Clinical Trial Protocol

	Document Number: **c43161925-02**
BI Trial No.	1466-0003
BI Investigational Medicinal Product	BI 3006337
Title	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising subcutaneous doses and multiple subcutaneous doses over 6 weeks of BI 3006337 in healthy male Japanese subjects (single-blind, randomised within dose groups, placebo-controlled, parallel group design)
Lay Title	A study in healthy Japanese men to test how well different doses of BI 3006337 are tolerated
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] FAX: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] FAX: [redacted]
Current Version, Date	Version 2.0, 15 Feb 2024
Original Protocol Date	18 Dec 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	18 December 2023
Revision date	Not applicable
BI trial number	1466-0003
Title of trial	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising subcutaneous doses and multiple subcutaneous doses over 6 weeks of BI 3006337 in healthy male Japanese subjects (single-blind, randomised within dose groups, placebo-controlled, parallel group design)
[redacted] **Investigator**	[redacted]
Trial site	[redacted] Phone: [redacted] FAX: [redacted]
Clinical phase	I
Trial rationale	To assess safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 3006337 in healthy male Japanese subjects receiving single rising doses (SRD) and multiple doses (MD) in order to provide the basis for a clinical development of BI 3006337 in Japan.
Trial objectives	To investigate safety, tolerability, pharmacokinetics, and pharmacodynamics following single rising doses and multiple doses of BI 3006337
Trial endpoints	Primary endpoint: Occurrence of any treatment-emergent adverse event assessed as drug-related by the investigator. This is expressed as the percentage of subjects treated with investigational drug who experience such an event. Secondary endpoints: SRD part: $AUC_{0-\infty}$, C_{max} of BI 3006337 MD part: $AUC_{\tau,ss}$, $C_{max,ss}$ of BI 3006337
Trial design	Single-blind, randomised within dose groups, placebo-controlled parallel-group design
Number of subjects **total entered** **on each treatment**	 36 SRD part: 24 8 per dose group (6 receiving BI 3006337 and 2 receiving placebo) MD part: 12 12 per dose group (9 receiving BI 3006337 and 3 receiving placebo) * 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 36, but is not to exceed 48.
Diagnosis	Not applicable

Main inclusion criteria	Healthy male subjects, age of 18 to 45 years (inclusive) , body mass index (BMI) of 18.5 to 25 kg/m^2 (inclusive)
Test product	BI 3006337 solution for injection 50 mg/mL
dose	SRD part: 50 mg, 100 mg, 150 mg MD part: 150 mg
mode of administration	subcutaneous (s.c.) after an overnight fast of at least 10 h
Comparator product	Matching placebo
dose	Not applicable
mode of admin.	s.c. after an overnight fast of at least 10 h
Duration of treatment	SRD part: Single dose MD part: 6 weeks, once weekly
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

SRD part: DG1 – DG3

Visit	Day	Planned time (relative to trial activities [8]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[15]	BI 3006337 in serum	Anti-Drug Antibodies/Neutralizing ADAs [7]	Blood biomarker[14]	Glucose, insulin in plasma	12-lead ECG[13]	Vital signs (BP, PR, BT)	Questioning for AEs and concomitant therapy[5]
1	-28 to -3			Screening (SCR)[1,11]	A[6]					x[12]	x	
2	-2	-41:00	16:00	Admission to trial site[4,11]								
	-1	-26:00	07:00	Randomisation[10]	B					x	x	x
		-25:10	07:50						x			
		-25:00	08:00	Start OGTT								
		-24:45	08:15						x			
		-24:30	08:30						x			
		-24:15	08:45						x			
		-24:00	09:00						x			
		-23:30	09:30						x			
		-23:00	10:00	240 mL fluid intake[9]					x			
		-22:00	11:00						x			
		-21:00	12:00	Lunch[9]					x			
		-20:00	13:00									
		-19:00	14:00									
		-17:00	16:00	Snack (voluntary)[9]								
		-15:00	18:00									
		-14:00	19:00	Dinner								
	1	-2:00	07:00	Body weight (BW) [2]	C[2]	x[2]	x[2]	x[2]		x[2]	x[2]	x[2]
		0:00	**09:00**	**s.c. injection of BI 3006337 or placebo**								
		1:00	10:00							x	x	x
		1:30	10:30	Light breakfast[9]		x				x		
		2:00	11:00	Local tolerability at injection site						x	x	x
		3:00	12:00	Lunch[9]		x				x	x	x
		7:00	16:00	Snack (voluntary)[9]		x				x	x	x
		10:00	19:00	Dinner								
		11:00	20:00			x				x	x	x
		15:00	24:00			x				x		
	2	22:00	07:00	Local tolerability at injection site	C							
		22:50	07:50						x			
		23:00	08:00	Start OGTT		x		x		x	x	x
		23:15	08:15						x			

Visit	Day	Planned time (relative to trial activities[8]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[15]	BI 3006337 in serum	Anti-Drug Antibodies/Neutralizing ADAs[7]	Blood biomarker[14]	Glucose, insulin in plasma	12-lead ECG[13]	Vital signs (BP, PR, BT)	Questioning for AEs and concomitant therapy[5]
2	2	23:30	08:30						x			
		23:45	08:45						x			
		24:00	09:00						x		x	x
		24:30	09:30						x			
		25:00	10:00	240 mL fluid intake[9]					x		x	x
		26:00	11:00						x			
		27:00	12:00	Lunch[9]		x			x	x	x	x
		28:00	13:00									
		29:00	14:00									
		31:00	16:00	Snack (voluntary)[9]		x				x	x	x
		33:00	18:00									
		34:00	19:00	Dinner								
		35:00	20:00			x				x	x	x
		36:00	21:00	Snack (voluntary)[9]								
		39:00	24:00			x				x		
	3	46:00	07:00	Local tolerability at injection site	C							
		47:00	08:00	Breakfast[9]		x				x	x	x
		51:00	12:00	Lunch								
		55:00	16:00	Snack (voluntary)								
		58:00	19:00	Dinner[9]		x					x	x
	4	70:00	7:00	Local tolerability at injection site	C							
		72:00	09:00	Breakfast[9](voluntary)		x				x	x	x
		73:00	10:00	Discharge from trial site								
	5	96:00	09:00	Ambulatory visit		x				x	x	x
	6	120:00	09:00	Ambulatory visit, body weight	D	x		x		x	x	x
	8	168:00	09:00	Ambulatory visit, local tolerability at injection site	C	x				x	x	x
	11	240:00	09:00	Ambulatory visit, body weight		x				x	x	x
	15	336:00	09:00	Ambulatory visit	C	x	x	x		x	x	x
	22	504:00	09:00	Ambulatory visit, body weight	E	x					x	x
	29	672:00	09:00	Ambulatory visit	E	x	x	x			x	x
3	32 to 40			End of trial (EOT) examination[3]	F	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, 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 3 h prior to drug administration on Visit 2 Day 1.
3. End of trial examination includes physical examination (potential injection site reactions), BW, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
4. In addition, a drug SCR and alcohol breath test will be done at this time point.
5. 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 above.
6. Including infectious serology test.
7. Blood sample for anti-drug antibody (ADA) analysis and neutralizing ADAs.
8. Planned time relative to administration of BI 3006337 or placebo in Visit 2.
9. If several actions are indicated at the same time point, the intake of meals or liquids will be the last action.
10. Randomisation will be done following enrolment, the latest prior to administration of trial medication (BI 3006337 or placebo) at Day 1 of Visit 2.
11. COVID-19 Antigen Rapid Test (Nasopharyngeal Swab) at SCR and Day -2 of Visit 2.
12. The ECG recording must be performed in triplicate ECGs at this time.
13. All resulting ECGs will be transferred electronically to the central ECG lab except for SCR and EOT.
14. Biomarker (BM) samples (refer to Section 5.4)
15. A, B, C, D, E, & F: safety laboratory sets (refer to section 5.2.3)

MD part: DG4

Visit	Day	Planned time (relative to trial activities [9]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[19]	Acetaminophen in plasma	BI 3006337 in serum	ADAs/Nab[8]	Blood biomarkers[13]	Glucose and insulin in plasma	Blood Biobanking (optional)	12-lead ECG[18]	C-SSRS examination	Vital signs (BP, PR, BT)	Questioning for AEs and concomitant therapy[6]
1	-28 to -3			SCR[1,3]	A[4]							x[17]	x	x	
2	-2	-41:00	16:00	Admission to trial site[3,5]											
	-1	-26:00	07:00	Randomisation[11]	B[7]	x						x	x	x	x
		-25:10	07:50							x					
		-25:00	08:00	Start OGTT and acetaminophen absorption test											
		-24:45	08:15			x				x					
		-24:30	08:30			x				x					
		-24:15	08:45			x				x					
		-24:00	09:00			x				x				x	x
		-23:30	09:30			x				x					
		-23:00	10:00	240 mL fluid intake[10]		x				x				x	x
		-22:00	11:00			x				x					
		-21:00	12:00	Lunch[10]		x				x				x	x
		-20:00	13:00			x									
		-19:00	14:00			x									
		-17:00	16:00	Snack (voluntary)[10]		x									
		-15:00	18:00			x									x
		-12:00	19:00	Dinner											
	1	-1:00	08:00	BW[2]			x[2]	x[2]	x[2]		x[2]	x[2]		x[2]	x[2]
		0:00	09:00	**s.c. injection of BI 3006337 or placebo**											
		1:30	10:30				x					x			
		2:00	11:00	Local tolerability at injection site[12] 240 mL fluid intake[10]											
		3:00	12:00				x					x		x	x
		4:00	13:00	Lunch											
		7:00	16:00	Snack (voluntary)[10]			x							x	x
		10:00	19:00	Dinner											
		11:00	20:00				x					x		x	x
		15:00	24:00				x					x			
	2	22:00	07:00		B	x						x	x	x	x
		22:50	07:50							x					
		23:00	08:00	Start OGTT and acetaminophen absorption test			x								
		23:15	08:15			x				x					
		23:30	08:30			x				x					

Visit	Day	Planned time (relative to trial activities[9]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[19]	Acetaminophen in plasma	BI 3006337 in serum	ADAs/Nab[8]	Blood biomarkers[13]	Glucose and insulin in plasma	Blood Biobanking (optional)	12-lead ECG[18]	C-SSRS examination	Vital signs (BP, PR, BT)	Questioning for AEs and concomitant therapy[6]
2	2	23:45	08:45	Local tolerability at injection site[12]		x				x					
		24:00	09:00			x				x				x	x
		24:30	09:30			x				x					
		25:00	10:00	240 mL fluid intake[10]		x				x				x	x
		26:00	11:00			x				x					
		27:00	12:00	Lunch[10]		x	x			x				x	x
		28:00	13:00			x									
		29:00	14:00			x									
		31:00	16:00	Snack (voluntary)[10]		x	x							x	x
		33:00	18:00			x						x			
		34:00	19:00	Dinner											
		35:00	20:00				x							x	x
		39:00	24:00				x					x			
	3	46:00	07:00	Local tolerability at injection site[12]	B										
		47:00	08:00	Breakfast[10]			x		x			x	x	x	x
		51:00	12:00	Lunch											
		55:00	16:00	Snack (voluntary)											
		58:00	19:00	Dinner											
	4	72:00	09:00	Local tolerability at injection site[12], Breakfast (voluntary)[10], Discharge from trial site	B		x		x				x	x	x
	8	168:00	09:00	Ambulatory visit[15] **s.c. injection of BI 3006337 or placebo**			x								
		170:00	11:00	Local tolerability at injection site[12]	B								x	x	x
	15	336:00	09:00	Ambulatory visit[15] **s.c. injection of BI 3006337 or placebo**	B[7]		x								
		338:00	11:00	Local tolerability at injection site[12]								x	x	x	x
	18	408:00	09:00	Ambulatory visit, local tolerability at injection site[12]	B		x					x	x	x	x
	22	504:00	09:00	Ambulatory visit[15] **s.c. injection of BI 3006337 or placebo**			x								
		506:00	11:00	Local tolerability at injection site[12]								x	x	x	x
	29	672:00	09:00	Ambulatory visit[15] **s.c. injection of BI 3006337 or placebo**			x	x							
		674:00	11:00	Local tolerability at injection site[12]	B							x	x	x	x

Visit	Day	Planned time (relative to trial activities[9]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[19]	Acetaminophen in plasma	BI 3006337 in serum	ADAs/Nab[8]	Blood biomarkers[13]	Glucose and insulin in plasma	Blood Biobanking (optional)	12-lead ECG[18]	C-SSRS examination	Vital signs (BP, PR, BT)	Questioning for AEs and concomitant therapy[6]
2	36	840:00	09:00	Ambulatory visit[15] **s.c. injection of BI 3006337 or placebo**			x								
		842:00	11:00	Local tolerability at injection site[12]	B							x	x	x	x
	43	1007:00	08:00	Admission to trial site, BW[3,5]								x			
		1008:00	09:00	**s.c. injection of BI 3006337 or placebo**			x	x							
		1010:00	11:00	Local tolerability at injection site[12] 240 mL fluid intake[10]	B								x		
		1011:00	12:00				x					x		x	x
		1012:00	13:00	Lunch											
		1015:00	16:00	Snack (voluntary)[10]			x							x	x
		1018:00	19:00	Dinner											
		1019:00	20:00				x					x		x	x
		1023:00	24:00				x					x			
	44	1030:00	07:00	Local tolerability at injection site[12]		x			x			x		x	x
		1030:50	07:50							x					
		1031:00	08:00	Start OGTT and acetaminophen absorption test			x								
		1031:15	08:15			x				x					
		1031:30	08:30	Local tolerability at injection site[12]		x				x					
		1031:45	08:45			x				x					
		1032:00	09:00			x				x				x	x
		1032:30	09:30			x				x					
		1033:00	10:00	240 mL fluid intake[10]		x				x				x	x
		1034:00	11:00			x				x					
		1035:00	12:00	Lunch[10]		x	x			x				x	x
		1036:00	13:00			x									
		1037:00	14:00			x									
		1039:00	16:00	Snack (voluntary)[10]		x	x							x	x
		1041:00	18:00			x						x			
		1042:00	19:00	Dinner											
		1043:00	20:00				x							x	x
		1047:00	24:00				x					x			
	45	1054:00	07:00	Local tolerability at injection site[12]											
		1055:00	08:00	Breakfast[10]			x					x	x	x	x
		1059:00	12:00	Lunch											
		1063:00	16:00	Snack (voluntary)											
		1066:00	19:00	Dinner											

Visit	Day	Planned time (relative to trial activities[9]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[19]	Acetaminophen in plasma	BI 3006337 in serum	ADAs/Nab[8]	Blood biomarkers[13]	Glucose and insulin in plasma	Blood Biobanking (optional)	12-lead ECG[18]	C-SSRS examination	Vital signs (BP, PR, BT)	Questioning for AEs and concomitant therapy[6]
2	46	1080:00	09:00	Breakfast (voluntary)[10], Discharge from trial site	B[7]		x		x				x	x	x
	50	1176:00	09:00	Ambulatory visit			x							x	
3	64 to 74			End of trial (EOT) examination[16], Ambulatory visit	A		x	x	x		x[14]	x	x	x	x

1. Trial participants must be informed and written informed consent obtained prior to starting any SCR procedures. 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.
2. The time is approximate; the respective procedures are to be performed and completed within 3 h prior to drug administration on Day 1 of Visit 2.
3. COVID-19 Antigen Rapid Test (Nasopharyngeal Swab) will be performed at SCR and prior to each admission to site.
4. Including infectious serology test.
5. In addition, a drug SCR and alcohol breath 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 Flow Chart above.
7. TSH will only be collected at this time.
8. Blood samples for ADA/Nab analysis.
9. Planned time relative to administration of BI 3006337 or placebo at Visit 1.
10. If several actions are indicated at the same time point, the intake of meals or liquids will be the last action.
11. Randomisation will be done following enrolment and the latest prior to administration of trial medication (BI 3006337 or placebo) at Day 1 of Visit 2.
12. Local tolerability (refer to Section 5.2.5.1)
13. BM samples (refer to Section 5.4)
14. Only blood samples for biobanking will be collected at EOT visit
15. For ambulatory visits, kits assignment must be performed the day before the visit, otherwise the IMP will not be ready for administration.
16. End of trial examination includes physical examination (potential injection site reactions), BW, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
17. The ECG recording must be performed in triplicate ECGs at this time.
18. All resulting ECGs will be transferred electronically to the central ECG lab except for SCR and EOT.
19. A & B: safety laboratory sets (refer to section 5.2.3)

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
API	Active Pharmaceutical Ingredient
AST	Aspartate Transaminase
$\%AUC_{tz-\infty}$	Percentage of $AUC_{tz-\infty}$ obtained by extrapolation
AUC	Area under the Curve
AUC_{0-10h}	Area under the concentration-time curve of the analyte in serum over the time interval from 0 to 10 h
AUC_{0-24h}	Area under the concentration-time curve of the analyte in serum over the time interval from 0 to 24 h
AUC_{0-168h}	Area under the concentration-time curve of the analyte in serum over the time interval from 0 to 168 h
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in serum over the time interval from 0 to the last quantifiable data point
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in serum over the time interval t_1 to t_2
BALP	Bone-specific Alkaline Phosphatase
BI	Boehringer Ingelheim
BMI	Body Mass Index (weight divided by height squared)
BP	Blood Pressure
BW	Body Weight
CA	Competent Authority
C_{avg}	Average concentration of the analyte in serum at steady state over a uniform dosing interval τ
CI	Confidence Interval
CL	Total clearance of the analyte in serum after intravascular administration
CL/F	Apparent clearance of the analyte in serum after extravascular administration
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
CTX	Carboxy-terminal Collagen Crosslinks
DEXA	Dual-Energy X-Ray Absorptiometry
DG	Dose Group
DILI	Drug Induced Liver Injury
DIO	Diet-induced
ECG	Electrocardiogram
ECGPCS	ECG pharmacokinetic concentration set
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
GI	Gastrointestinal
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_{ex}	Mean residence time of the analyte in the body after extravascular administration
MTC	Medullary Thyroid Carcinoma
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
NOAEL	No Observed Adverse Effect Level
OC	Osteocalcin
OGTT	Oral Glucose Tolerance Test
P1NP	Procollagen Type 1 N-terminal Propeptide
PD	Pharmacodynamic(s)
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
$t_{1/2}$	Terminal half-life
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
V_{ss}	Apparent volume of distribution at steady state after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

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 GLP-1 and 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 with glucose-lowering features achieved by inducing insulin secretion and reducing the production of glucagon. It also suppresses appetite and retards gastric emptying.

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 (mostly 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 non-alcoholic fatty liver disease (NAFLD) activity score [R16-3177]. Additionally, GLP-1 analogue semaglutide, administered once-daily, was associated with histological NASH resolution in a phase 2b trial [R21-0690] in patients with NASH F2-3, although its effects on fibrosis (including in patients with

compensated cirrhosis) have not been proven [R23-2928]. A phase 3 trial is ongoing [NCT04822181].

The FGF family of hormones mediates 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, a long acting FGF21 analogue efruxifermin showed beneficial effects on steatosis, inflammation, and fibrosis. Efruxifermin was associated with significant improvement vs. placebo in NASH resolution (76% vs. 15%, p <0.001) and 1-stage fibrosis improvement (41% vs. 20%, p<0.05) after 24 weeks of treatment in patients with NASH F2-3 [R23-0311]. The Phase IIb trial in patients with NASH compensated cirrhosis is ongoing [NCT05039450].

Dual GLP-1/FGF21 receptor agonism is therefore expected to reduce liver cell injury (steatosis, oxidative stress, and 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 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.

1.2 DRUG PROFILE

The test product BI 3006337 is a dual GLP-1/ FGF21 receptor agonist designed for the treatment of NASH. It is a GLP-1 and FGF21 antibody 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

BI 3006337 is a highly potent dual GLP-1/FGF21 agonist. In preclinical models of NASH, BI 3006337 significantly improved multiple disease-related components. In the DIO-NASH mice model, BI 3006337 treatment resulted in a superior weight loss compared with a mono-GLP 1 agonist dulaglutide. BI 3006337 reduced liver fat content, and decreased steatosis, lobular inflammation, and ballooning resulting in significant improvement of the mean NAFLD activity score (NAS). While improvements in liver histology may reflect the effect of BI 3006337 on body weight, anti-fibrotic effects of BI 3006337 in the chemically induced rat TAA fibrosis model are weight-loss independent. BI 3006337 treatment (30 nmol/kg) resulted in significant reduction of hepatic hydroxyproline content compared with mono-GLP 1 treatment groups, providing a compelling rationale for positioning BI 3006337 in NASH patients with fibrosis.
There were no BI 3006337 related adverse findings in neurological, cardiovascular, respiratory, and renal function assessments. BI 3006337 effects on gastrointestinal function are expected pharmacodynamics effects and are therefore not considered adverse. These

effects weakened during the course of the treatment and did not produce adverse outcomes on the overall animal health, implicating an acceptable and manageable safety profile for clinical trials.
Further details are shown in the IB Section 5.1.

1.2.2 Toxicology

GLP-1 agonists stimulate glucose-dependent insulin secretion, inhibit food intake and/or suppress appetite, slow gastric emptying, and increase satiety [R18-2829] whilst FGF21 agonists induce increased energy expenditure ([R20-0504, R20-0506]) and are known metabolic regulators of glucose and lipid metabolism ([R20-0508]). Consistent with the modes of action, BI 3006337 treatment-related findings were directly or indirectly (consequential responses due to the decreased food intake, body weight loss and decreased body weight gain) attributable to the expected pharmacological effects of BI 3006337, a GLP 1/FGF21 dual agonist.

The most prominent treatment-related effects were gastrointestinal effects including body weight loss and decreased body weight gain which were associated with the reduced food consumption. The extent of the effect on body weight was the most pronounced during the first week of the treatment period, after which animals started gaining weight (rat) or there was general weight stasis or only minimal weight gain for the remainder of the treatment period (monkey). Similar effects including emesis have been shown with other GLP-1 agonists and the up-titration method has been used to improve tolerability in the clinical trials.

Anticipated with the possible role of FGF21 signaling in skeletal homeostasis [R19-2365], there was a trend of slight decreases in bone formation markers (BAP and OC) in monkeys, but no changes in bone resorption marker (CTX-1), bone density (DEXA and micro-CT), or microscopic correlates. Although these slight changes were minimal in magnitude and not considered adverse, it is recommended that the potential effect on bone mass be monitored by serum bone biomarkers and bone densitometry assessment during the clinical trials with longer duration.

In summary, the toxicology package did not indicate any adverse systemic toxicities nor embryo-fetal toxicity with sufficient margins to the exposures expected at the dose levels in this MD trial. Therefore, the nonclinical safety data support the chronic administration of BI 3006337 to men and women with childbearing potential.

For details, please see IB Sections 5.3 and 8.3.

1.2.3 Nonclinical pharmacokinetics

Two enzyme-linked immunosorbent assay (ELISA) assays were designed to measure full length and therefore active components of the molecule (GLP1 and FGF21). The pharmacokinetics (PK) of BI 3006337 was dose linear after i.v. and s.c. dosing in mice, rats, Cynomolgus monkeys, and minipigs. The ka and bioavailability (F) in non-clinical 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 104 kDa, 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 a slightly higher exposure to active GLP1 than to active FGF21. Monkeys showed a substantially shorter PK profile for active GLP1 than for active FGF21. The cause of the discrepancies in the exposure between GLP1 and FGF21 is unknown.

1.2.4 Clinical experience in humans

The first clinical trial in humans exposed to BI 3006337 (trial 1466-0001, single rising dose [SRD] study) is clinically completed (CTR under preparation) and available data showed that s.c. administration of single doses of BI 3006337 was safe and well-tolerated up to 150 mg.

Investigator defined drug-related AEs were reported for a small proportion of subjects receiving BI 3006337 (7 out of 61 subjects receiving BI 3006337 11.5%). The incidence of drug related AEs was not dose dependent and the drug-related AEs were reported as follows: gastrointestinal disorders (diarrhoea or abdominal discomfort) were observed in two subjects from BI 3006337 group. Injection site reaction with mild severity was reported as AE in one subject only. AEs referring to elevated pancreatic enzymes were reported in 4 subjects (6.6%): pancreatic enzymes increased (both lipase and amylase) in 1 subject, lipase increased in 2 subjects and amylase increased in 1 subject. An AE of lipase increased was also reported in 1 subject (5.3 %) in the placebo group but was considered not related to BI 3006337 by the investigator. There were no severe drug-related AEs, and the majority of AEs was resolved before the end of the study. No hepatotoxicity (protocol specific AE of special interest) was reported for all participants and no clinically significant findings were reported for vital signs. One subject in the 150 mg DG experienced a QRS complex abnormal in the ECG, which was reported as an AE but was not considered related to BI 3006337 by the investigator. [c39685874].

After single subcutaneous dosing, median t_{max} was generally early, in the range of 7 to 15 h, except for 100 mg where median t_{max} was 61.5 h. $AUC_{0-\infty}$ and C_{max} increased dose proportionally (overall dose range 0.2 to150 mg). Inter-individual variability in C_{max} and $AUC_{0-\infty}$ was high (gCV >50%) and moderate (30% <gCV <50%), respectively. Half-lives $t_{1/2}$ (gMeans) ranged from 42.8 to 73.3 h (1.8 to 3.1 days) with moderate inter-individual variability.

Results from an exploratory ANOVA model indicated no effect of 150 mg BI 3006337 on acetaminophen's absorption. The exploratory OGTT showed a reduction of glucose AUC_{0-2} at 150 mg BI 3006337 in comparison with placebo whereas changes in insulin and C-peptide were not different between 150 mg BI 3006337 and placebo.

Body weight did not change under BI 3006337 single dose treatment. However, at the highest doses of BI 3006337 increased HMW adiponectin levels were observed. The highest overall increases were seen at 100 mg and 150 mg with +89 and 81% placebo-corrected HMW adiponectin increases from baseline at 336 h (Day 14) after single s.c. administration of BI 3006337. In addition, a decrease in triglyceride levels was observed at 168 h post dosing with -46, -36, and -35% compared with baseline for 50, 100 and 150 mg BI 3006337. However, when corrected for the placebo response only the difference at 50 mg remained significant.

Single s.c. doses of BI 3006337 did not appear to affect bone formation (BALP, OC) and bone resorption (CTX-1) biomarkers. Small effects regarding a lowering of P1NP in the 50 and 100 mg dose groups could be detected, however the P1NP values remained still in the reference range reported for healthy subjects.

In addition, ADA was assessed pre-dose, 2 weeks after dosing, 4 weeks after dosing and at the end-of-trial visit in 1466-0001. Preliminary data up to 150 mg are available. A total of 7 of 61 subjects receiving BI 3006337 had a positive ADA response. Of these 7 subjects, 4 had pre-existing antibodies and 3 subjects (1 subject in dose group 2 mg, 1 subject in dose group 50 mg, and 1 subjection in dose group 150 mg) had treatment-induced antibodies at the end-of-trial visit. Titres ranged from 21 to 42. Three of 19 placebo-dosed subjects had an ADA response. All 3 placebo-dose subjects had pre-existing antibodies. Titres ranged from 21 to 336. There was no indication of an association between the development of ADAs in some healthy subjects and the overall reported AEs [c39685874].

Further, experience with the single pharmacologically active components of BI 3006337 is 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 (mostly 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 hypoglycaemia, even after prolonged fasting. Among the most common adverse effects for the GLP-1 class are nausea, vomiting, diarrhoea, 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. First degree atrioventricular block was described for GLP1R agonists in clinical trials as well as in the prescribing information for liraglutide (Saxenda) and dulaglutide (Trulicity) [R22-1865, R22-1871, R22-1870]. Other cardiac conduction disorders such as right or left bundle branch block were reported for liraglutide (Saxenda) [R22-1865].

In clinical trials, there were more cases of pancreatitis among GLP1R-agonist treated patients than among placebo-treated patients. Pancreatitis was also reported from marketed use. If pancreatitis is suspected, GLP-1 agonists should be discontinued. They should be used with caution in patients with a history of pancreatitis. The incidence of acute gallbladder disease in clinical trials was greater among GLP1R treated patients compared with placebo in clinical trials. There have been post marketing reports of acute renal failure and worsening of chronic renal failure in patients treated with GLP1R agonists, with a majority of reported events occurring in patients who had experienced nausea, vomiting, diarrhoea, or dehydration. Suicidal behavior and ideation have been mentioned in the US prescribing information for liraglutide (Saxenda) [R22-1865] and semaglutide (Wegovy) [R21-3011].

As the human relevance of GLP1R-induced rodent thyroid C-cell tumours has not been determined, according to US Pis 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, [R22-1865, R22-1867, R22-1871, R21-3011, R22-1874]).

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 AEs in studies with FGF21 agonists were gastrointestinal (diarrhoea 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, and with efruxifermin, a long-acting Fc-FGF21 fusion protein, showing no obvious changes [R20-0507, R22-0899, R22-4307], while a 2017 trial of an intravenously administered, long-acting FGF21 analogue showed increases in BP and HR [R20-0509].

1.2.5 Residual Effect Period

Residual effect period (REP) is the period after the last dose with measurable drug levels and/or with still likely to be present PD effects. The estimated REP of BI 3006337 in humans is 3 weeks.

1.2.6 Drug product

For a more detailed description of the BI 3006337 profile, please refer to the current IB [c30782091].

1.3 RATIONALE FOR PERFORMING THE TRIAL

The current trial will be performed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 3006337 in Japanese male subjects, thus supporting the Phase II clinical development program of BI 3006337 in NASH in Japanese patients. Moreover, the trial will be performed to gain PK information at steady state exposure.

BI 3006337 is a dual GLP-1/FGF21 receptor agonist being developed for the treatment of compensated cirrhosis due to NASH to prevent a first clinical decompensating event and improve all-cause survival. Both GLP-1 and FGF21 agonists are currently in clinical development for this same indication either as monotherapy or as part of combination therapies, with promising results.

Cumulative data for BI 3006337 from non-clinical disease models demonstrate treatment effects across multiple NASH-relevant pathological aspects, including weight loss, improved lipid profile, insulin sensitivity, liver steatosis, hepatic lobular inflammation, and reduced hepatocyte injury and liver fibrosis (see the current IB [c30782091]). These results warrant clinical development for patients with NASH cirrhosis.

Preliminary data from 26-week chronic toxicity studies showed that there were no adverse target organs of toxicity associated with systemic exposures providing high safety margins. Overall, the nonclinical safety data support the administration of BI 3006337 to humans for up to chronic duration.

Single doses of BI 3006337 have been investigated in healthy male subjects in trial 1466-0001. BI 3006337 was administered s.c. at doses of 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. BI 3006337 was safe and well-tolerated for the doses up to 150 mg.

The multiple rising dose (MRD) and proof of clinical principle (PoCP) trial 1466-0002 is currently assessing safety, tolerability, PK and PD, and signs of efficacy of BI 3006337 in overweight or obese trial participants.

The study of exploratory and probable valid biomarkers will be hypothesis-generating or supportive to endpoints. Study findings will be used to expand our understanding of the mechanism of BI 3006337 action to support subsequent trial designs regarding dose and schedule selection.

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

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

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.

1.4.2 Risks

The trial participants are exposed to the risks of the trial 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, 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 venepuncture for blood sampling.

For SRD part, the total volume of blood withdrawn during the entire trial per trial subject will not exceed the volume of a normal blood donation (400 mL) and no health-related risk to the trial subjects is expected from this blood withdrawal. For MD part, the total volume of blood withdrawn during the entire trial per trial subject will exceed 400 ml but will not exceed 600 ml. This is acceptable considering the duration of the trial, and no health-related risk to the trial subjects is expected from this blood withdrawal.

In the usual Phase I settings, the trial participants stay on site in small groups for several days and there is a potential risk for spreading SARS-CoV-2 across the trial participant group or site staff. Some trial procedures, e.g., collecting blood samples, recording of ECGs, 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 sites detailing specific cautionary measures (e.g., hygiene rules, wearing of face masks, and physical distance), which is filed in the investigator site file (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 core safety pharmacology endpoints (cardiovascular, respiratory, and neurological function) were evaluated as part of a 26-week GLP repeat dose toxicity study in monkeys.

No mortality or adverse findings were associated with BI 3006337 administration in the neurological or respiratory function. Although a trend of BI 3006337 related increase in the heart rate was detected, it was considered non-adverse based on the lack of apparent dose-related relationship and associated effects on other ECG parameters. This and other BI 3006337 related non-adverse effects were fully reversible after the 12-week recovery period.

The most prominent treatment-related effects were gastrointestinal effects including body weight loss and decreased body weight gain, which were associated with the reduced food consumption. In monkeys, the extent of the effect on the body weight was the most pronounced during the first 5 weeks of the treatment period and during the recovery period, marked body weight gain was observed. Similar effects including emesis have been shown with other GLP-1 agonists, and the up-titration method has been used to improve tolerability in the clinical trials.

Based on the injection site reactions observed in monkeys, local irritation in humans is possible. Monitoring the injection site is recommended in human trials.

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 (Dual energy X-ray absorptiometry [DEXA] and micro-CT) or microscopic correlates. The nonclinical toxicology package did not indicate any adverse toxicities at doses providing high safety margins.

Assuming linear and dose-proportional pharmacokinetics, an accumulation of +10% with once weekly dosing (based on a half-life of 45 h) and based on the observed single dose parameters C_{max} (1290 µg/L) and $AUC_{0-\infty}$ (80600 µg*h/L) at 150 mg in trial 1466-0001, the steady state parameters at 150 mg are predicted as $C_{max,ss}$ =1290 µg/L* 1.1 = 1419 µg/L and $AUC_{\tau,ss}$ = 80600 µg*h/L. Hence, these predicted exposures at the proposed dose levels in this MD trial are covered by sufficient margins in the toxicity studies (IB Section 5.3 and 8.3).

Biological agents have an inherent potential for immune-mediated effects with a variety of associated adverse effects, including immediate and delayed reactions. The risk of immunogenicity for BI 3006337 has been assessed in the SRD study in humans. So far there is no indication of an association between the development of ADAs in some healthy subjects and the overall reported AEs. However, the immunogenicity results at this stage of drug development, considering the low number of subjects and the short duration of the single-dose trials, should be interpreted with caution. ADA generation and immunogenicity-related safety monitoring will continue in future trials with BI 3006337. Due to the s.c. administration, local intolerabilities may occur. Trial participants are exposed to risks of trial procedures and risks related to the exposure to the trial medication.

Non-clinical 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 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.

The following safety measures will be applied in this trial to minimize the risk for the trial participants:

- Careful dose selection (refer to Section 4.1.2)
- Preliminary measurement of BI 3006337 serum concentrations and preliminary determination of PK parameters
- Subjects with conditions that may pose a safety risk in the trial will be excluded (refer to Section 3.3.3)
- An extensive safety laboratory will be performed with special focus on full blood exam also including bone turnover biomarkers
- For safety reasons, the drug administrations of each cohort in SRD part will be separated by at least 72 h (between last trial subject in the current cohort and first trial participant of the next cohort) to cover the period of highest risk/peak effect.
- A thorough ECG monitoring during in-house days and additionally on selected ambulatory visits
- 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)
- The trial participants will be monitored for vital signs and local tolerability at the injection site
- During the stay on site, the trial participants will be under medical observation and thoroughly monitored for AEs such as systemic hypersensitivity reactions including anaphylactic reaction (refer to Section 4.1.4 and 4.2.1)
- A documented safety review of all available safety data will be conducted at least prior to proceeding to multiple dose part.
- In addition, a screening of SARSCoV2 has been implemented to be performed as part of the safety assessments at the screening visit (Visit 1). Trial participants positive in the results for this virus are not eligible for the trial in accordance with exclusion criterion 19 and will be excluded from the trial. During the ambulatory visits, trial participants are allowed to enter the site only after it was confirmed that trial participants 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 trial participants´ safety; see also Section 5.2.6.1.4.

Consistent with the FDA draft guidance intitled “Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials,” due to a potential centrally mediated mechanism of action of the compound, prospective assessment of suicidal ideation and behaviour is included in the MD part of this trial.

1.4.3 Discussion

In summary, 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, trial participants 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. 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 trial participants.

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, pharmacokinetics (PK), and pharmacodynamics (PD) of BI 3006337 in healthy male subjects following s.c. administration of single rising doses and multiple doses over 6 weeks.

2.1.2 Primary endpoint

The primary endpoint to assess safety and tolerability of BI 3006337 is the occurrence of any treatment-emergent adverse event assessed as drug-related by the investigator. This is expressed as the percentage of subjects treated with investigational drug who experience such an event.

2.1.3 Secondary endpoints

The following pharmacokinetic parameters will be determined if feasible:

SRD part:

- $AUC_{0-\infty}$ (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)

MD part (after the last dose):

- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in serum over the dosing interval tau at steady state) after the last dose in Week 6
- $C_{max,ss}$ (maximum measured concentration of the analyte in serum at steady state) after the last dose in Week 6

[redacted]

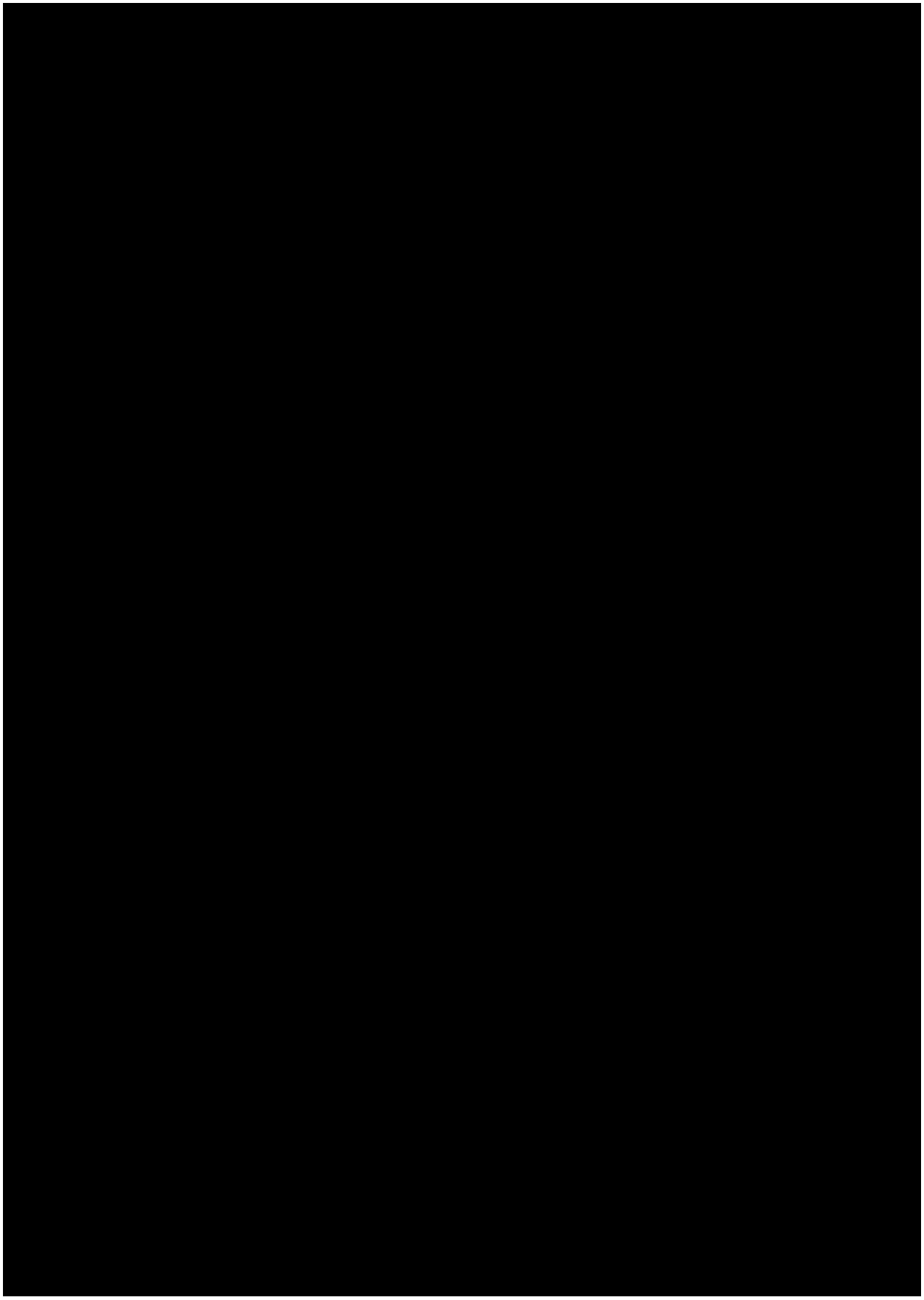
[redacted]

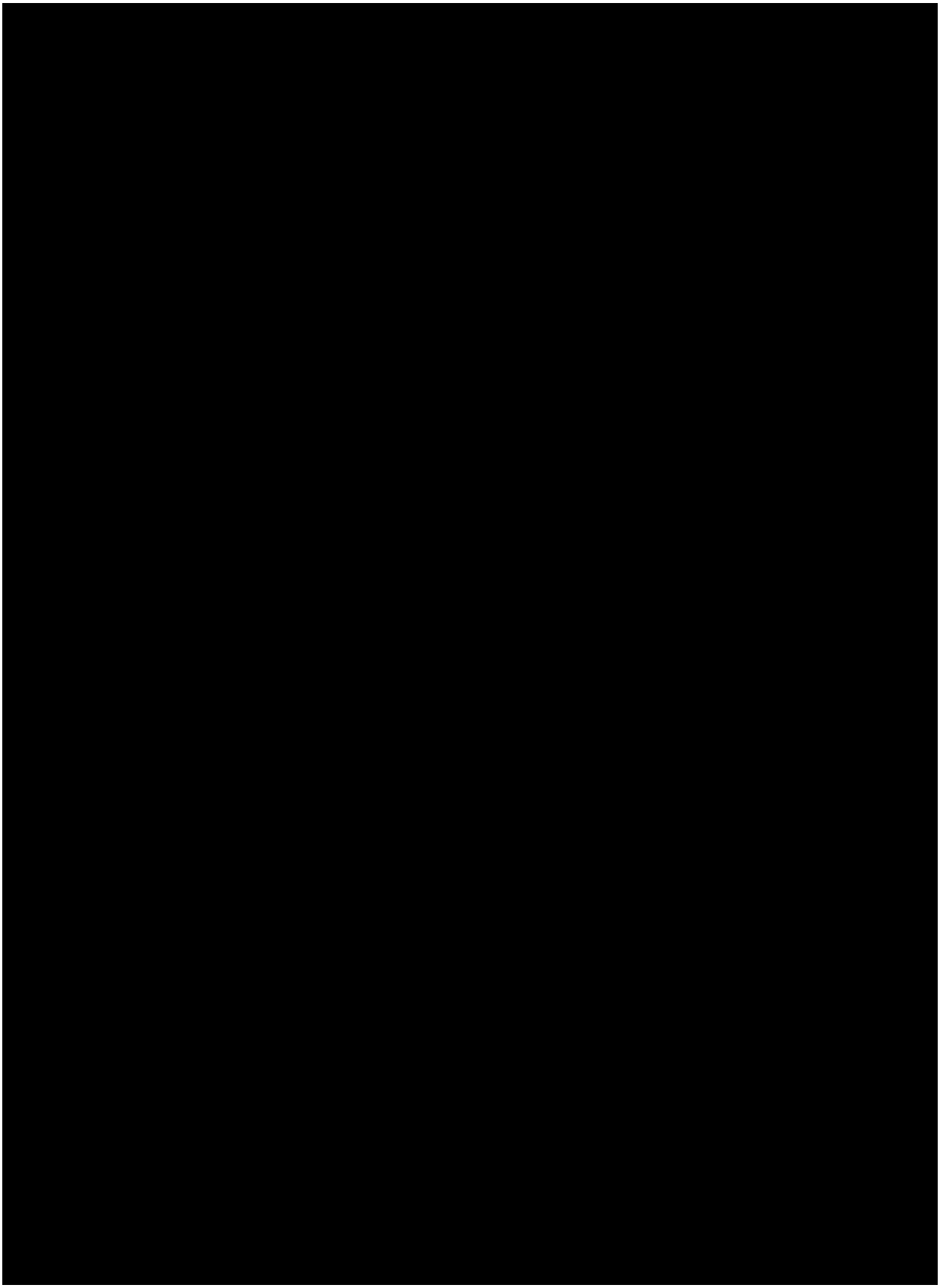
2.2.2.1 Safety and tolerability

Safety and tolerability of BI 3006337 will be assessed based on:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure (BP), pulse rate (PR), and intra-axillary body temperature (BT))
- Local tolerability assessed by investigator
- Columbia-Suicide Severity Rating Scale (C-SSRS) (MD part)

[redacted]





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This single-rising dose and multiple dose trial is designed as blinded to subject (refer to Section 4.1.5), randomised, and placebo-controlled within parallel dose groups.

SRD part:

It is planned to include a total of 24 healthy male subjects in the single dosing part. The subjects will be assigned to 3 groups consisting of 8 subjects per group; the groups will be dosed sequentially (see Figure 3.1: 1). However, the addition of further dose groups for the evaluation of safety findings is subject to a substantial CTP amendment and requires approval by the competent authority.

MD part:

It is planned to include a total of 12 healthy male subjects in the multiple dosing part (see Table 3.1: 1). Within this dose group, 9 subjects will receive BI 3006337 and 3 will receive placebo. Only one dose is tested within each dose group.

The trial schedule and design are depicted in Figure 3.1:1 below.

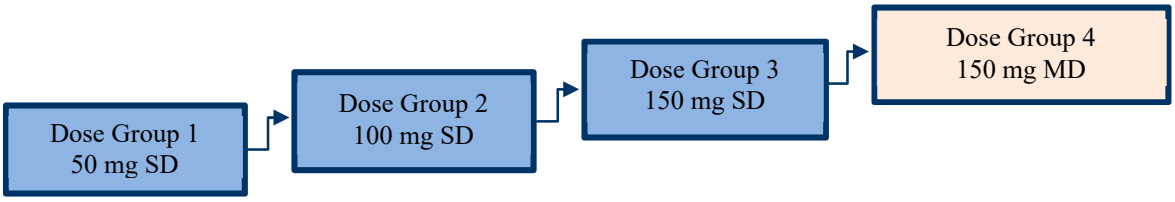


Figure 3.1: 1 Trial design

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

Table 3.1: 1 Dose groups

Dose Group	1	2	3	4
Dose (mg)	50	100	150	150
Number of subjects	8	8	8	12
Subjects to receive placebo	2	2	2	3
Subjects to receive BI 3006337	6	6	6	9

In SRD part, the groups will be dosed consecutively in ascending order, and a time interval of at least 3 days will be maintained between the last drug administration to subjects in the previous dose group and the first drug administration to subjects in the subsequent dose group. The decision to treat the next dose group will be based upon safety of all the preceding dose groups. The next dose group will only be treated if, in the opinion of the investigator, no

safety concerns have arisen in the preceding dose groups, and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.1 and 3.3.4.3).

The decision proceeding to MD part will be based upon safety and tolerability of all the preceding dose groups in SRD part. MD part will only be treated if, in the opinion of the principal investigator and clinical trial leader (CT Leader), no safety concerns have arisen in the preceding dose groups, and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.1 and 3.3.4.3).

At minimum, data from 4 subjects who received active drug in each dose group need to be available for escalation to a higher dose. The minimum data set for review consists of the following:

- AEs in the current and preceding dose groups up to at least 72 h after injection 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 at the site, as provided in the preliminary cardiac safety summary reports by the central ECG laboratory (see Section 5.2.4) in the current and preceding dose groups up to at least 72 h after start of injection
- Vital signs in the current and preceding dose groups up to at least 72 h after injection
- Clinical laboratory tests in the current and preceding dose groups up to at least 72 h after injection
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

A documented safety review of all available safety data will be conducted at least prior to proceeding to MD part. Safety reviews can be conducted face-to-face or by video/telephone conference. The CT Leader is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the principal investigator (or an authorised deputy) and the CT Leader (or an authorised deputy) and will be filed in the investigator site file (ISF) and trial master file (TMF).

Furthermore, an unscheduled safety review meeting can be requested anytime by the principal investigator or the sponsor of the trial (for instance, due to the occurrence of any unforeseen adverse events).

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

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

For single-rising dose and multiple dose trials, the sequential rising dose design described in Section 3.1 is widely established in Phase I clinical development and includes adequate measures to ensure subjects' safety.

Single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. 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 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 single or multiple rising dose trials involving healthy volunteers to include a placebo group to control for safety and tolerability of the trial medication.

SRD part: Each dose group consists of 8 subjects, with 6 randomised to active treatment, and 2 randomised to placebo. For data analysis purposes, the placebo control group will include all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics.

MD part: Each dose group consists of 12 subjects, with 9 randomised to active treatment, and 3 randomised to placebo. For data analysis purposes, the placebo control group will include all subjects of all dose groups treated with placebo. 9 subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 24 healthy males in SRD part and 12 healthy males in MD part will enter the trial. The actual number of subjects entered may exceed the total of 36 if additional intermediate doses are tested (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the trial because no data on reproductive toxicology are available at this time.

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 trial will be performed in healthy subjects.

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

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 (BP, PR), 12-lead ECG, and clinical laboratory tests
2) Japanese ethnicity, according to the following criteria: born in Japan, have lived outside of Japan < 10 years, and have parents and grandparents who are Japanese
3) Age of 18 to 45 years (inclusive)
4) BMI of 18.5 to 25.0 kg/m^2 (inclusive)
5) Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
6) Subjects who agree to minimise the risk of making their partner pregnant by fulfilling any of the following criteria starting from the start of injection of trial medication until 30 days after end of injection of trial medication:
    - Use of adequate contraception, any of the following methods plus condom: intrauterine device, combined oral contraceptives that started at least 2 months prior to the first drug administration
    - Vasectomized (vasectomy at least 1 year prior to enrolment)
    - Surgical sterilization (including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy) of the subject's female partner
    - Female partner is postmenopausal, defined as no menses for 1 year without an alternative medical cause

3.3.3 Exclusion criteria

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

1) Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2) Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or PR outside the range of 50 to 90 bpm at screening visit
3) Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4) Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5) Clinically relevant gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6) Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)

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) Relevant chronic or acute infections (including positive result for human immunodeficiency virus (HIV), hepatitis A virus, hepatitis B virus, hepatitis C virus, and syphilis infection at screening)
10) History of tuberculosis (TB) or positive finding in interferon-gamma release assay (IGRA)
11) Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
12) History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
13) 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)
14) Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
15) Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
16) Inability to refrain from smoking during in-house confinement
17) Alcohol intake (from signing of ICF to EOT)
18) Drug abuse or positive drug screening
19) Positive result for COVID-19 Antigen Rapid Test (Nasopharyngeal Swab) or clinical symptoms suggestive for this disease at screening visit
20) Blood donation of more than 200 mL within 30 days or 400 mL within 12 weeks, or plasmapheresis and platelet apheresis within 2 weeks prior to planned administration of trial medication or intended blood donation during the trial
21) Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
22) Inability to comply with the dietary regimen of the trial site
23) A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or any other relevant ECG finding at screening
24) A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
25) 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, or has a condition that would not allow safe participation in the study

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

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

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

28) 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

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

30) Any lifetime history of suicidal behaviour, any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months prior to screening (MD part only)

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may withdraw consent to trial participation as a whole (‘withdrawal of consent’) with quite 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, 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, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.6), the subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP 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 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1) The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer

2) The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future

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

4) The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events (AEs), or diseases)
5) 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
6) The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
7) Occurrence of signs of suicidal behaviour or ideation (see section 5.2.5.2)
8) Occurrence of pancreatitis

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

If new safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.

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 and dose stopping criteria

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reason 4 is met, the trial should be discontinued immediately):

1) Failure to meet expected enrolment goals overall or at a particular trial site
2) The sponsor decides to discontinue the further development of the investigational product
3) Deviation from GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4) New toxicological findings, serious AEs, or any safety information invalidating the earlier positive benefit-risk assessment (see Section 3.3.4.1)

The dose escalation of BI 3006337 will be stopped if:

5) More than 50% of the subjects at one dose level show drug related and clinically relevant adverse events of moderate or severe intensity, or if at least two subjects of the same dose

group have drug-related severe non-serious adverse events, or if at least one drug-related serious adverse event is reported

6) At least 2 subjects who received active treatment at one dose level have relevant individual QT prolongations, i.e., a QTc increase of greater than 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording

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 some subjects do not complete the trial (including subjects non-evaluable for PK), they may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacologist and the Trial Statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

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
Mode of administration:	s.c.
Duration of use:	SRD part: Single dose, MD part: 6 weeks q.w. dosing

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
Mode of administration:	s.c.
Duration of use:	SRD part: Single dose, MD part: 6 weeks q.w. dosing

4.1.2 Selection of doses in the trial and dose modification

The doses in the trial were selected on the bases of the data obtained from Caucasian SRD trial (1466-0001) to allow ethnic comparison in PK and safety.

The doses selected for this trial cover the subtherapeutic as well as the estimated therapeutic range and include a safety margin (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects are allocated to a dose group, the following subjects will be allocated to one of the other dose groups. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. Because the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. For this purpose, the randomisation scheme will be provided to the trial site in advance. Numbers of the randomisation scheme will be allocated to subjects with “first come first served” principle. Subjects are then assigned to treatment according to the randomisation scheme.

The randomisation procedure is described in Section 7.4.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The dose volume for placebo corresponds to dose volume of the corresponding dose level.

Table 4.1.4: 1 BI 3006337 and placebo treatments, s.c. administration

Dose group	Substance	Pharmaceutical form	Unit strength	Total dose per injection
1	BI 3006337	Solution for injection	50 mg/mL	50 mg
2	BI 3006337	Solution for injection	50 mg/mL	100 mg
3	BI 3006337	Solution for injection	50 mg/mL	150 mg
4	BI 3006337	Solution for injection	50 mg/mL	150 mg
1-4	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 Instruction for Preparation and Administration of Parenteral study medication provided by the sponsor. The investigator can decide at any time to discontinue dosing in case of intolerability or safety concerns.

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®, B. Braun Melsungen, 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 on the same side of the abdominal wall. In the MD part, the subsequent doses should be administered on the alternate side 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.For restrictions with regard to diet, see Section 4.2.2.2.

In SRD part, subjects will be kept under close medical surveillance until at least 72 h after drug administration.

In MD part, subjects will be kept under close medical surveillance until at least 72 h after drug administration during hospitalisation and until at least 2 h after drug administration at the ambulatory visits. Hypersensitivity reactions should be treated according to medical standards (see Section 4.2.1).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 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.

The table below summarises the masking/blinding level of individual functions, roles and responsibilities involved in the trial.

Table 4.1.5.1: 1 Blinding level of individual functions

Role/function	Timing of Unblinding / receiving access to the treatment information (including rationale)
Subject/Participant	This trial is blinded to the subject /participant. The subject/participant's treatment information will be provided to the site after the trial has completed.
Investigator/Site Staff	The randomisation scheme will be provided to the trial site prior to randomisation for preparation of medication.
Sponsor trial team	As requested during trial conduct.
Bioanalytical Staff	As requested for analysis of bioanalytical samples.
Pharmacologist/ Pharmacometrician	As requested for analysis of pharmacokinetic, pharmacodynamic data or Pharmacometric modelling.

Table 4.1.5.1: 1 Blinding level of individual functions (cont.)

Role/function	Timing of Unblinding / receiving access to the treatment information (including rationale)
ECG laboratory	Within the central ECG lab, the staff involved with interval measurements will be blinded with respect to subject, treatment, recording date and time as well as planned time points of the ECGs. The staff involved with the morphological analyses will be blinded with respect to treatment. For the quality control of the measurements, certain members of the ECG evaluation team will review the entire portfolio of ECG measurements for each subject blinded to date, time, and time point. For preliminary cardiac safety reports for dose escalation decisions the central lab will be fully blinded.

During the time a role/function is blinded according to the table above, the randomisation schemes and medication kit lists (i.e., the treatment information) are kept restricted by the global Randomisation Team per Sponsor SOP.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

4.1.5.2 Unblinding and breaking the code

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

4.1.6 Packaging, labelling, and re-supply

4.1.6.1 BI 3006337 and placebo

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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. Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 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

Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the Institutional Review Board (IRB)
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site
- Approval/notification of the regulatory authority, e.g., competent authority
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol

Only authorised personnel documented in the form 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

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 return 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 returned to the sponsor. 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

Except for acetaminophen administration to perform the acetaminophen absorption test (see Section 4.2.1.1.1) and glucose administration to perform the OGTT (see Section 4.2.1.1.2) , no additional treatment is planned. However, in case of AEs in need of treatment, the investigator can authorize symptomatic therapy. In those cases, trial participants 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.

Prolonged or severe gastrointestinal (GI) events

There are no special emergency procedures to be followed. Most frequent AEs of GLP-1 and 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.

Hypoglycaemic events

Symptoms of mild to moderate hypoglycaemia, or blood glucose levels below 49 mg/dL (measured using a 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 hypoglycaemia 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 hypoglycaemia may lead to unconsciousness. Trial participants experiencing hypoglycaemia 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 trial participant safe for discharge.

Hypoglycaemic 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 5.2.6.2.4).

Suicidality

In case of signals of suicidal ideation or behaviour, the Investigator should discontinue treatment with the trial medication, notify the Sponsor and the subject should be referred to an appropriate psychiatric clinic.

Systemic hypersensitivity

In case of any systemic hypersensitivity including anaphylactic reaction emerging during or after injection(s) of trial medication, the investigator should:

- Immediately stop further injections for this individual subject
- Treat in accordance with severity of the reaction and local standard of care, with systemic antihistamines, i.v. steroids, and in case of a severe allergic reaction (e.g., anaphylactic reaction), epinephrine
- Draw a blood sample for the evaluation of IgE, histamine, serum tryptase, and complement components (see laboratory manual in the ISF)
- Draw a blood sample for the evaluation of ADA

When a delayed hypersensitivity reaction is suspected, please draw a blood sample for laboratory assessment and evaluate for signs of extra-cutaneous organ involvement. The decision to discontinue treatment and/or restart treatment after resolution of the reaction should be based on reaction type and severity.

4.2.1.1 Non-investigational medicinal product

4.2.1.1.1 Acetaminophen Syrup

Table 4.2.1.1.1:1 below displays the characteristics of the non-investigational medicinal product for the acetaminophen absorption test performed in this trial.

Table 4.2.1.1.1:1 Characteristics of Acetaminophen Syrup

Substance:	Acetaminophen Syrup
Pharmaceutical formulation:	Solution
Unit strength:	20 mg per 1 mL
Posology:	Single doses on Day -1, Day 2, and Day 44 of Visit 2 (MD part only)
Route of administration:	Oral
Frequency of dosing:	Single doses

Calonal Syrup 2% will be supplied as commercially available product by a public pharmacy (R23-4465). Transport and storage are under the responsibility of the investigator and must comply with the pertinent information in the prescribing information of the drug product used in the clinical trial. No additional labelling is planned.

Documentation on the commercial drug product, containing at least the following information, must be available on-site in the ISF:

- BI trial number
- Investigator name
- Trade name of drug product
- Substance International non-proprietary name
- Holder of marketing authorization
- Pharmaceutical dosage form, quantity of dosage units
- Storage conditions
- Use-by date
- Batch/lot number
- Point of purchase
- Date of receipt
- Recipient (name and function)

In addition, documentation of drug purchase, including identification of the drug product and quantity, must be available at the clinical site and filed in the ISF.

4.2.1.1.2 TRELAN-G75

Table 4.2.1.1.2:1 below displays the characteristics of the non-investigational medicinal product for the oral glucose tolerance test performed in this trial.

Table 4.2.1.1.2:1 Characteristics of TRELAN-G75

Substance:	Carbohydrate solution
Pharmaceutical formulation:	Solution
Unit strength:	75 mg per bottle (225 ml)
Posology:	SRD part: Single doses on Day -1 and Day 2 of Visit 2 MD part: Single doses on Day -1, Day 2, and Day 44 of Visit 2
Route of administration:	Oral
Frequency of dosing:	Single doses

TRELAN-G75 will be supplied as commercially available product by a public pharmacy (R23-4466). Transport and storage are under the responsibility of the investigator and must comply with the pertinent information in the prescribing information of the drug product used in the clinical trial. No additional labelling is planned.

Documentation on the commercial drug product, containing at least the following information, must be available on-site in the ISF:

- BI trial number
- Investigator name
- Trade name of drug product
- Substance International non-proprietary name
- Holder of marketing authorization
- Pharmaceutical dosage form, quantity of dosage units
- Storage conditions
- Use-by date
- Batch/lot number
- Point of purchase
- Date of receipt
- Recipient (name and function)

In addition, documentation of drug purchase, including identification of the drug product and quantity, must be available at the clinical site and filed in the ISF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and lifestyle

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. Standardised meals will be served at the times indicated in the Flow Chart.

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, subjects are allowed to have an evening Snack (voluntary).

Furthermore, no food is allowed within at least 12 h before and 4 h after each OGTT or intake of acetaminophen for testing gastric emptying.

From 1 h before start of each OGTT/acetaminophen intake until lunch (4h after start), fluid intake is restricted to the liquid administered with OGTT or acetaminophen, and an additional 240 mL of water served at 2 h after start.

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.

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 trial centre under supervision of the investigating physician or a designee. The measured plasma 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 screening, the medical examination will include demographics, height, and body weight, smoking and alcohol history (alcohol history 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 (BP, PR, and intra-axillary body temperature), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of body weight 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 (heart rate is considered to be equal to pulse rate) will be measured by a BP monitor at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible. Intra-axillary 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 the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required. The parameters to be assessed are listed in Tables 5.2.3: 1, 5.2.3: 2, and 5.2.3: 3. Reference ranges will be provided in the ISF.

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 SRD Part: Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	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 (International Normalization Ratio)	X	X	X	--	X	X
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	X	--	X	X
	ALT [Alanine aminotransferase] /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	--	--	--	--	--

A: parameters to be determined at Visit 1 (SCR examination)
B: parameters to be determined at Visit 2 on Day -1
C: parameters to be determined at Visit 2 on Days 1, 2, 3, 4, 8, and 15
D: parameters to be determined at Visit 2 on Day 6
E: parameters to be determined at Visit 2 on Days 22 and 29
F: parameters to be determined at Visit 3 (EOT examination)

Table 5.2.3: 1 SRD part: Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D	E	F
Substrates	Glucose	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
	High density lipoprotein (HDL) cholesterol	X	--	X	--	--	X
	Low density lipoprotein (LDL) cholesterol	X	--	X	--	--	X
Electrolytes	Sodium	X	X	X	--	--	X
	Potassium	X	X	X	--	--	X
	Calcium	X	X	X	--	--	X
	Inorganic phosphate	X	X	X	--	--	X
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

A: parameters to be determined at Visit 1 (SCR examination)
B: parameters to be determined at Visit 2 on Day -1
C: parameters to be determined at Visit 2 on Days 1, 2, 3, 4, 8, and 15
D: parameters to be determined at Visit 2 on Day 6
E: parameters to be determined at Visit 2 on Days 22 and 29
F: parameters to be determined at Visit 3 (EOT examination)

Table 5.2.3: 2 MD Part: Routine laboratory tests

Functional lab group	Test name	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	Reticulocytes, absol.	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
	HbA1c	X	X
Automatic WBC differential (relative and absolute)	Neutrophils	X	X
	Eosinophils	X	X
	Basophils	X	X
	Monocytes	X	X
	Lymphocytes	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
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X
Enzymes	AST/GOT, SGOT	X	X
	ALT/GPT, SGPT	X	X
	ALP	X	X
	GGT	X	X
	CK	X	X
	CK Isoenzyme MB [only if CK is elevated]	X	X
	Insulin	X	X
	Lactate Dehydrogenase	X	X
	Lipase	X	X
	Amylase	X	X
	Calcitonin	X	--
Hormones	TSH	X	X*
Urinalysis (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leucocytes (qual)	X	X
	Urine pH	X	X

A: parameters to be determined at Visit 1 (screening examination) and Visit 3 (EOT examination)

B: parameters to be determined at Visit 2 on Day -1, 2, 3, 4, 8, 15, 18, 29, 36, 43, and 46 (*with the exception that TSH will only be tested at Day -1, 15, and Day 46)

Table 5.2.3: 2 MD part: Routine laboratory tests (cont.)

Functional lab group	Test name	A	B
Substrates	Glucose	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	C-Peptide	X	X
	Protein, Total	X	X
	C-Reactive Protein (Quant)	X	X
	Uric Acid	X	X
	Cholesterol, total	X	X
	Triglyceride	X	X
	High density lipoprotein (HDL) cholesterol	X	X
	Low density lipoprotein (LDL) cholesterol	X	X
Electrolytes	Calcium	X	X
	Sodium	X	X
	Potassium	X	X
	Inorganic phosphate	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

A: parameters to be determined at Visit 1 (screening examination) and Visit 3 (EOT examination)

B: parameters to be determined at Visit 2 on Day -1, 2, 3, 4, 8, 15, 18, 29, 36, 43, and 46 (*with the exception that TSH will only be tested at Day -1, 15, and Day 46)

The tests listed in Table 5.2.3: 3 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. Infectious serology test is planned to be performed at screening only. Drug screening and COVID-19 Antigen Rapid Test (Nasopharyngeal Swab) will be performed at SCR and before each admission to the site (Day -2 of Visit 2 for SRD part and Day -2 of Visit 2 and Day 43 of Visit 2 for MD part).

Table 5.2.3: 3 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Alcohol Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/Ecstasy Opiates Tricyclic antidepressants
Infectious serology (blood)	Hepatitis A antibodies (qualitative) Hepatitis B surface antigen (qualitative)[1] Hepatitis B core antibody (qualitative)[1] Hepatitis B surface antibody (qualitative)[1] Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) TB test (IGRA: QuantiFERON® Gold assay/T-SPOT®.TB) Syphilis test (RPR, TP antibody method)
COVID-19 infection	COVID-19 Antigen Rapid Test (Nasopharyngeal Swab)

1 If hepatitis B surface antigen and/or hepatitis B core antibody is positive, subject will be not allowed participating in this trial. If hepatitis B surface antibody is positive, hepatitis B surface antigen and hepatitis B core antibody is negative, and there is evidence that subject gets hepatitis B virus vaccine, subject will be allowed participating in this trial.

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed prior to each treatment period and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

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

It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4).

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart. 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 to allow reproducible placement throughout the trial.

To achieve a stable heart rate 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 trial 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 the Flow Chart.

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.

Storing

All ECGs will be stored electronically in the system provided by the central ECG lab and stored as print outs.

Data transfer

For time points specified in the Flow Chart, ECGs will be transferred electronically to the central ECG lab<[redacted]> for evaluation (per dose group for preliminary data analysis and at the end of trial for final evaluation).

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded.

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 per time point as specified in the Flow Chart.

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.

The preliminary cardiac safety summary reports from the central lab, which are required for dose escalation meetings, will be based on a statistical analysis of the automatically determined cardiac intervals (HR, QT/QTc, PR, and QRS) from the respective ECG machines. In case of unreliable measurements, a preliminary manual adjudication may be performed and will be noted in the respective report, where applicable.

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 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 locally printed 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 trial, 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 (if identified at the screening visit) 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 receive the appropriate medical treatment.

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, 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.

5.2.5.2 Suicidality assessment

At the time points, specified in the Flow Chart, potential suicidality or suicidal ideations will be assessed using the ‘Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a semi-structured interview which was developed to assess both suicidal behaviour and suicidal ideation to address the need for a summary measure to track change in the severity of suicidality across both clinical settings and treatment trials. Two versions of the C-SSRS will be used in this study: the ‘Baseline/ Screening’ version and the ‘Since-last-visit’ version. The ‘Baseline/ Screening’ questionnaire will be used at the Screening visit and the ‘Since-last-visit’ questionnaire will be used at the rest of the visits including EOT. The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, nurse, or coordinator with C-SSRS training. It has a typical duration of 5 minutes and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 questions related to suicidal behaviour and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed. The investigator has to directly evaluate the scale and write a report considering plausibility and clinical relevance of results. Doubtful outcomes may be repeated, or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behaviour or suicidal ideation type 2, 3, 4 or 5 after start of trial, the investigator is to immediately interview the patient during the clinic visit. If the investigator did not administer the C-SSRS leading to the positive report, he/she has to consult a psychiatrist, if considered necessary. If the positive report is confirmed, appropriate actions for the patient’s safety have to be initiated.

For each report of suicidal ideation type 1, 2 or 3 after start of the trial, the investigator has to decide, based on his/her clinical judgment, whether it represents an AE as defined in the protocol, and, if it is considered to be an AE, reported it accordingly.

All C-SSRS reports of suicidal ideation type 4 to 5 and all reports of suicidal behavior must be reported as SAEs by the investigator and appropriate actions must be taken.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An adverse event (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 considered related or not.

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

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

If such abnormalities already 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 serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- Results in death
- Is life-threatening, which refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- Requires inpatient hospitalisation, or prolongation of existing hospitalisation
- 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 subject 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
- An event that possibly leads to disability will be handled as ‘deemed serious for any other reason’ and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered 'Always Serious'

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described Section 5.2.6.2.

Cancers of new histology 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'**.

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.

Potential severe DILI

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by any of the following alerts (alterations) of hepatic laboratory parameters that occur after the first dose of IMP:

1. AST or ALT elevation ≥3 × ULN and total bilirubin ≥2 × ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
2. AST or ALT elevation ≥3 × ULN and INR ≥1.5 × ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
3. AST or ALT elevation ≥3 × ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), OR
4. AST or ALT elevation ≥5 × ULN

These laboratory 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 laboratory results (ALT, AST, total bilirubin) 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.

Additionally, with subjects having a normal AST and ALT at baseline, the emergence of an isolated AST or ALT elevation between ≥3-fold and <5 × ULN requires repeat testing within 72 hours. DILI Checklist is not required unless repeat testing trigger alerts 1, 2, 3, or 4.

The following events should lead to immediate discontinuation of trial IMP (active or placebo):

- Hepatic injury alert number 1, 2 or 3
- Hepatic injury alert number 4, if persists >2 weeks
- AST or ALT elevation >8 × ULN

Following completion of the DILI Checklist, if the Boehringer Ingelheim IMP cannot be excluded as a possible cause of the DILI event, discontinuation should be made permanent without rechallenge. If an alternate causality, e.g., acute viral hepatitis, is confirmed by the DILI Checklist evaluation, Boehringer Ingelheim IMP may be re-started, if warranted.

5.2.6.1.5 Intensity (severity) of AEs

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

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

5.2.6.1.6 Causal relationship of AEs

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

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

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

- An indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if dose is reduced)

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g., pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, 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
- There is an alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned)
- Disappearance of the event even though the trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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. 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 the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary to describe an AE more precisely.

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 end of trial (the End of Study (EOT) visit):
    - 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 screening 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 and will not be reported in the CTR.

- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g., phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

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 to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

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

5.2.6.2.3 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.

5.2.6.2.4 Hypoglycaemia

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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for BI 3006337 pharmacokinetic analysis

For quantification of BI 3006337 concentrations in serum, 3.5 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.

Details on PK sample collection, processing, handling, and shipment are provided in the Laboratory Manual.

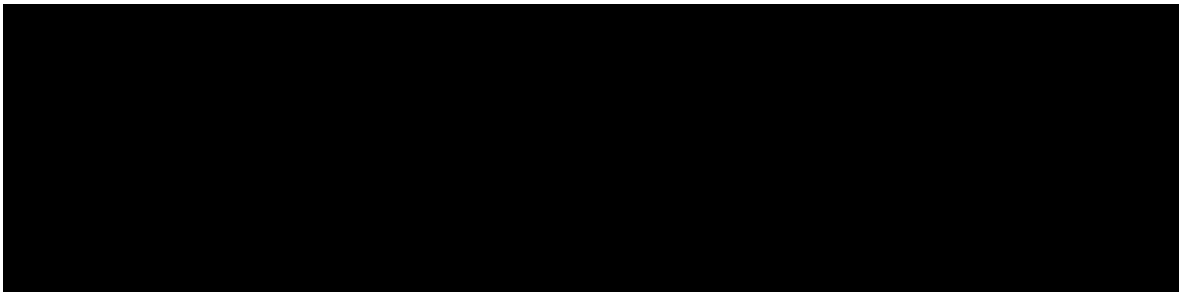
After analysis, the serum samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte including anti-drug antibodies (if applicable) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.

5.3.2.2 Blood sampling for ADA/Nab analysis

For assessment of ADA and Nabs to BI 3006337, 3.5 mL of blood will be taken from an antecubital or forearm vein into a serum (SST_II_Advance_tube) blood drawing tube at the times indicated in Flow Chart. Data regarding Nabs may not be part of the CTR.

Details on ADA and Nab sample collection, processing, handling, and shipment are provided in the Laboratory Manual.

The samples may be used to further characterize ADA/Nab response or to address Health Authority questions regarding the results/methodology, however only data related to the ADA/Nabs will be generated by these addition investigations. The study samples will be discarded no later than 5 years after the final study report has been generated.



5.3.4 Pharmacokinetic – pharmacodynamic relationship

Exposure-response relationships may be investigated graphically for selected PK parameters (e.g. $C_{max,ss}$ and $AUC_{\tau,ss}$) and selected PD, safety/tolerability endpoints including gastric emptying, nausea/vomiting, and HR. If it is considered necessary to further investigate a particular relationship, exposure-response model(s) will be developed. This pharmacometric analysis will then not be part of the CTR but will be reported separately.

5.4 ASSESSMENT OF BIOMARKERS

5.4.1 Biochemical and cellular biomarkers

Blood samples will be collected for the analysis of exploratory biomarkers at visits specified in Flow Chart. The change from baseline measurements may include the following:

- Adiponectin (HMW and total)
- Glucagon
- Markers for bone formation:
  - Procollagen Type 1 N-terminal Propeptide（P1NP)
  - Bone-specific Alkaline Phosphatase (BALP)
  - Osteocalcin (OC)
- Marker for bone resorption:
  - Carboxy-terminal Collagen Crosslinks（CTX-1)

5.4.2 Methods and timing of sample collection

For the measurement of the exploratory biomarkers, 18 ml of blood will be drawn from an antecubital or forearm vein at the time points indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.
The trial samples will be discarded after completion of any investigations, but not later than 2 years after the final trial report has been signed. Any leftover samples or derived material from pre-specified analyses may be used for method development/validation but will be

destroyed no later than 2 years after the final trial report has been signed. Exceptions are remainders of trial samples for which a participant has voluntarily accepted a biobanking option and has provided a signed ICF (see Section 5.5).
Detailed instructions for biomarker blood sampling, processing, and shipment of the different biofluids are provided in a laboratory manual. All lab kit supplies will be provided by the central lab vendor designated by the sponsor.

[redacted]

5.5 BIOBANKING

Blood samples will be collected for biobanking. Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

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

5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment, and storage are provided in the laboratory manual. Samples will be collected prior to the IMP administration. For sampling timepoints, see Flow Chart.

Approximately 8.5 mL blood will be drawn for DNA, 4 mL for plasma and 8.5 mL serum banking purposes. Any analyses on DNA or plasma/serum samples will not be reported in the main CTR. Samples will be collected only where all applicable local regulatory and ethics approvals have been obtained for biobanking.

5.6 OTHER ASSESSMENTS

As indirect PD responses to study drug administration, glucose and insulin in plasma in the OGTT as well as endpoints of acetaminophen in the acetaminophen absorption test (MD part only) are measured and derived at ‘baseline’ on Day -1 of Visit 2 and post-dose on Day 2 and Day 44 (MD part only) of Visit 2.

Endpoints for the exploratory evaluation of the pharmacodynamics of BI 3006337 are:

- Change of plasma glucose, plasma insulin and plasma C-peptide ($AUEC_{0-2}$ and $AUEC_{0-4}$) during an oral glucose tolerance test (OGTT) following administration of BI 3006337 relative to placebo and an OGTT conducted at baseline
- change from baseline in Homeostasis Model of Assessment regarding insulin resistance (HOMA-IR) and regarding β cell function (HOMA-ß) derived from insulin and glucose values obtained during OGTT.
- Change in acetaminophen absorption (AUC_{0-10}, C_{max} and t_{max}) following administration of BI 3006337 relative to placebo and an absorption test conducted at baseline as an indirect determination of the gastric emptying rate

5.6.1 Oral glucose tolerance test

An OGTT will be performed on Day -1, Day 2, and Day 44 (MD part only) of Visit 2.
For the OGTT, a commercially available and ready-prepared glucose solution (TRELAN-G75, see Section 4.2.1.1.2 for details) will be used. Glucose administration will be performed following an overnight fast, which is to start no later than 12 h before the scheduled glucose intake. Before each OGTT subjects are told to empty their bladders. After blood drawing for determination of fasting glucose and insulin in plasma, 225 mL of this glucose solution containing 75 g glucose will be swallowed by the subject, while in a sitting or standing position, under supervision of the investigating physician or an authorised designee.
The glucose solution should be ingested within 3 minutes. At the predefined time points before and after glucose intake indicated in the Flow Chart, blood samples for the determination of plasma glucose and insulin will be collected.
Subjects will be kept under close medical surveillance until after at least 4h following glucose administration. During the first 4 hours after glucose intake, subjects will be confined to bed in a half-supine position unless supine positioning is required for trial-related measurements (e.g., recording of vital signs). For restrictions with regard to diet see Section 4.2.2.2.
Refer to Sections 5.6.1.1.1 and 5.6.1.1.2 for details on blood collection and sample work-up.

Additionally, the following indices of insulin secretion and sensitivity will be derived:
HOMA-IR and HOMA-β% will be calculated from insulin and glucose values according to the calculations below:
$HOMA - IR = (FPI\ [mU/L] * FPG[mmol/L])/22.5$
$HOMA - \beta\% = (20 * FPI\ [mU/L]) / (FPG\ [mmol/L] - 3.5) * 100.$

5.6.1.1 Sampling for OGTT

5.6.1.1.1 Plasma glucose

For determination of plasma glucose, blood samples of 2 mL will be drawn from an antecubital or forearm vein into NaF (sodium fluoride) blood drawing tubes at times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The plasma samples will be discarded after completion of the investigations but not later than 2 years upon the final study report has been signed. The final instruction of blood sampling and processing will be written in a Laboratory Manual.

5.6.1.1.2 Plasma insulin

For quantification of insulin in plasma, 3 mL of blood will be collected from an antecubital or forearm vein into an K3-EDTA (ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.
The plasma samples will be discarded after completion of the investigations but not later than 2 years upon the final study report has been signed. The final instruction of blood sampling and processing will be written in a Laboratory Manual.

5.6.2 Acetaminophen absorption test

An acetaminophen absorption test will be performed on Day -1, Day 2, and Day 44 of Visit 2 for MD part only. The acetaminophen absorption test investigates the gastric emptying rate. For the test, commercially available liquid acetaminophen will be used (Acetaminophen syrup, see Section 4.2.1.1.1 for details). Calonal Syrup 2% (concentration 20 mg/1 mL) to be used as 31 mL to make 620 mg acetaminophen will be administered orally to the trial participant, while in a sitting or standing position, under supervision of the investigating physician or an authorised designee. The acetaminophen syrup should be ingested within 3 minutes. The so-called four-eye principle (two-person rule) should be applied for acetaminophen administration and – if applicable – its preparation if correct dosage cannot be ensured otherwise. Administration will be performed following an overnight fast, which is to start not later than 12 h before the scheduled acetaminophen dosing. For restrictions with regard to diet see Section 4.2.2.2. Subjects will be kept under close medical surveillance until after at least 10 h following acetaminophen administration. During the first 4 hours after acetaminophen intake, subjects will be confined to bed in a half-supine position unless supine positioning is required for trial-related measurements. At the predefined time points indicated in the Flow Chart before and after acetaminophen administration, blood samples for the determination of acetaminophen plasma concentrations will be collected. Refer to Section 5.6.2.1 for details on blood collection and sample work-up and Section 5.6.2.2 for analytics.

5.6.2.1 Plasma sampling for acetaminophen absorption test

For quantification of acetaminophen plasma concentrations, 1 mL of blood will be taken from an antecubital or forearm vein into a K2-EDTA (dipotassium ethylenediaminetetraacetic

acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle. Immediately after drawing the tubes will gently be inverted 5 - 10 times. The sample will be put on wet ice bath in an upright position until centrifugation.

The final instruction of blood sampling and processing will be written in a Laboratory Manual.

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, and planned sampling time. Further information such as matrix and analyte may also be provided.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed to monitor subjects' safety and to determine pharmacokinetic and biomarker parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of a s.c. administered drug and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The biomarkers outlined in Section 5.4 are of exploratory nature.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the Flow Chart.

Trial measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK and biomarkers).

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day -1 and for the first 72 h after trial drug administration, except for urine safety laboratory tests, which can be obtained in the morning of the given day. 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, except for urine safety laboratory tests, which can be obtained in the morning of the given day.

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

For planned blood sampling times, refer to the Flow Chart. 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 pharmacokinetic parameters.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 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 trial. For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.4.

6.2.2 Treatment period

SRD part: Each subject will receive one dose of BI 3006337 or placebo at Visit 2.

MD part: Each subject will receive multiple weekly doses of BI 3006337 or placebo for 6 weeks.

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.

In SRD part, trial 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.

In MD part, trial participants will be kept under close medical surveillance for at least 72 h following s.c. administration of the trial medication during hospitalisation and for at least 2 h following s.c. administration of the trial medication during the ambulatory visits. The trial participants will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee.

For details on time points and procedures for collection of blood samples for PK analysis, ADA/Nab analysis, and analysis of acetaminophen PK, refer to the Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from the time of the subject's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue after the treatment in SRD part and subjects who discontinue treatment before the end of the planned treatment period in MD part should undergo the EOT Visit.

If needed in the opinion of the investigator, additional visits may be scheduled after the EOT Visit for continued safety monitoring.

If a subject discontinues from the trial, the subject will be followed until the investigator or sub-investigator is convinced of the subject's safety. If follow-up is not possible or comes to an end, follow-up should be formally completed after discussion with the sponsor. If a subject stop attending trial assessments, the investigator should assess the subject's status as comprehensively as possible, and the well-being of the subject should be monitored. However, if the subject withdraws from the trial, it is the subject's choice whether or not to participate in further assessments; he or she cannot be compelled.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

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

Any confidence intervals computed are to be interpreted in the perspective of the exploratory character of the trial; i.e., confidence intervals are considered as interval estimates for effects.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.
- Pharmacokinetic 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 deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.
- ECG PK concentration set (ECGPCS): This subject set includes all subjects from the TS who provide at least one pair of a valid drug serum concentration and a corresponding (i.e., time-matched) ECG endpoint to be used in the exposure-response analyses. For placebo subjects, the serum concentration is set to zero and hence always considered as valid. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the Report Planning Meeting (RPM) before database lock. The ECGPCS will be used for the exposure-response analyses.
- Biomarker parameter analysis set (BMS): This set includes all subjects in the TS who provide at least one evaluable observation for at least one of the exploratory biomarkers without protocol deviation relevant to the evaluation of biomarkers (as specified in the following subsection ‘Biomarkers’). Descriptive and model-based analysis of the biomarkers will be based on the BMS.

Descriptions of additional analysis sets may be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be suggested in the iPD specification file. IPDs will be identified no later than in the RPM, and the iPD categories will be updated as needed.

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 3006337 and acetaminophen will be calculated according to the relevant BI internal procedure.

Serum/plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation 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.

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- Missing samples/concentration data at important phases of PK disposition curve.

Serum/plasma concentration data and parameters of a subject which are 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 pharmacokinetic parameters. Concentrations used in the pharmacokinetic 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).

7.2.1.3 Biomarkers

In general, biomarkers/PD endpoints of a subject will be included in the statistical analyses, if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation thereof (to be decided no later than in the RPM) or due to non-evaluability (as revealed during data analysis, based on the criteria specified below).

Relevant protocol deviations may be as listed for PK in Section 7.2.1.2. Biomarker data and/or parameters of a subject may for example be considered as non-evaluable, if the time-matched blood PK sample is considered as non-evaluable.

Exclusion of a subject's data will be documented in CTR. Biomarker 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.

7.2.2 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. The analysis will be based on the TS and will be descriptive in nature.

7.2.3 Secondary endpoint analyses

Primary analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively. Analyses will be performed for the parent drug.

Further exploratory analyses

In the SRD part, dose proportionality will be explored via graphical checks and if applicable via the power model stated below. The analysis will be performed for the PK endpoints $AUC_{0-\infty}$ and C_{max} as specified in Section 2.1.3.

The power model describes the functional relationship between the dose level and PK endpoint on the log scale via

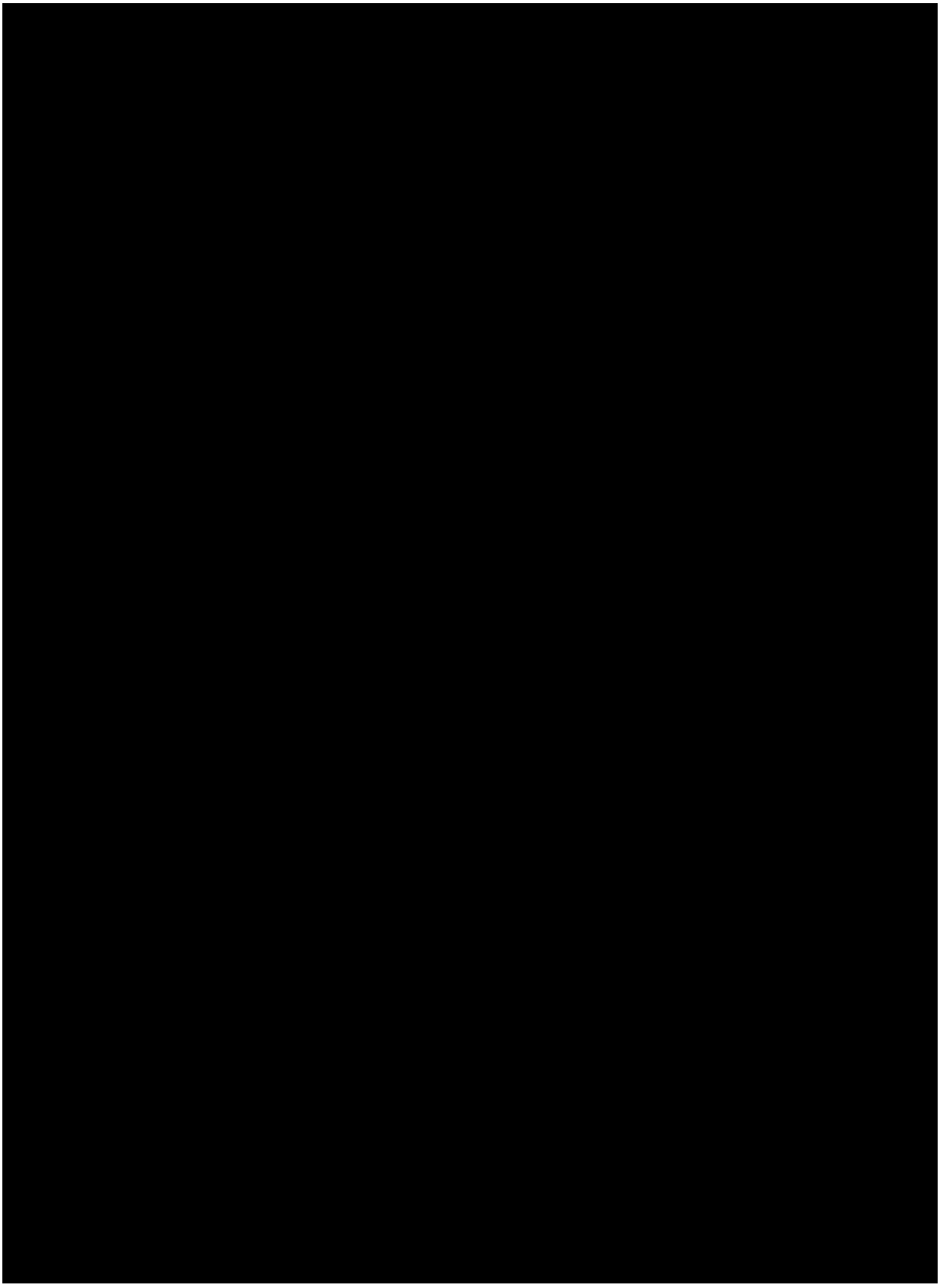
$$y_{km} = \log(x_{km}) = \mu + b \cdot \log(D_k) + e_{km},$$

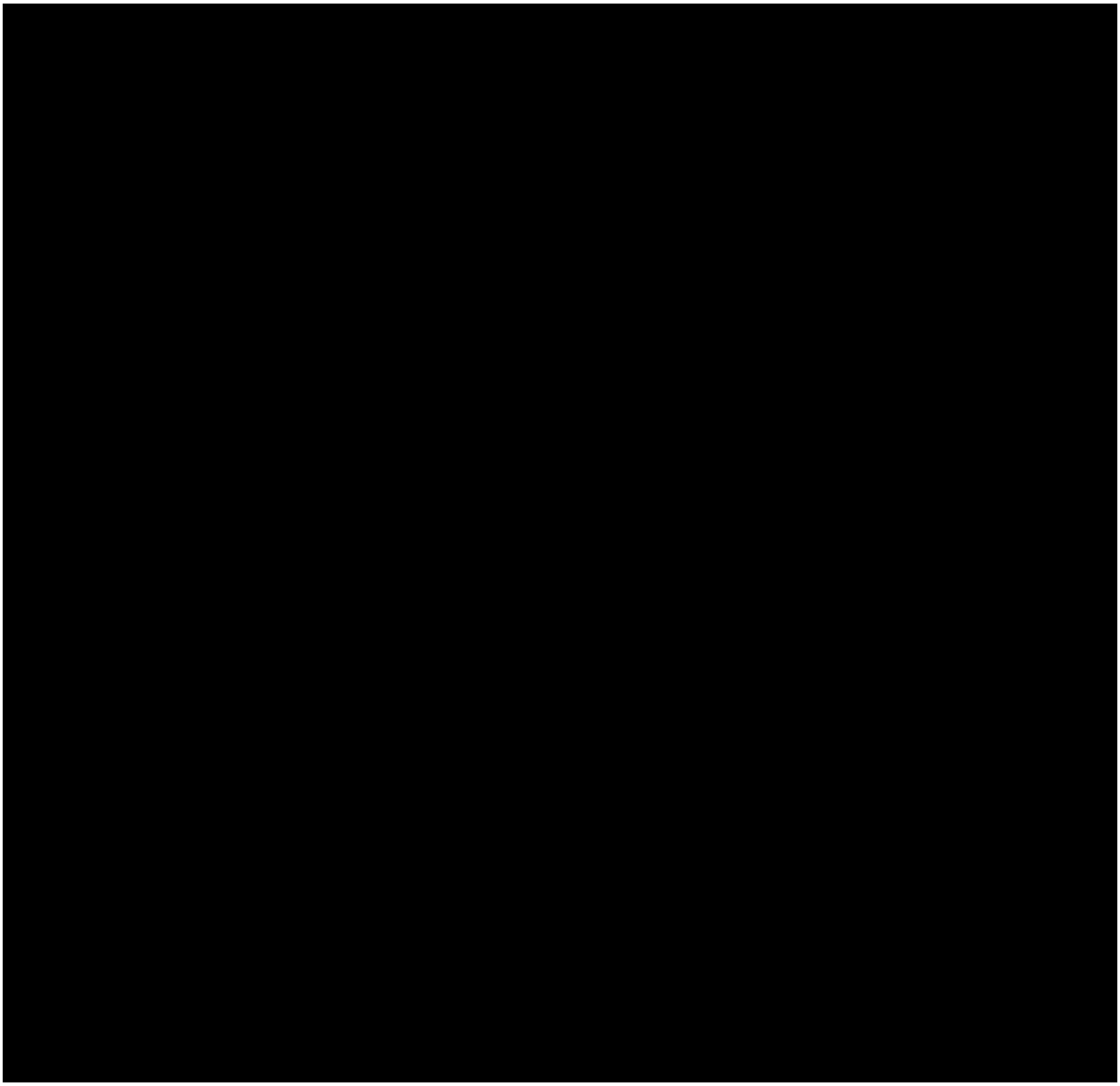
where

- y_{km} logarithm of response (PK parameter) measured on subject m receiving dose k,
- μ the overall mean,
- β slope parameter of linear regression line,
- D_k level of dose k, k=1,…,3,
- e_{km} the random error associated with the m^{th} subject who was administered dose k ($e_{km} \sim N(0, \sigma^2)$ iid).

The slope parameter β together with its two-sided 90% confidence interval will be estimated. Additionally, the r-fold change $r^{\beta-1}$ together with its 90% CI will be derived.

As some small doses at the beginning and/or some doses at the upper end might not contribute to the linear relationship between dose and PK, dose proportionality over the entire dose range investigated might not be shown. In that case an attempt will be made to identify a subrange of at least 3 consecutive doses where dose proportionality can be concluded.





7.2.5 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

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 for SRD and MD part respectively, regardless of the dose group 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 at the time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs). Therefore, measurements performed, or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between the first trial medication intake and end of REP (see Section 1.2.5) will be assigned to the treatment period. Events occurring after the REP but prior to trial termination date will be assigned to 'follow-up.' 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 unblinding the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (called analysing treatments) may be defined in the TSAP in order to provide summary statistics for other than above periods, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and post-study intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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 time intervals and treatment 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, 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 with regard to QT/QTc interval, HR, PR interval and QRS duration. These endpoints and their analyses will be described in the TSAP.

Results regarding the C-SSRS will only be listed.

7.2.6 Other analysis

The relationship between plasma concentrations and ECG endpoints will be investigated in an exploratory manner. Further details will be specified in the TSAP.

7.2.7 Interim analyses

No formal interim analysis is planned.

A preliminary, exploratory analysis of the PK parameters (e.g., $AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$ and C_{max} of substance) may be performed based on all evaluable data prior to data base lock. This may be

necessary, e.g., in case the information is needed to inform other activities during the development of substance such as concomitant treatment restrictions in other studies. In contrast to the final PK calculations, the preliminary, exploratory analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. Results will be provided as individual values and geometric means as well as the adjusted gMean ratios determined according to the planned primary analysis. The preliminary, exploratory results will be distributed to the trial team. No formal preliminary PK report will be written.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedure.

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

7.3.3 Biomarkers/pharmacodynamics

Handling of missing data of PD endpoints will be performed according to the relevant BI internal procedure. Imputation rules will be described in the TSAP.

7.4 RANDOMISATION

Subjects will be randomised in a 3:1 ratio (test treatment to placebo) within each dose group.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation scheme 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 randomisation scheme will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 36 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group in SRD part (6 on active treatment, and 2 on placebo) and 12 subjects per dose group in MD part (9 on active treatment, and 3 on placebo) is commonly used in single-rising and multiple dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics.

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 and none of the stopping criteria apply. Thus, the actual number of subjects entered may exceed 36, but will not exceed 48 subjects entered.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation.'

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 ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation 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 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to 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 investigator or delegate must give a full explanation to trial subjects based on the subject information form. A language understandable to the subject should be chosen and technical terms and expressions avoided, if possible.

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 or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, 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: gender, 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 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 Clinical Research Associate, 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 must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

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 subject data in accordance with the principles 7 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, storage and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage 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 (e.g., biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

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 the whole trial ('Last Subject Completed').

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

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.

When the trial is completed, the investigator should inform the head of the trial site in writing of the completion of the trial, and the head of the trial site should promptly inform the IRB and sponsor in writing of the completion.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted], under the supervision of the principal investigator. Relevant documentation on the participating (principal) investigators (e.g., their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a CT Leader, responsible for coordinating all required trial activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [redacted].

Safety laboratory tests will be performed by the local laboratory of the trial site.

Analyses of BI 3006337 concentrations in plasma will be performed at the [redacted]

The analyses of acetaminophen will be performed at [redacted].

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation ([redacted]) for evaluation.

On-site monitoring will be performed by BI, or a contract research organisation appointed by BI.

Data management and statistical evaluation will be done by BI or a contract research organisation 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.

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10. APPENDIX

10.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

10.1.1 Columbia-Suicide Severity Rating Scale (C-SSRS) Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted]. *Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted] *inquiries and training requirements contact* [redacted]

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AUS.1_eng-USori.doc

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) ____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) ____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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10.1.2 Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted]. *Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted] *inquiries and training requirements contact* [redacted]

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AUS.1_eng-USori.doc

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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11. DESCRIPTION OF GLOBAL AMENDMENT

11.1 GLOBAL AMENDMENT 1

Date of amendment		15 Feb 2024
BI Trial number		1466-0003
BI Investigational Medicinal Product(s)		BI 3006337
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising subcutaneous doses and multiple subcutaneous doses over 6 weeks of BI 3006337 in healthy male Japanese subjects (single-blind, randomised within dose groups, placebo-controlled, parallel 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		PROTOCOL SYNOPSIS
Description of change		Title of trial Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising subcutaneous doses and multiple subcutaneous doses <u>over 6 weeks</u> of BI 3006337 in healthy male Japanese subjects (single-blind, randomised within dose groups, placebo-controlled, parallel group design)
Rationale for change		Correction and clarification
Section to be changed		PROTOCOL SYNOPSIS
Description of change		Trial site [redacted]
Rationale for change		Correction and clarification
Section to be changed		FLOWCHART SRD part: DG1 – DG3
Description of change		Some planned times shown XX.XX format were changed to XX:XX format to be consistent with other planned times
Rationale for change		Correction and clarification

Section to be changed		FLOWCHART SRD part: DG1 – DG3
Description of change		Planned time of Day 2 of Visit 2 From: 23:50 Change to: 22:50
Rationale for change		Correction and clarification
Section to be changed		FLOWCHART MD part: DG4
Description of change		Header of the flowchart From: Serum biomarkers[13] Change to: Blood biomarkers[13]
Rationale for change		Correction and clarification
Section to be changed		FLOWCHART MD part: DG4
Description of change		Planned time of Day 2 of Visit 2 From: 23:30 Change to: 23:45
Rationale for change		Correction and clarification
Section to be changed		FLOWCHART MD part: DG4
Description of change		Timing of discharge from trial site From: Planned time of 47:00 on Day 3 of Visit 2 Change to: Planned time of 72:00 on Day 4 of Visit 2 From: Planned time of 1055:00 on Day 45 of Visit 2 Change to: Planned time of 1080:00 on Day 46 of Visit 2
Rationale for change		To enhance the safety monitoring
Section to be changed		FLOWCHART MD part: DG4
Description of change		The following events were newly added: Lunch at planned time of 51:00 on Day 3 of Visit 2 and 1059:00 on Day 45 of Visit 2

		Snack (voluntary) at planned time of 55:00 on Day 3 of Visit 2 and 1063:00 on Day 45 of Visit 2 Dinner at planned time of 58:00 on Day 3 of Visit 2 and 1066:00 on Day 45 of Visit 2 Breakfast (voluntary)[10] at planned time of 72:00 on Day 4 of Visit 2 and 1080:00 on Day 46 of Visit 2
Rationale for change		Updated in accordance with the changes in timing of discharge from trial site
Section to be changed		FLOWCHART MD part: DG4
Description of change		Footnote No. 14 Only blood~~plasma/serum~~ samples for biobanking will be collected at EOT visit
Rationale for change		Correction and clarification
Section to be changed		ABBREVIATIONS AND DEFINITIONS
Description of change		The following terminology was newly added: Gastrointestinal (GI)
Rationale for change		Clarification
Section to be changed		ABBREVIATIONS AND DEFINITIONS
Description of change		$\%AUC_{tz-\infty}$: Percentage of $AUC_{tz-\infty}$ obtained by extrapolation ~~PCR: Polymerase chain reaction~~ VzF~~,ss~~: Apparent volume of distribution during the terminal phase after extravascular administration
Rationale for change		Correction and clarification
Section to be changed		Section 1.4.2
Description of change		Although a trend of BI 3006336~~6~~7 related increase in the heart rate was detected, it was considered non-adverse based on the lack of apparent dose-related relationship and associated effects on other ECG parameters.
Rationale for change		Correction and clarification
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		Section 3.1
Description of change		Minimum safety data set required for each dose escalation was changed from at least 48 hours to 72 hours following the IMP administration.
Rationale for change		To enhance the safety monitoring
Section to be changed		Section 4.1.4
Description of change		In SRD part, subjects will be kept under close medical surveillance until at least 72 h after drug administration. In MD part, subjects will be kept under close medical surveillance until at least 7247 h after drug administration during hospitalisation and until at least 2 h after drug administration at the ambulatory visits. Hypersensitivity reactions should be treated according to medical standards (see Section 4.2.1).
Rationale for change		To enhance the safety monitoring
Section to be changed		Section 4.2.1
Description of change		Except for acetaminophen administration to perform the acetaminophen absorption test (see Section 4.2.1.1.1) and glucose administration to perform the OGTT (see Section 4.2.1.1.2) , no additional treatment is planned. However, in case of AEs in need of treatment, the investigator can authorize symptomatic therapy. In those cases, trial participants 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. Prolonged or severe gastrointestinal (GI) events
Rationale for change		Correction and clarification

Section to be changed		Section 5.2.3
Description of change		Drug screening and COVID-19 Antigen Rapid Test (Nasopharyngeal Swab)~~SARS-CoV-2 PCR test~~ will be performed at SCR and before each admission to the site (Day -2 of Visit 2 for SRD part and Day -2 of Visit 2 and Day 43 of Visit 2 for MD part). Table 5.2.3:3 Exclusionary laboratory tests COVID-19 infection: COVID-19 Antigen Rapid Test (Nasopharyngeal Swab) ~~SARS-CoV-2 PCR test (nasal swab)~~
Rationale for change		Correction and clarification
Section to be changed		Section 5.4.1

Description of change		• Markers for bone formation:
		  • Procollagen Type 1 N-terminal Propeptide (P1NP)
		  • Bone-specific Alkaline Phosphatase (BALP)
		  • Osteocalcin (OC)
		• Markers for bone resorption:
		  • Carboxy-terminal Collagen Crosslinks (CTX-1)

Rationale for change		Correction and clarification
Section to be changed		Section 5.5.1
Description of change		Approximately 8.5 mL blood will be drawn for DNA, 4~~10~~ mL for plasma and 8.5 mL serum banking purposes.
Rationale for change		Blood volume updated
Section to be changed		Section 5.6.1
Description of change		At the predefined time points before and after glucose intake indicated in the Flow Chart, blood samples for the determination of plasma glucose and insulin~~, and C-peptide~~ will be collected.
Rationale for change		Correction and clarification
Section to be changed		Section 5.6.2.1
Description of change		For quantification of acetaminophen plasma concentrations, 1 mL of blood will be taken from an antecubital or forearm vein into a K2-EDTA (di~~tri~~potassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart.
Rationale for change		Correction and clarification

Section to be changed		Section 6.2.2
Description of change		In MD part, trial participants will be kept under close medical surveillance for at least 72~~47~~ h following s.c. administration of the trial medication during hospitalisation and for at least 2 h following s.c. administration of the trial medication during the ambulatory visits. The trial participants will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee.
Rationale for change		To enhance the safety monitoring

APPROVAL / SIGNATURE PAGE

Document Number: c43161925 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising subcutaneous doses and multiple subcutaneous doses over 6 weeks of BI 3006337 in healthy male Japanese subjects (single-blind, randomised within dose groups, placebo-controlled, parallel group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	19 Feb 2024 02:47 CET
Author-Trial Statistician		19 Feb 2024 08:22 CET
Approval-Clinical Program [redacted]		19 Feb 2024 08:44 CET
Verification-Paper Signature Completion		20 Feb 2024 02:10 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed