include demographics, height and BW, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (Temperature, BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the EOT examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical examination including determination of BW and potential injection site reactions as well as recording of AEs and concomitant therapies.

5.2.2 Vital signs

Systolic and diastolic BPs as well as HR (HR is considered to be equal to PR) will be measured by a BP monitor at the times indicated in Flow Chart (DG 1-10) and Flow Chart (DG-11), after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of BP recording instrument on the same arm, if possible. Body temperature will also be measured.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in Flow Chart (DG 1-10) and Flow Chart (DG-11) after the subjects have fasted for at least 10 h for blood lab safety samples. For retests, at the discretion of the investigator or designee, overnight fasting is not required. The parameters that will be determined are listed in Table 5.2.3: 1 and 5.2.3: 2.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name	A	B	C	D	E	F
Haematology	Haematocrit	X	X	X	--	X	X
	Haemoglobin	X	X	X	--	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X	--	X	X
	Reticulocytes, absol.	X	X	X	--	X	X
	White Blood Cells/Leucocytes	X	X	X	--	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X	--	X	X
	Glycosylated haemoglobin A1c (HbA1c)	X	--	--	--	--	--
Automatic WBC differential (relative and absolute)	Neutrophils	X	X	X	--	X	X
	Eosinophils	X	X	X	--	X	X
	Basophils	X	X	X	--	X	X
	Monocytes	X	X	X	--	X	X
	Lymphocytes	X	X	X	--	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), relat.; Neutrophils Bands; Neutrophils Bands, relat.; Eosinophils/Leukocytes; Eosinophils, relat.; Basophils/ Leukocytes; Basophils, relat.; Monocytes/ Leukocytes; Monocytes, relat.; Lymphocytes/Leukocytes; Lymphocytes, relat.	X	X	X	--	X	X
Coagulation	Activated partial thromboplastin time	X	X	X	--	X	X
	Prothrombin time – (INR)	X	X	X	--	X	X
Enzymes	AST (Aspartate transaminase) /GOT, SGOT	X	X	X	--	X	X
	ALT (Alanine transaminase) /GPT, SGPT	X	X	X	--	X	X
	Alkaline Phosphatase (ALP)	X	X	X	--	X	X
	Gamma-Glutamyl Transferase (GGT)	X	X	X	--	X	X
	Creatine Kinase (CK)	X	X	X	--	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X	--	X	X
	Insulin	--	--	--	X	--	--
	Lactate Dehydrogenase	X	X	X	--	X	X
	Lipase	X	X	X	--	X	X
	Amylase	X	X	X	--	X	X
Hormones	Thyroid Stimulating Hormone (TSH)	X	--	--	--	--	--
Substrates	Glucose (Plasma or Serum)	X	X	X	X	--	X
	Creatinine	X	X	X	--	--	X
	Bilirubin, Total	X	X	X	--	--	X
	Bilirubin, Direct	X	X	X	--	--	X
	C-Peptide	--	--	--	X	--	--
	Protein, Total	X	X	X	--	--	X
	C-Reactive Protein (Quant)	X	X	X	--	--	X
	Uric Acid	X	--	X	--	--	X
	Cholesterol, total	X	--	X	--	--	X
	Triglyceride	X	--	X	--	--	X
Electrolytes	Calcium	X	X	X	--	--	X
	Sodium	X	X	X	--	--	X
	Potassium	X	X	X	--	--	X
	Inorganic phosphate	X	X	X	--	--	X

Table 5.2.3: 1 Routine laboratory tests (continued)

Functional lab group	Test name	A	B	C	D	E	F	G
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X	--	--	X	--
	Urine Protein (qual)	X	X	X	--	--	X	--
	Urine Glucose (qual)	X	X	X	--	--	X	--
	Urine Ketone (qual)	X	X	X	--	--	X	--
	Urobilinogen (qual)	X	X	X	--	--	X	--
	Urine Bilirubin (qual)	X	X	X	--	--	X	--
	Urine RBC/Erythrocytes (qual)	X	X	X	--	--	X	--
	Urine WBC/Leucocytes (qual)	X	X	X	--	--	X	--
	Urine pH	X	X	X	--	--	X	--
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	X	X	X	--	--	X	
PCR Test	SARS-CoV-2	--		--	--	--	--	X

A: parameters to be determined at Visit 1 (SCR examination)

B: parameters to be determined at Visit 2 on Day -1 (for time points refer to Flow Chart (DG 1-10) and Flow Chart (DG-11))

C: parameters to be determined at Visit 2 on Days 1, 2, 3, 4, 5, 8, 15 (for time points refer to Flow Chart (DG 1-10) and Flow Chart (DG-11))

D: parameters to be determined at Visit 2 on Day 6 (for time points refer to Flow Chart (DG 1-10) and Flow Chart (DG-11))

E: parameters to be determined at Visit 2 on Days 22, 29 (for time points refer to Flow Chart (DG 1-10) and Flow Chart (DG-11))

F: parameters to be determined at Visit 3 (EOT examination)

G: parameters to be determined at Visit 2 on Day -2 and to the internal requirements of the site (for time points refer to Flow Chart (DG 1-10) and Flow Chart (DG-11))

A bedside glucose test will be performed for safety reasons as indicated in Flow Chart (DG 1-10) and Flow Chart (DG-11) using Glucometers Nova StatStrip Xpress from [redacted] or Accu-Chek type Aviva from [redacted] For quantification of blood glucose one drop (50 µL) of blood taken from a fingertip will be sufficient. The results will be listed in the trial report but will not enter statistical analysis.

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Drug SCR, will be performed at SCR and visit 2, D-2.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Alcohol Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates
Drug screening (serum)	Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody

To encourage compliance with alcoholic restrictions, a breath or urine alcohol test (e.g. Alcotest® 65107410 or 55106810, [redacted]) will be performed prior to each treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.3: 1 and Table 5.2.3: 2 will be performed at:

[redacted]

In Belgium the drug SCR and D-2 tests will be performed at the trial site using Triage Tox Drug Screen 94600 from [redacted] or comparable test systems. SARS-CoV-2 virus PCR test will be performed either by [redacted] or the trial site.

Laboratory data will be transmitted electronically from the laboratory to the trial site.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting Electrocardiogram

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph [redacted] at the time points given in Flow Chart (DG 1-10) and Flow Chart (DG-11).

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin or a similar procedure to allow reproducible placement throughout the study.

To achieve a stable HR at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG recording will always precede all other study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in Flow Chart (DG 1-10) and Flow Chart (DG-11).

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs the time window of 180 sec applies as well. The repeat ECGs are assigned to the respective scheduled time point.

Additional (unscheduled) ECGs may be recorded for safety reasons. These ECGs are assigned to the prior scheduled time point in the sponsor's database.

Storing
All ECGs will be stored electronically at the ECG core lab for a minimum of 10 years.

Data transfer
All ECGs will be transferred electronically to the central ECG lab [redacted], [redacted] for evaluation.

Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation

a) Central ECG lab

   Central ECG lab evaluation will be performed post-study for the first of each triplicate ECGs per time point on Days 1, 2, 3, 4, 5, 6, 8, 11, 15.

This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically.

HR and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see Trial Statistical Analysis Plan (TSAP) for details).

All semi-automatic interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.

For automatic interval measurements no lead will be provided.

For blinding arrangements see Section 4.1.5. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by a single reader. For quality assurance and control of the measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician supervisor or his/her designee to assess the overall variance of the measured intervals and, to detect accidental switching of leads and/or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site

All local ECGs will be evaluated by the investigator or a designee.

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcF values generated by the computerised ECG system or their manual corrections by the investigators will be used.

In doubtful cases, ECGs may be sent upfront (i.e. prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at SCR) if judged clinically relevant by the investigator.
Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will be asked to see a medical specialist to receive the appropriate medical treatment.

5.2.4.2 Continuous Holter ECG recording

HR will be continuously recorded by means of 2-channel Holter ECGs for at least 24 hours in Visit 1 (SCR examination), in Visit 2 on Day -1 (for baseline assessment) and Visit 2 on Days 1, 2 and 3 (following drug administration) during the recording intervals indicated in Flow Chart (DG 1-10) and Flow Chart (DG-11) using 5-lead ECG Holter recorders (e.g.

CardioMem® CM-3000, [redacted]). All recordings will be performed with five leads to create a two-channel ECG output.

The Holter devices and procedures and the evaluation of all Holter data will be managed by an ECG core lab [redacted]). The ECG Holter recording and transmission procedures will be explained in detail in a study specific 'ECG Holter manual' which will be given to the trial site and stored in ISF. All recorded Holter data will be electronically transferred to the core lab using a program supplied by the lab.

Each Holter recording will also be assessed by a board-certified cardiologist. The interpretation of Holter ECGs will include an overall assessment and a classification of each finding (normal, abnormal clinically relevant, abnormal clinically not relevant, not assessable). Abnormalities detected during centralised Holter ECG evaluation will be entered as AEs if assessed as clinically relevant based on the investigator's judgment.

If the maximum serum concentrations of BI 3006337 reveal a significantly different t_{max} than anticipated, the timing of the Holter HR recording in Visit 2 can be altered for the succeeding DGs.

For blinding arrangements see Section 4.1.5.

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

Assessment of injection site should be performed after s.c. drug administration, at the timepoints indicated in Flow Chart (DG 1-10) and Flow Chart (DG-11), and more frequently, if deemed necessary by the investigator. For assessment, the quadrant of the injection site will be captured in the eSource after injection. Local tolerability will be assessed by the investigator or authorised designee according to 'swelling', 'induration', 'heat', 'redness', 'pain', or 'other findings'. Injection site reactions with clinically relevant findings must be recorded as AE. The diameter of the affected area will be measured. Digital photography should be used by the investigator to document clinically relevant injection site reactions.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

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
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities already pre-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 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
- Requires prolongation of existing hospitalisation
- 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 upon appropriate medical judgment 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 Adverse Events considered ‘Always Serious’

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

In accordance with the European Medicines Agency initiative on Important Medical Events, BI has set up a list of further 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, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

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 and/or ALT ≥3-fold ULN combined with an elevation of T-BIL ≥2-fold ULN measured in the same blood sample, and/or
- Aminotransferase (ALT and/or AST) elevations ≥10-fold ULN

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, T-BIL) available, the Investigator should make sure that 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 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following except for vomiting:

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 nausea, vomiting and diarrhea have been shown to be associated with pharmacological doses of GLP1R agonists, the intensity of such AEs is defined as follows for this clinical trial:

Nausea:

Mild:	Early satiety and bloating, able to maintain caloric intake on regular diet
Moderate:	Able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention
Severe:	Prolonged inadequate oral caloric or fluid intake; severe or medically significant but not immediately life-threatening; hospitalization (different from trial site) indicated

Vomiting:

Mild:	Increase of < 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)
Severe:	≥6 episodes in 24 hours (individual episodes separated by at least 30 min); 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

Diarrhea:

Mild:	Increase of <4 stools in 24 hours over baseline
Moderate:	Increase of 4 - 6 stools in 24 hours over baseline
Severe:	Increase of ≥7 stools in 24 hours over baseline; severe or medically significant but not immediately life-threatening; requiring i.v. fluids, or is resistant to antidiarrheal treatment, hospitalization (different from trial site) indicated

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine the relationship, 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, taking into account 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 Adverse event collection

Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end time, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in Flow Chart (DG 1-10) and Flow Chart (DG-11). Assessment will be made

using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards until an individual subject's EOT:
  - All AEs (serious and non-serious) and all AESIs.
  - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to SCR failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's EOT:
  - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

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.

5.2.6.2.3 Information required

All (S)AEs, including those persisting after the individual subject's EOT, must be followed up until they have resolved, have been assessed as 'chronic' or 'stable', or no further information can be obtained.

5.2.6.2.4 Pregnancy

Once the male subject has been enrolled in the clinical trial and has taken trial medication, and, if a partner of the male trial participant becomes pregnant, the investigator must report any drug exposure during pregnancy in a partner of the male trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner was obtained.

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 Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent form for the pregnant partner.

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 Trials 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.

5.2.6.2.5 Hypoglycemia

Hypoglycaemic events will be recorded as AEs if symptomatic, if serum glucose levels (local safety laboratory) are below 54 mg/dL or blood glucose levels (bedside glucose test) are below 49 mg/dL.

5.2.6.2.6 Neurological examination

A neurological examination will be performed at the time points specified in Flow Chart (DG 1-10) and Flow Chart (DG-11). The neurological assessment includes:

- General level of arousal (vigilance)
- Orientation
- Eye movement
- Pupil size and pupil reactivity
- Deep tendon reflexes
- Assessment of muscle strength
- Tremor
- Point-to-point movements
- Romberg test
- Gait
- Sensitivity

Documentation, Assessment and Reporting
Results will be documented in source data at the clinical trial site and assessed for clinical relevance by an investigator, deputy investigator or sub-investigator. Clinically relevant findings of the neurological examination will be reported as baseline conditions (at screening) and/or collected and reported as (S)AEs (during the trial, deviation/worsening from baseline). Case narratives may be written, if necessary.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Date and clock times of drug administration and PK sampling will be recorded in the CRFs. PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK data), including addition of

samples and visits, as long as the total blood volume taken per subject does not exceed 375 mL for DG 1-10 and 500 mL for DG-11. Such changes would be implemented via non-substantial CTP Amendments.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 3006337 concentrations in serum, 6.0 mL of blood will be drawn from an antecubital or forearm vein into a serum (SST_II_Advance_tube) blood drawing tube at the times indicated in Flow Chart (DG 1-10) and Flow Chart (DG-11). Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle. The tube should be inverted 6 times (without shaking) and left upright at room temperature and undisturbed for 30 to 60 minutes to allow the sample to thoroughly clot.

The blood samples will be centrifuged for approximately 10-15 minutes at approximately 1500 g to 2000 g and at room temperature. Three serum aliquots will be obtained and stored in polypropylene (PP) tubes. The first aliquot should contain at least 0.5 mL of serum. The remainder of the serum will be divided over aliquot 2 and 3. The process from end of centrifugation until transfer of serum aliqouts into the freezer should be completed within 30 minutes. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -70°C or below at the trial site. The second and third aliquots will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the serum samples will be stored at approximately -70°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time. Further information such as matrix, analyte and aliquot number may also be provided. The final instruction of blood sampling and processing will be written in a Laboratory Manual.

After completion of the trial, the samples may be used for further methodological investigations (e.g. for stability testing). However, only data related to the analyte (including ADA, if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.

[redacted]

5.5 BIOBANKING

Not applicable.

[redacted]

[redacted]

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for SCR and the EOT examination are provided in Flow Chart (DG 1-10) and Flow Chart (DG-11).

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 of Visit 2 are to be performed and completed within a 1 h- or 2 h- or 3h period, respectively, prior to the trial drug administration (including blank values for PK and PD/biomarkers).

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min for the first 72 h after trial drug. For the 24 h Holter ECG the maximum deviation will be ± 60 min for the first 72 h after trial drug. Starting from 96 h post trial drug administration a deviation from the scheduled time for all the planned trial activities of ± 120 min is acceptable.

Subjects are allowed to have a shower moment in the morning on Day 1, 2 and 3 of max 15 minutes.

If several activities are scheduled at the same time point in Flow Chart (DG 1-10) and Flow Chart (DG-11), ECG should be the first and meal the last activity. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual serum concentration sampling times refer to Flow Chart (DG 1-10) and Flow Chart (DG-11). While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of PK parameters.

If a subject misses an appointment (e.g. ambulatory visit), it will be rescheduled if possible. A time window of ± one day would be acceptable. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting (RPM).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Visit 1 - Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the study. For information regarding laboratory tests (including drug and virus SCR), ECG, 24 h Holter ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

6.2.2 Visit 2 - Baseline period

On Day -2, the subjects will be admitted to the trial site, a drug SCR and alcohol urine or breath test will be done at this time point. Additionally, a PCR test on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) will be performed. On Day -1, the examination of

laboratory parameters, ECG, vital signs for the generation of baseline values as well as Holter monitoring of HR take place. Subjects are instructed not to perform any tasks or physical activity that may influence the 24-hour ECG Holter recordings of HR.

In the morning of Day 1 (i.e. the day with administration of BI 3006337 or placebo), subjects will undergo the examination of laboratory parameters, ECG, vital signs and start of Holter monitoring of HR for each subject prior to administration of BI 3006337 or placebo.

6.2.3 Visit 2 - Treatment period

Each subject will receive one dose of trial medication (BI 3006337 or placebo) on Day 1 of Visit 2 according to a randomized allocation.

Trial medication will be administered as s.c. injection by the investigating physician (or authorised designee). Details on treatments and procedures of administration are described in Section 4.1.4.

Study participants will be kept under close medical surveillance for at least 72 h following s.c. administration of the trial medication. The subjects will then be allowed to leave the trial site at Day 4 after formal assessment and confirmation of their fitness by the investigator or [redacted] designee. On all other study days, the study will be performed in an ambulatory fashion.

For details on time points and procedures for collection of serum samples for PK analysis, refer to Flow Chart (DG 1-10) and Flow Chart (DG-11) and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in Flow Chart (DG 1-10) and Flow Chart (DG-11). For details on times of all other trial procedures, refer to Flow Chart (DG 1-10) and Flow Chart (DG-11). AEs and concomitant therapy will be assessed continuously from SCR until the EOT examination.

6.2.4 Visit 3 - End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the EOT period, see Sections 5.2.2 to 5.2.5.
Subjects who discontinue before the end of the planned treatment period should undergo the EOT Visit.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EOT Visit must be followed until they have resolved, have been sufficiently characterized, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objectives of this trial (see Section 2.1.1) will be assessed based on descriptive statistics for primary and secondary endpoints as defined in Section 2.1.2 and 2.1.3. The treatment and DGs will be compared based on these results.

[redacted]

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in this study.

Safety and tolerability of different DGs of BI 3006337 are to be determined on the basis of the investigated parameters in comparison to placebo evaluated by descriptive statistical methods.

Confidence intervals (CIs) will be computed and will have to be interpreted in the perspective of the exploratory character of the study, i.e. CIs are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

Analysis sets
Statistical analyses will be based on the following analysis sets:

- Enrolled set (ES): This subject set includes all subjects having signed informed consent, who were screened for inclusion into the study. The ES will be used for analyses of subject disposition.
- Treated set (TS): The TS includes all subjects who were randomized and treated with any dose of BI 3006337 or placebo. The TS will be used for safety analyses.
- PK parameter analysis set (PKS): This set includes all subjects in the TS who provide at least one PK endpoint that was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'PKs'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.
- [redacted]

- [redacted]

Adherence to the protocol will be assessed by the trial team. IPD categories will be specified in the Domain DV. IPDs will be identified no later than in the RPM and the iPD categories will be updated as needed.

Pharmacokinetics

The PK parameters listed in Section 2.1 for drug BI 3006337 will be calculated according to the relevant SOP of the sponsor (001-MCS-36-472).

Serum concentration data and parameters of a subject will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the RPM) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.
Relevant protocol deviations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

Serum concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- Missing samples/concentration data at important phases of PK disposition curve.

Serum concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK parameters for BI 3006337. Concentrations used in the PK calculations will be in the same format as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

[redacted]

[redacted]

7.3.1 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards, refer to "Analysis and presentation of AE data from Clinical Trials" (BI-KMED-BDS-HTG-0041). The analysis will be based on the TS and will be descriptive in nature.

7.3.2 Secondary endpoint analyses

Primary analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively. Analyses will be performed for BI 3006337, separately for each DG.

[redacted]

7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the TS. Safety analyses will be descriptive in nature and will be based on BI standards, refer to "Analysis and presentation of AE data from Clinical Trials" (BI-KMED-BDS-HTG-0041) and "Display and Analysis of Laboratory Data" (BI-KMED-BDS-HTG-0042).

For all analyses the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the RPM).

Treatments will be compared in a descriptive way. The placebo group in the safety evaluation will consist of all subjects treated with placebo, regardless of the DG in which they were treated. The test treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment. Therefore, measurements planned or AEs recorded prior to first intake of the trial medication (BI 3006337 or placebo) will be assigned to the SCR period, those recorded between intake of trial medication and the EOT visit will be assigned to the on-treatment period of either BI 3006337 (see Section 1.2.6) or placebo, and those after the EOT examination will be assigned to 'post-study'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database. The primary interest will be the on-treatment period.

Additionally, further treatment intervals (called analysing treatments) may be defined in the TSAP in order to provide summary statistics for other than above periods.

AEs will be coded using the Medical Dictionary for Regulatory Activities. Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.6.1) and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of any study periods.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

The ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints. These endpoints and their analyses will be described in the TSAP.

For laboratory data, vital sign measurements and ECG assessments, the last measurement prior to intake of trial medication (BI 3006337 or placebo) is considered as baseline value.

Clinical relevant findings in the glucose bedside test will be reported as AE.

7.4 INTERIM ANALYSES

No formal interim analysis is planned.

A preliminary analysis of PK parameters ($AUC_{0-\infty}$,C_{max} and t_{max} of BI 3006337) as well as nausea/vomiting and HR provided as individual values and appropriate summary measures, will be performed for

- Dose levels 1, 2 and 3 before proceeding to dose level 7, and subsequently dose level 8 and 9
- Dose levels 4, 5, 6 before proceeding to dose level 10

In contrast to the final PK[redacted] calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results. The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without subject identification information. The preliminary results will be distributed to the investigator and the trial team.

Depending on the results of available preliminary PK[redacted] analyses and the tolerability and safety of the compound, changes to the dosing schedule (e.g., additional intermediate doses), and additional PK[redacted] preliminary analysis may be performed if requested by the Clinical Trial Lead, the investigator or Trial Clinical pharmacokineticist. Preliminary PK[redacted] results will not be reported in the CTR.

No inferential statistical interim analysis is planned. However, after completion of each DG the investigator (or his or her deputy) is allowed to postpone further dose progression until a preliminary analysis of the data has been performed.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

It is not planned to impute missing values for safety parameters.

7.5.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant Corporate Procedure (001-MCS-36-472).

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.6 RANDOMIZATION

Each DG will be divided into three cohorts. The subjects of the first 2 cohorts (2 subjects per cohort) will not be randomized to maintain a treatment sequence of active-placebo (Cohort 1) and active-active (Cohort 2) due to safety reasons. In the third cohort of each dose level (4 subjects) the subjects will be randomized to active or placebo treatment using a 3:1 allocation ratio (test treatment to placebo).

The sponsor will arrange for the randomization as well as packaging and labelling of trial medication. The randomization list will be generated using a validated system that uses a

pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable. The block size will be documented in the CTR.

The randomization list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 92 subjects in this trial. The planned sample size is not based on a power calculation. The first 10 DGs have a sample size of 8 subjects. The size of 8 subjects per DG (6 on active treatment, and 2 on placebo) is commonly used in SRD studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and PK [R95-0013]. DG-11 has a sample size of 12 subjects due to [redacted].

Additional subjects may be entered to allow testing of 2 additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of randomized subjects may exceed 92, but no more than 108 subjects are expected in this study.

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 GCP, relevant BI SOPs, the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of International Conference of Harmonization - Good Clinical Practice (ICH-GCP).

The BI 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 general rule, no trial results should be published prior to archiving of the CTR.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the responsible IRB/Independent Ethics Committee (IEC) and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject'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 subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject 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.

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 subjects will be provided by the sponsor. 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 for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. 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.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (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)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject 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 subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and inhouse data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

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:
The trial site(s) must retain the source and essential documents (including ISF) according to the 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.

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 SUBJECT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Individual subject 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 subject's personal physician or to other appropriate medical personnel responsible for the subject'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

- 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

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first subject in the whole trial signs informed consent.

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

Early termination of the trial is defined as the premature termination of the trial for any reason before the end of the trial as specified in this protocol.

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.

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n00276740	A 2-Week Repeated Dose Subcutaneous Dose Range Finding Toxicity Study and Toxicokinetic Study of BI 3006337 in ICR Mice. Report in finalization.
n00276741	Two-Week Repeated Subcutaneous Injection Toxicity and Toxicokinetic Study of BI 3006337 in Sprague-Dawley Rats. Report in finalization.
n00276743	Two-Week Repeated Subcutaneous Injection Toxicity and Toxicokinetic Study of BI 3006337 in Sprague-Dawley Rats. Report in finalization.
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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		28 Jan 2021
EudraCT number **EU number**		2020-002600-38
BI Trial number		1466-0001
BI Investigational Medicinal Product(s)		BI 3006337
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in overweight healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Flow Chart, Section 1.4, Section 3.1, Table 5.2.3.1, Section 5.2.4.2
Description of change		Observation time for each subject was prolonged to 72h. Time interval between each subject in cohort 1, 2 and the first subject of cohort 3 was prolonged to 72h.
Rationale for change		HA request
Section to be changed		Section 3.1
Description of change		Dosing of cohort 3 of each dosing group will start if the data from all subjects of the first 2 cohorts are available and reviewed.
Rationale for change		HA request
Section to be changed		Section 3.1
Description of change		Data from all subjects from one dosing groups need to be available prior escalation to the next higher dose.
Rationale for change		HA request
Section to be changed		Section 3.3.5
Description of change		Subjects will not be replaced on study. If a subject is considered as non-evaluable for the minimum data set, enrolment of a new subject to the current cohort will be considered in order to support the benefit-risk assessment for dose escalation.

Rationale for change		HA request
Section to be changed		Section 3.1
Description of change		Misleading wording regarding time interval between dosing groups was corrected.
Rationale for change		HA request
Section to be changed		Flow Chart, Footnote 17
Description of change		Close monitoring measures at post-dose, 1h after dosing and 2 h after dosing were implemented.
Rationale for change		HA request
Section to be changed		Flow Chart, Footnote 2, Footnote 7, Footnote 14, Footnote 18, numbering of Footnotes, Table of content, Section 1.2, Section 1.2.6, Section 1.2.7, Section 1.3, Section 1.4, Section 2.2.2.3, Section 3.1, Section 3.1.2, Section 3.3.3, Section 3.3.4, Section 4.1, Section 4.1.1, Section 4.1.3, Section 4.1.7.2, Section 4.2.1, Section 4.2.2.2, Section 5.4.2, Section 5.4.3.1, Section 5.4.4.2, Section 6.1, Section 6.2.2, Section 7.3, Section 7.3.3.2, Section 7.3.4, Section 7.4
Description of change		Removal of the paracetamol test from the protocol.
Rationale for change		HA request
Section to be changed		Flow Chart
Description of change		Consistence in the protocol regarding 1.5h fasting after dosing BI3006337
Rationale for change		HA request
Section to be changed		Section 4.1.5
Description of change		Detailed description of rescue procedure and personnel in case of an emergency situation during and after drug administration.
Rationale for change		HA request
Section to be changed		Section 3.1, Section 3.1.1, Section 4.1.5
Description of change		Clarification that the implementation of new dosing groups, that are not predefined in the protocol, are considered substantial.
Rationale for change		HA request
Section to be changed		Table of content, Section 3.1.1
Description of change		Clarification regarding the Data Safety Monitoring Board
Rationale for change		HA request
Section to be changed		Clinical trial protocol synopsis, Section 1.3, Section 4.1.3, Table 3.1.1, Table 4.1.5.1
Description of change		Definition of new lower DGs
Rationale for change		Maximize safety for subjects
Section to be changed		Flow Chart, Section 1.4, Section 5.3.1, Section 5.4.2
Description of change		Decreasing maximum total volume of blood withdrawn to 350ml

Rationale for change		Due to removal of the paracetamol test and for consistency with the subject informed consent form

11.2 GLOBAL AMENDMENT 2

Date of amendment		28 Jan 2021
EudraCT number **EU number**		2020-002600-38
BI Trial number		1466-0001
BI Investigational Medicinal Product(s)		BI 3006337
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in overweight healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		Flow Chart
Description of change		Space of time from Dinner (day-1) until drug administration
Rationale for change		Typing error
Section to be changed		Section 3.3.3
Description of change		Space of time in the EC19 description regarding the excessive physical activities prior to the administration of trial medication.
Rationale for change		Error in the earlier Version regarding the space of time.
Section to be changed		Section 5.2.3
Description of change		Drug SCR tests will be performed only at SCR
Rationale for change		Inconsistency in the earlier version between Flow Chart and Section 5.2.3
Section to be changed		Flow Chart, Section 2.2.2.3, Section 3.1.2
Description of change		Serum samples for adiponectin and bone biomarker assessments.
Rationale for change		Error in the earlier Version regarding measurements of adiponectin and bone biomarker.
Section to be changed		Section 5.3.2.1, Section 5.3.2.2
Description of change		Update of storage conditions for blood samples
Rationale for change		Error in the earlier Version

Section to be changed		Section 1.4
Description of change		Implementation of a SARS-CoV-2 risk mitigation strategy
Rationale for change		Maximize safety for subjects
Section to be changed		Section 3.1
Description of change		DG
Rationale for change		Typing error in earlier Version
Section to be changed		Section 3.3.2
Description of change		Estradiol assessment (FISH) was removed from IC 5
Rationale for change		Inconsistency between CTP and ICF
Section to be changed		Section 3.3.3
Description of change		Clarification of repetitive measurements in EC3, EC4 and EC21
Rationale for change		Misleading wording
Section to be changed		Section 3.3.4.1
Description of change		Clarification of subject removal due to ECGs findings (2)
Rationale for change		Error in the earlier Version regarding ECGs findings
Section to be changed		Flow Chart, Section1.4
Description of change		Screening process timeframe from day -24 until day -5
Rationale for change		Inconsistency within the earlier protocol version
Section to be changed		Flow Chart, 5.2.4.1
Description of change		Implement 12 lead ECG on day 11
Rationale for change		Error in the earlier Version regarding repeated 12-lead ECGs over 336 hours following SC drug administration
Section to be changed		Section 4.2.1
Description of change		Refer to Section 5.2.6.2.5 regarding Hypoglycemic events
Rationale for change		For clarification purpose
Section to be changed		Section 7.3.4
Description of change		Refer to Section 1.2.6 for declaration to which period recorded data will assigned.
Rationale for change		For clarification purpose
Section to be changed		Section 3.1
Description of change		Simultaneous dosing for one subject on active and one on placebo in cohort 1 of each DG
Rationale for change		For clarification purpose

11.3 GLOBAL AMENDMENT 3

Date of amendment		21 Jul 2021
EudraCT number **EU number**		2020-002600-38
BI Trial number		1466-0001
BI Investigational Medicinal Product(s)		BI 3006337
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in overweight healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
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Section to be changed		Clinical Trial Protocol Synopsis, Section 1.3, Section 3.3.2
Description of change		Age of overweight Subject increase to 55 years
Rationale for change		IMP supply for a larger cohort of healthy, overweight, male subjects and clarification
Section to be changed		Flow Chart, Section 1.4, Section 3.3.3, Section 5.2.3, Section 6.2.2, Table 5.2.3:1
Description of change		Implemented an additional overnight stay. Subject admission at day -2
Rationale for change		Due to administrative reasons
Section to be changed		Flow Chart, Section 1.4, Section 3.3.3, Section 5.2.3, Section 6.2.2, Table 5.2.3:1
Description of change		Drug SCR tests will be performed at SCR, day-2 and end of day -1. PCR test (SARS CoV-2) will performed at day -2
Rationale for change		Administrative reasons and avoid alcohol abuse.
Section to be changed		Flow Chart
Description of change		Assess local tolerability at injection site on day 4
Rationale for change		Maximize safety for subjects
Section to be changed		Section 2.2.2.3, Section 5.4.1, Section 5.4.2, Section 7.3.3.2
Description of change		[redacted]
Rationale for change		Error in the earlier Version
Section to be changed		Section 3.1

Description of change		In cohort 1 both subjects will be dosed sequentially
Rationale for change		Administrative reasons
Section to be changed		Section 3.1
Description of change		Dosing of each subject in cohort 2 will be separated by a minimum of 10min
Rationale for change		Inconsistency within the earlier Version regarding dosing sequence.
Section to be changed		Section 3.1.1
Description of change		At minimum data from 4 subjects on active drug need to be available for escalation to a higher dose.
Rationale for change		Inconsistency within the earlier Version
Section to be changed		Section 3.1.2
Description of change		The trial will be conducted at [redacted]
Rationale for change		Initial submission in [redacted], new CRO
Section to be changed		Section 3.1.2
Description of change		[redacted]
Rationale for change		Initial submission in [redacted], new CRO
Section to be changed		Section 3.3.2
Description of change		Increase BMI to <32 kg/m2 at SCR
Rationale for change		Alignment to the expected BMI of healthy, overweight male subjects
Section to be changed		Section 3.3.2
Description of change		Modify the use of adequate contraception
Rationale for change		Maximize safety to avoid accidental pregnancy
Section to be changed		Section 3.3.3
Description of change		Update the range of systolic BP and PR
Rationale for change		Alignment to the expected BP and PR of healthy, overweight male subjects
Section to be changed		Section 3.3.3
Description of change		Update the range of hepatic and renal parameters
Rationale for change		Alignment to the expected hepatic and renal parameters of healthy, overweight male subjects
Section to be changed		Section 3.3.3
Description of change		Clinically relevant gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
Rationale for change		For clarification purpose
Section to be changed		Section 3.3.3
Description of change		Remove excl. criteria 7
Rationale for change		Not affect the potential subjects
Section to be changed		Section 3.3.3, Section 5.2.3.2
Description of change		Updating the wording regarding HIV testing
Rationale for change		For clarification purpose
Section to be changed		Section 3.3.3

Description of change		Update excl. criteria 10 regarding alcohol abuse
Rationale for change		To avoid alcohol abuse
Section to be changed		Section 3.3.3, Section 5.2.4.1
Description of change		Specify the QT/QTcF interval
Rationale for change		For clarification purpose
Section to be changed		Section 3.3.3
Description of change		Specifiy the forbiddance of sperm donation
Rationale for change		Maximize safety to avoid accidental pregnancy
Section to be changed		Section 3.3.4
Description of change		Misleading wording
Rationale for change		Error in the earlier Version
Section to be changed		Section 4.1.5
Description of change		IMP administration in supine position
Rationale for change		Administrative reasons
Section to be changed		Section 4.1.5, Section 5.2.5.1
Description of change		Specify the mark of the injection site
Rationale for change		Due to local process
Section to be changed		Section 4.1.5
Description of change		Specify fasting after IMP administration
Rationale for change		For clarification purpose
Section to be changed		Section 4.1.5
Description of change		Remove the emergency process from the former CRO
Rationale for change		For administrative reasons
Section to be changed		Section 4.2.1
Description of change		Implement SARS-CoV-2 vaccination
Rationale for change		For administrative reasons
Section to be changed		Section 4.2.2.2
Description of change		Update the alcohol prohibition
Rationale for change		Avoid alcohol abuse
Section to be changed		Section 5.2.2
Description of change		Update the device for BP monitoring
Rationale for change		Administrative reasons
Section to be changed		Section 5.2.3
Description of change		Reference values will be provided by the CRO
Rationale for change		Administrative reasons
Section to be changed		Section 5.2.3
Description of change		Update the devices for Glucose monitoring, breath alcohol test, drug test and SARS CoV-2 test.
Rationale for change		Administrative reasons
Section to be changed		Section 5.2.4.1
Description of change		Update the device for the twelve-lead resting ECG
Rationale for change		Administrative reasons
Section to be changed		Section 5.3.2.1
Description of change		Update the process of blood sampling for pharmacokinetic analysis
Rationale for change		For clarification purpose

Section to be changed		Section 5.3.2.2
Description of change		[redacted]
Rationale for change		For clarification purpose
Section to be changed		Section 6.1
Description of change		Increase the period within the measurements and assessments have to performed
Rationale for change		Administrative reasons at the responsible CRO
Section to be changed		Section 7.3.5
Description of change		Remove misleading wording
Rationale for change		Error in the earlier Version

11.4 GLOBAL AMENDMENT 4

Date of amendment		02 Sep 2021
EudraCT number **EU number**		2020-002600-38
BI Trial number		1466-0001
BI Investigational Medicinal Product(s)		BI 3006337
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in overweight healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
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Section to be changed		Flow Chart, Table of Contents, Section 5.2.6.2.6
Description of change		Implementation of a neurological examination on SCR, Visit 2/day 4, day 15 and EOT
Rationale for change		HA request

11.5 GLOBAL AMENDMENT 5

Date of amendment		29 Sep 2021
EudraCT number **EU number**		2020-002600-38
BI Trial number		1466-0001
BI Investigational Medicinal Product(s)		BI 3006337

Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in overweight healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
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Section to be changed		Address of principle investigator
Description of change		New address of [redacted]
Rationale for change		[redacted] move to a new site
Section to be changed		Flow Chart
Description of change		Remove drug screen and alcohol breath test on day -1.
Rationale for change		Error in the earlier Version
Section to be changed		Flow Chart
Description of change		Remove safety test in the evening at 7:00pm of day -1
Rationale for change		Error in the earlier Version
Section to be changed		Section 5.4.2
Description of change		[redacted]
Rationale for change		Error in the earlier Version, alignment to the ICF Version 4.0
Section to be changed		Reference Product
Description of change		Change “matching placebos” to “Placebo of BI 3006337”
Rationale for change		Misleading wording
Section to be changed		Section 3.3.2
Description of change		Implementation of neurological examination
Rationale for change		For clarification purpose
Section to be changed		Section 6.1
Description of change		For the 24 h Holter ECG the maximum deviation will be ± 60 min for the first 72 h after trial drug.
Rationale for change		Administrative reason
Section to be changed		Section 5.3.2.2
Description of change		[redacted]
Rationale for change		Clarification purpose

11.6 GLOBAL AMENDMENT 6

Date of amendment		07 Dec 2021
EudraCT number **EU number**		2020-002600-38
BI Trial number		1466-0001
BI Investigational Medicinal Product(s)		BI 3006337
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		Title page
Description of change		Remove overweight status of eligible subjects
Rationale for change		Extend BMI range from ≥20 to <32 kg/m^2
Section to be changed		Clinical trial protocol synopsis
Description of change		Remove overweight status of eligible subjects, extend body mass index (BMI) ≥20 to <32 kg/m^2
Rationale for change		Extend BMI range for a broader study population to assess safety, tolerability, PK [redacted]
Section to be changed		Flow Chart
Description of change		Implement a breakfast on Visit 2, day -1
Rationale for change		Administrative reasons
Section to be changed		Table of Content
Description of change		Update 4.1.8.
Rationale for change		Formatting error in earlier Version
Section to be changed		Section 1.3, Section 1.4, Section 2.1.1, Section 3.1, Section 3.3, Section 3.3.1, Section 4.1.3
Description of change		Remove overweight status of eligible subjects
Rationale for change		Extend BMI range from ≥20 to <32 kg/m^2
Section to be changed		Section 3.1.2
Description of change		Update new address of [redacted]
Rationale for change		Typing error in earlier Version
Section to be changed		Section 3.2.2
Description of change		Extend body mass index (BMI) ≥20 to <32 kg/m^2
Rationale for change		Extend BMI range for a broader study population to assess safety, tolerability, PK and [redacted]

Section to be changed		Section 3.3.3
Description of change		Increase BP range from 90 to 150 mmHg and left the decision of eligibility to the investigator in case of documented white coat hypertension.
Rationale for change		BMI > 25 kg/m^2 is usually associated with a higher blood pressure
Section to be changed		Section 4.1.7.1
Description of change		Update Section 4.1.7.1
Rationale for change		Formatting error in earlier Version
Section to be changed		Table 1.2.4:1
Description of change		Editorial reason
Rationale for change		Typing error in earlier version.
Section to be changed		Section 3.3.3
Description of change		Reduce the time of participation in another trial where an investigational drug has been administered to 30 days prior to planned administration of trial medication
Rational of change		Alignment to standard recruitment for healthy volunteers

11.7 GLOBAL AMENDMENT 7

Date of amendment		18 Jul 2022
EudraCT number **EU number**		2020-002600-38
BI Trial number		1466-0001
BI Investigational Medicinal Product(s)		BI 3006337
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
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Section to be changed		Section 3.3.2
Description of change		Decrease the minimum absolute BW from 75 kg to 70 kg at SCR
Rationale for change		Align the body weight to the BMI range from ≥20 to <32 kg/m2

11.8 GLOBAL AMENDMENT 8

Date of amendment		05 Sep 2022
EudraCT number **EU number**		2020-002600-38
BI Trial number		1466-0001
BI Investigational Medicinal Product(s)		BI 3006337
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
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Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		Title Page
Description of change		[redacted] assigned as coordinating investigator
Rationale for change		Open an additional site in [redacted])
Section to be changed		Clinical Trial Protocol, Synopsis
Description of change		Trial Sites
Rationale for change		Multi-Centre Trial
Section to be changed		Flow Chart
Description of change		Extend screening period to 28 days (day-33 – day -5)
Rationale for change		To obtain more time for proper screening of potential subjects
Section to be changed		Flow chart (footnote 5)
Description of change		Perform breath or urine test to avoid alcohol abuse
Rationale for change		To be more flexible to test alcohol abuse
Section to be changed		Flow Chart, Section 1.4, Section 5.3.1, Section 5.4.2
Description of change		Increase the total blood volume from 350ml to 375ml taken per subject
Rationale for change		Calculation error in earlier version
Section to be changed		Flow chart (footnote 15)
Description of change		Perform additional PCR test if locally necessary
Rationale for change		To increase safety of subjects and trial personnel
Section to be changed		Section 3.1

Description of change		Clarifying the minimum data for set up dose escalation meeting
Rationale for change		Misleading wording
Section to be changed		Section 3.1.1
Description of change		Clarifying the minimum data for set up dose escalation meeting
Rationale for change		Misleading wording
Section to be changed		Section 3.1.2
Description of change		Implemented an additional site and the corresponding local safety lab
Rationale for change		Open additional site in Netherlands
Section to be changed		Section 4.1.4
Description of change		Sites will receive the randomization list from the Clinical Trial Leader to assign the subjects for the treatment
Rationale for change		Clarify the randomization process after an additional site was added
Section to be changed		Section 5.2.2
Description of change		Remove the devices for the measurement of systolic and diastolic BPs as well as HR
Rationale for change		To be more flexible regarding the measurements of the vital signs
Section to be changed		Section 5.2.3
Description of change		Implementation of the [redacted] safety lab in [redacted] and performing breath or urine test to avoid alcohol abuse
Rationale for change		Open additional site in Netherlands and be more flexible to test alcohol abuse
Section to be changed		Section 5.3.2.2
Description of change		[redacted]
Rationale for change		Error in the earlier Version
Section to be changed		Section 6.2.2
Description of change		Implement the additional option for a urine alcohol test
Rationale for change		To be more flexible to test alcohol abuse

11.9 GLOBAL AMENDMENT 9

Date of amendment		24 Nov 2022
EudraCT number **EU number**		2020-002600-38
BI Trial number		1466-0001
BI Investigational Medicinal Product(s)		BI 3006337

Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
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Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Add an additional dosing group (DG-11)
Rationale for change		Add dose group 11 (9 subjects on BI 3006337 and 3 subjects on placebo) due to [redacted]
Section to be changed		Flow Chart
Description of change		Add separate Flow Chart for DG-11
Rationale for change		[redacted]
Section to be changed		Table of Contents
Description of change		[redacted]
Rationale for change		Clarify the additional assessments
Section to be changed		Abbreviations
Description of change		Add OGTT
Rationale for change		Clarification purpose
Section to be changed		Section 1.4
Description of change		Add an additional dosing group (DG-11) and increase the total volume of blood withdrawn during DG-11
Rationale for change		Add dose group 11 and [redacted]
Section to be changed		Section 1.3
Description of change		Rational for [redacted]
Rationale for change		Clarification purpose
Section to be changed		[redacted]
Description of change		
Rationale for change		

		[redacted]
Section to be changed		Section 3.1, Section 3.2
Description of change		Add dose group 11 (9 subjects on BI 3006337 and 3 subjects on placebo) due to [redacted]
[redacted]		[redacted]
Section to be changed		Section 3.3
Description of change		Increase number of healthy male subjects will enter the study
Rationale for change		Additional dosing group (DG-11)
Section to be changed		Section 4.1.3
Description of change		Increase dosing range to 150mg
Rationale for change		Additional dosing group (DG-11)
Section to be changed		Table 4.1.5:1
Description of change		Additional dosing group (DG-11)
Rationale for change		Due [redacted]
Section to be changed		Section 4.1.7.2
Description of change		Add Paracetamol solution
Rationale for change		Due to [redacted]
[redacted]		[redacted]
[redacted]		[redacted]
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		Section 5.6
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		Section 5.6, Section 5.6.1, Section 5.6.1.1, Section 5.6.1.1.1, Section 5.6.1.1.2, Section 5.6.1.1.3
Description of change		Adding of the [redacted]
Rationale for change		Describe the assessment, evaluation process and the clinical laboratory ([redacted])
Section to be changed		Section 5.6.2, Section 5.6.2.1, Section 5.6.2.2
Description of change		Add the [redacted]

Rationale for change		Describe the assessment, evaluation process and the clinical laboratory ([redacted]
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 7.7
Description of change		Additional dosing group (DG-11)
Rationale for change		Due to exploratory investigation of [redacted]
Section to be changed		Section 6.1
Description of change		Opportunity for the subjects to take a shower
Rationale for change		Increase the comfort for the subjects

APPROVAL / SIGNATURE PAGE

Document Number: c31412745 **Technical Version Number:10.0**

Document Name: clinical-trial-protocol-version-10

Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising subcutaneous doses of BI 3006337 in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	25 Nov 2022 11:00 CET
Approval-Biostatistics		25 Nov 2022 11:09 CET
Approval-Clinical Program [redacted]		25 Nov 2022 15:03 CET
Verification-Paper Signature Completion		25 Nov 2022 15:26 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed