Clinical Trial Protocol

	Document Number:	**c39013879-05**
BI Trial No.	1466-0002	
BI Investigational Medicinal Product	BI 3006337	
Title	Phase Ib trial to assess safety and tolerability of multiple subcutaneous doses of BI 3006337 in patients with overweight or obesity and hepatic steatosis	
Lay Title	A study to test how well different doses of BI 3006337 are tolerated by people with overweight or obesity and with fatty liver disease	
Clinical Phase	Phase Ib	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted]	
Current Version and Date	Version 5.0, 08 Feb 2024	
Original Protocol Date	17 Mar 2023	Page 1 of 110

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date **Latest revision date**	17 Mar 2023 08 Feb 2024
BI trial number	1466-0002
Title of trial	Phase Ib trial to assess safety and tolerability of multiple dosing of BI 3006337 in patients with overweight/obesity and hepatic steatosis.
Coordinating Investigator	NA
Trial sites	Multi-centre trial
Clinical phase	Phase Ib
Trial rationale	BI 3006337 is a dual glucagon-like peptide 1 (GLP-1)/fibroblast growth factor 21 (FGF21) receptor agonist being developed for the treatment of compensated cirrhosis due to non-alcoholic steatohepatitis (NASH). Cumulative data for BI 3006337 from non-clinical disease models demonstrate treatment effects across multiple pathological aspects of relevance to patients with NASH compensated cirrhosis including weight loss, improved lipid profile, insulin sensitivity, liver steatosis, hepatic lobular inflammation, and reduced hepatocyte injury and liver fibrosis. This multiple rising dose and proof of clinical principle (PoCP) trial will assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and signs of efficacy of BI 3006337 in trial participants with overweight/obesity and hepatic steatosis.
Benefit-risk assessment and ethical considerations	In the context of the unmet medical need in NASH, the anticipated benefit-risk of this trial is expected to be favourable, given the available preclinical and clinical information generated to date and the extensive safety monitoring planned in this trial.
Trial objectives	The objective of this trial is to assess the safety, tolerability, PK, and PD of 3 multiple rising dose levels and of the highest tolerated dose (repeated in a separate group) by subcutaneous (s.c.) injection of up to [redacted] BI 3006337 over 12 weeks in comparison with placebo in trial participants with overweight/obesity and hepatic steatosis. The main objective is to descriptively assess the frequency (N [%]) of trial participants with drug-related AEs. Secondary objectives are to descriptively assess the PK parameters for BI 3006337 and to explore superiority of clinical efficacy vs. placebo for BI 3006337 at the highest tolerated dose.

Trial endpoints	Primary endpoint: Occurrence of drug-related adverse events occurring between first administration of trial medication (BI 3006337 or placebo) and end of study (EOS) Secondary endpoints: **PK** • $AUC_{\tau,ss}$ (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 12 • $C_{max,ss}$ (maximum measured concentration of the analyte in serum at steady state after the last dose in Week 12) • $t_{max,ss}$ (time from dosing to the maximum measured concentration of the analyte in serum at steady state) after the last dose in Week 12 **Efficacy** • Relative percentage change in liver steatosis (as measured by MRI-PDFF) from baseline after 12 weeks of treatment
Trial design	Single-blind and randomised within dose groups, placebo-controlled trial with 3 treatment groups over 12 weeks
Total number of trial participants randomised	Approximately 56 trial participants (40 on BI 3006337 and 16 on placebo; including repetition of the highest tolerated dose level for PoCP analysis). Number of randomised trial participants will not exceed 72 in total.
Number of trial participants per treatment group	14 trial participants (10 on BI 3006337 and 4 on placebo) in dose group 1-3. Number of trial participants in dose group 4 will not exceed 30 in total.
Diagnosis, main inclusion and exclusion criteria	Trial participants with overweight/obesity and steatosis Inclusion: • Male or female patients ≥18 years and ≤75 years of age at time of consent • 25≤BMI<40 kg/m^2 • Liver fat fraction ≥8% as measured by MRI-PDFF Main exclusion criteria: • Any of the following liver-related conditions: significant alcohol consumption (past or present), intake of medications associated with liver injury, hepatic steatosis, or steatohepatitis for more than 14 consecutive days within 12 weeks prior to screening, any acute or chronic disease other than simple steatosis, suspicion, confirmed diagnosis or history of hepatocellular carcinoma, treatment with vitamin E

	or pioglitazone within 90 days before screening, and liver stiffness >10 kPa as measured by Fibroscan • Any of the following metabolic conditions: history of type 1 diabetes, use of GLP-1 receptor agonists within 3 months before screening, use of glucose lowering or weight loss medication within 30 days before screening, bariatric surgery or treatment with weight-loss device in the past or planned during the trial, unstable body weight within the last 12 months. • ALT and/or AST >5x ULN at the screening visit • Any major surgery (major according to Investigator's assessment) performed within 12 weeks prior to randomization or planned during trial conduct • A marked prolongation of QT/QTc (Fridericia) interval that is greater than 450 ms for men or 470 ms for women at Visit 1 or any other abnormal clinically significant ECG finding at Visit 1 (e.g. type 2 second-degree AV block (Type Mobitz II) or third-degree AV block)
Trial intervention and test product	BI 3006337 solution for injection Placebo for BI 3006337 solution for injection
Dose and mode of administration	[redacted] BI 3006337 will be given s.c. once weekly.
Comparator product	Placebo
Dose and mode of administration	Matching the doses and mode of administration of BI 3006337
Duration of treatment	12 weeks
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Table 1 Flow Chart: Overall schedule

Trial Periods	**SCR**	**Treatment period**															**EOS**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Days	-48 to -4	-1 to 3	4	8	15-17	18	22	29	36	43	50	57	64	71	78-80	81	85	99
Informed consent	X																	
Randomisation		X																
BW & waist circumference	X	X			X	X											X	X
Height	X																	
Demographics	X																	
Relevant medical history	X																	
Concomitant therapy	X																	X
Review of inclusion and exclusion criteria	X																	
Drug administration		X		X	X		X	X	X	X	X	X	X	X	X			
Local tolerability at injection site[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
C-SSRS completion[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]																		
BI 3006337 in serum (PK)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		
Glucose bedside test		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X			X	X	X	X	X	X	X				X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X																	X
MR imaging[2]	X																X	
[redacted]																		
Pregnancy testing[3]	X	X					X					X			X			X

1. Including SARS-CoV-2, hepatitis B and C testing
2. [redacted]
3. Serum pregnancy test at screening visit (test performed at central lab), and urine pregnancy test at the study site for other visits. Menstrual cycle status (not delayed or missed period) should be checked before the first dose (Visit 2). Applicable to only women of childbearing potential.
4. Local tolerability: see Section 5.2.5.1
5. C-SSRS, Columbia-Suicide Severity Rating Scale questionnaires will be administered at Visit 1 using the "baseline/screening" version. The "since last visit" version will be used at the following visits. Paper forms will be used for the assessment of C-SSRS (refer to Section 5.2.5.3).

6. Blood sample should be collected before administration of trial medication.
7. [redacted]
8. [redacted]

Table 2 Flow Chart: Detailed schedule

Visit	Day	Planned time (relative to trial activities[8]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	[redacted]	BI 3006337 in serum[6]	[redacted]	Glucose bedside test	12-lead ECG	C-SSRS examination[12]	Vital signs (Temperature, BP, PR)	[redacted]	Questioning for AEs and concomitant therapy[5]
1	-48 to -4			SCR[1, 2]	x[3, 4]					x	x	x		
2	-1	-26:00	07:00	Admission to trial site, Randomisation[10]	x[4]				x	x	x	x		x
		-25:10	07:50	Liquid meal										
		[redacted]												
		-24:45	08:15											
		-24:30	08:30											
		-24:15	08:45											
		-24:00	09:00									x		x
		-23:30	09:30											
		-23:00	10:00	240 mL fluid intake[9]								x		x
		-22:00	11:00											
		-21:00	12:00	Lunch[9]					x			x		x
		-20:00	13:00											
		-19:00	14:00											
		-17:00	16:00	Snack (voluntary)										
		-15:00	18:00											x
		-14:00	19:00	Dinner										
	1	-1:00	08:00	BW & waist circumference	x		x		x	x		x		x
		0:00	09:00	**s.c. injection of BI 3006337 or placebo**			x					x[17]		
		2:00	11:00	Local tolerability at injection site[11] 240 mL fluid intake[9]										
		3:00	12:00				x		x	x		x		x
		4:00	13:00	Lunch[9]										
		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		x				x	x	x	x		x
		22:50	07:50	Liquid meal										
		[redacted]												
		23:15	08:15											
		23:30	08:30											
		23:45	08:45	Local tolerability at injection site[11]										
		24:00	09:00									x		x
		24:30	09:30											
		25:00	10:00	240 mL fluid intake[9]								x		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	[redacted]	BI 3006337 in serum[6]	[redacted]	Glucose bedside test	12-lead ECG	C-SSRS examination[12]	Vital signs (Temperature, BP, PR)	[redacted]	Questioning for AEs and concomitant therapy[5]
		26:00	11:00											
		27:00	12:00	Lunch[9]			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							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[11]	x[4]									
		47:00	08:00	Breakfast (voluntary)[9], Discharge from trial site			x		x	x	x	x		x
3	4	72:00	09:00	Ambulatory visit, local tolerability at injection site[11]	x[4]		x		x		x	x		x
4	8	168:00	09:00	Ambulatory visit[16] **s.c. injection of BI 3006337 or placebo**			x					x[17]		
		170:00	11:00	Local tolerability at injection site[11]	x				x		x	x		x
5	15	335:00	08:00	Admission to trial site, BW & waist circumference[16]	x				x	x	x	x		x
		336:00	09:00	**s.c. injection of BI 3006337 or placebo**			x					x[17]		
		338:00	11:00	Local tolerability at injection site[11] 240 mL fluid intake[9]										
		339:00	12:00				x		x	x		x		x
		340:00	13:00	Lunch[9]										
		343:00	16:00	Snack (voluntary)[9]			x		x			x		x
		346:00	19:00	Dinner										
		347:00	20:00				x			x		x		x
		351:00	24:00				x			x				
	16	358:00	07:00						x	x		x		x
		359:00	08:00				x							
		359:30	08:30	Local tolerability at injection site[11]										
		360:00	09:00									x		x
		361:00	10:00									x		x
		363:00	12:00	Lunch[9]			x		x			x		x
		367:00	16:00	Snack (voluntary)[9]			x		x			x		x
		369:00	18:00							x				
		370:00	19:00	Dinner										
		371:00	20:00				x					x		x
		375:00	24:00				x			x				
	17	382:00	7:00	Local tolerability at injection site[11]	x[4]									

Visit	Day	Planned time (relative to trial activities [8]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	[redacted]	BI 3006337 in serum[6]	[redacted]	Glucose bedside test	12-lead ECG	C-SSRS examination[12]	Vital signs (Temperature, BP, PR)	[redacted]	Questioning for AEs and concomitant therapy[5]
		383:00	8:00	Breakfast (voluntary)[9], discharge from trial site			x		x	x	x	x		x
6	18	408:00	09:00	Ambulatory visit, local tolerability at injection site[11] BW & waist circumference[16]	x		x		x	x	x	x		x
7	22	504:00	09:00	Ambulatory visit[16] **s.c. injection of BI 3006337 or placebo**			x					x[17]		
		506:00	11:00	Local tolerability at injection site[11]	x				x	x	x	x		x
8	29	672:00	09:00	Ambulatory visit[16] **s.c. injection of BI 3006337 or placebo**			x					x[17]		
		674:00	11:00	Local tolerability at injection site[11]	x				x	x	x	x		x
9	36	840:00	09:00	Ambulatory visit[16] **s.c. injection of BI 3006337 or placebo**			x					x[17]		
		842:00	11:00	Local tolerability at injection site	x				x	x	x	x		x
10	43	1008:00	09:00	Ambulatory visit[16] **s.c. injection of BI 3006337 or placebo**			x					x[17]		
		1010:00	11:00	Local tolerability at injection site[11]	x				x	x	x	x		x
11	50	1176:00	09:00	Ambulatory visit[16] **s.c. injection of BI 3006337 or placebo**			x					x[17]		
		1178:00	11:00	Local tolerability at injection site[11]	x				x	x	x	x		x
12	57	1344:00	09:00	Ambulatory visit[16] **s.c. injection of BI 3006337 or placebo**			x					x[17]		
		1346:00	11:00	Local tolerability at injection site[11]	x				x		x	x		x
13	64	1512:00	09:00	Ambulatory visit[16] **s.c. injection of BI 3006337 or placebo**			x					x[17]		
		1514:00	11:00	Local tolerability at injection site[11]	x				x		x	x		x
14	71	1680:00	9:00	Ambulatory visit[16] **s.c. injection of BI 3006337 or placebo**			x					x[17]		
		1682:00	11:00	Local tolerability at injection site[11]	x				x		x	x		x
15	78	1847:00	08:00	Admission to trial site,					x	x	x	x		
		1848:00	09:00	**s.c. injection of BI 3006337 or placebo**			x					x[17]		

Visit	Day	Planned time (relative to trial activities [8]) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	[redacted]	BI 3006337 in serum[6]	[redacted]	Glucose bedside test	12-lead ECG	C-SSRS examination[12]	Vital signs (Temperature, BP, PR)	[redacted]	Questioning for AEs and concomitant therapy[5]
		1850:00	11:00	Local tolerability at injection site[11] 240 mL fluid intake[9]										
		1851:00	12:00				x		x	x		x		x
		1852:00	13:00	Lunch[9]										
		1855:00	16:00	Snack (voluntary)[9]			x		x			x		x
		1858:00	19:00	Dinner										
		1859:00	20:00				x			x		x		x
		1863:00	24:00				x			x				
	79	1870:00	07:00	Local tolerability at injection site[11]	x[4]				x	x		x		x
		1870:50	7:50	Liquid meal										
		[redacted]												
		1871:15	08:15											
		1871:30	08:30	Local tolerability at injection site[11]										
		1871:45	08:45											
		1872:00	09:00									x		x
		1872:30	09:30											
		1873:00	10:00	240 mL fluid intake[9]								x		x
		1874:00	11:00											
		1875:00	12:00	Lunch[9]			x		x			x		x
		1876:00	13:00											
		1877:00	14:00											
		1879:00	16:00	Snack (voluntary)[9]			x		x			x		x
		1881:00	18:00							x				
		1882:00	19:00	Dinner										
		1883:00	20:00				x					x		x
		1887:00	24:00				x			x				
	80	1894:00	07:00	Local tolerability at injection site[11]	x[4]									
		1895:00	08:00	Breakfast (voluntary)[9], discharge from trial site			x		x	x	x	x		x
16	81	1920:00	09:00	Ambulatory visit	x		x		x		x	x		x
17	85	2016:00	09:00	Ambulatory visit BW & waist circumference[16]			x		x			x		
EOS	99	2352:00	09:00	Ambulatory visit BW & waist circumference[16]	x		x			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. Additionally, an MRI-PDFF and [redacted] must be performed. If a trial participant misses an appointment (ambulatory visits and site admission visits), it will be rescheduled if possible. A time window of ± 1 day would be acceptable (see Section 6.1)
2. A PCR test on SARS-CoV-2 will be performed at Visit 1.
3. Including hepatitis B and C testing, HIV-1 and HIV-2 antibody and HIV-1 p24 Antigen. Tests will be done at screening and then if needed during the study (refer to section 5.2.3).

4. In addition, urine drug screening will be performed 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 Table 1 (Flow Chart).
6. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 1050 mL per trial participant. A front and a back-up sample will be collected.
7. [redacted]
8. Planned time relative to administration of BI 3006337 or placebo at Visit 1.
9. If several actions are indicated at the same time point, the intake of meals or liquids will be the last action. Only exception is the liquid meal for the acetaminophen absorption test which must be performed according to the flow chart.
10. Randomisation will be done following enrolment and the latest prior to administration of trial medication (BI 3006337 or placebo) at Visit 2 Day 1.
11. Local tolerability: see Section 5.2.5.1
12. C-SSRS completion (refer to Section 5.2.5.3).
13. BM samples (refer to Section 5.4.2)
14. Only plasma/serum samples for biobanking will be collected at EOS visit
15. [redacted]
16. For ambulatory visits, kits assignment must be performed the day before the visit, otherwise the IMP will not be ready for administration.
17. At dosing visits for subcutaneous drug administration, vital signs evaluations (BP, PR) will be performed pre-dose and at 30 min. after the end of drug administration.

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS AND DEFINITIONS

[redacted]	[redacted]
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
[redacted]	
API	Active pharmaceutical ingredient
AST	Aspartate transaminase
[redacted]	
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in serum over the dosing interval tau at steady state
AV	Atrioventricular
[redacted]	
BI	Boehringer Ingelheim
BMI	Body mass index
BP	Blood pressure
BW	Body weight
CA	Competent Authority
[redacted]	
CCS	Canadian Cardiovascular Society
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	
$C_{max,ss}$	Maximum measured concentration of the analyte in serum at steady state

[redacted]

COVID-19	Coronavirus disease 2019
CPL	Clinical Program Leader
CRA	Clinical research associate
CRF	Case report form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Leader
CTP	Clinical trial protocol
CTR	Clinical trial report

[redacted]

DEC	Dose Escalation Committee
DEXA	Dual energy X-ray absorptiometry
DG	Dose group
DILI	Drug-induced liver injury
DIO	Diet-induced
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eDC	Electronic data capture
eGFR	Estimated glomerular filtration rate

[redacted]

ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
FC	Fragment crystallizable
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGF21	Fibroblast growth factor 21
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

GLP-1	Glucagon-like peptide 1
GLP1R	Glucagon-like peptide 1 receptor
GGT	Gamma-glutamyltransferase
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
HbA_{1c}	Glycosylated haemoglobin A1c
HbsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
[redacted]	
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator site file
i.v.	Intravenous
[redacted]	
kDa	Kilodalton
kPa	Kilopascal
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Drug Regulatory Activities
MEN 2	Multiple endocrine neoplasia syndrome type 2
micro-CT	Micro-computer tomography

MRD	Multiple rising dose
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging proton density fat fraction
MTC	Medullary thyroid carcinoma
[redacted]	
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NASH-CRN	NASH Clinical Research Network
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
[redacted]	
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PoCP	Proof of clinical principle
PP	Polypropylene
PR	Pulse Rate or time between start of the P-wave and start of the QRS complex in an electrocardiogram
[redacted]	
q2 d	Every second day
qd	Daily (once daily)
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)
RBC	Red blood cell
REP	Residual effect period
RNA	Ribonucleic acid
RR	Time between 2 R-waves in an electrocardiogram
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

s.c.	Subcutaneous
SCR	Screening
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOP	Standard operating procedure
T-BIL	Total bilirubin
[redacted]	
TAA	Thioacetamide
TB	Total bilirubin
TC	Total cholesterol
TG	Triglycerides
TGFß	Transforming growth factor beta
[redacted]	
$t_{max,ss}$	Time from dosing to the maximum measured concentration of the analyte in serum at steady state
TMF	Trial master file
TSH	Thyroid stimulating hormone
TSTAT	Trial statistician
ULN	Upper limit of normal
vs.	Versus
WBC	White blood cell
XTC	Ecstasy

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].

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, pegbelfermin s.c. showed beneficial effects of FGF21 on steatosis, injury, and fibrosis markers. Pegbelfermin significantly reduced the absolute hepatic fat fraction in the groups receiving either 10 mg daily (-6.8% vs. -1.3%) or 20 mg once a week (qw) (-5.2% vs. -1.3%), compared with the placebo group. It also decreased ALT and AST, and reduced the serum fibrosis biomarker Pro-C3 in both treatment groups (-30%, 10 mg qd; -19%, 20 mg qw) relative to the placebo group [R20-0507].

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

[redacted]

1.2.2 Toxicology

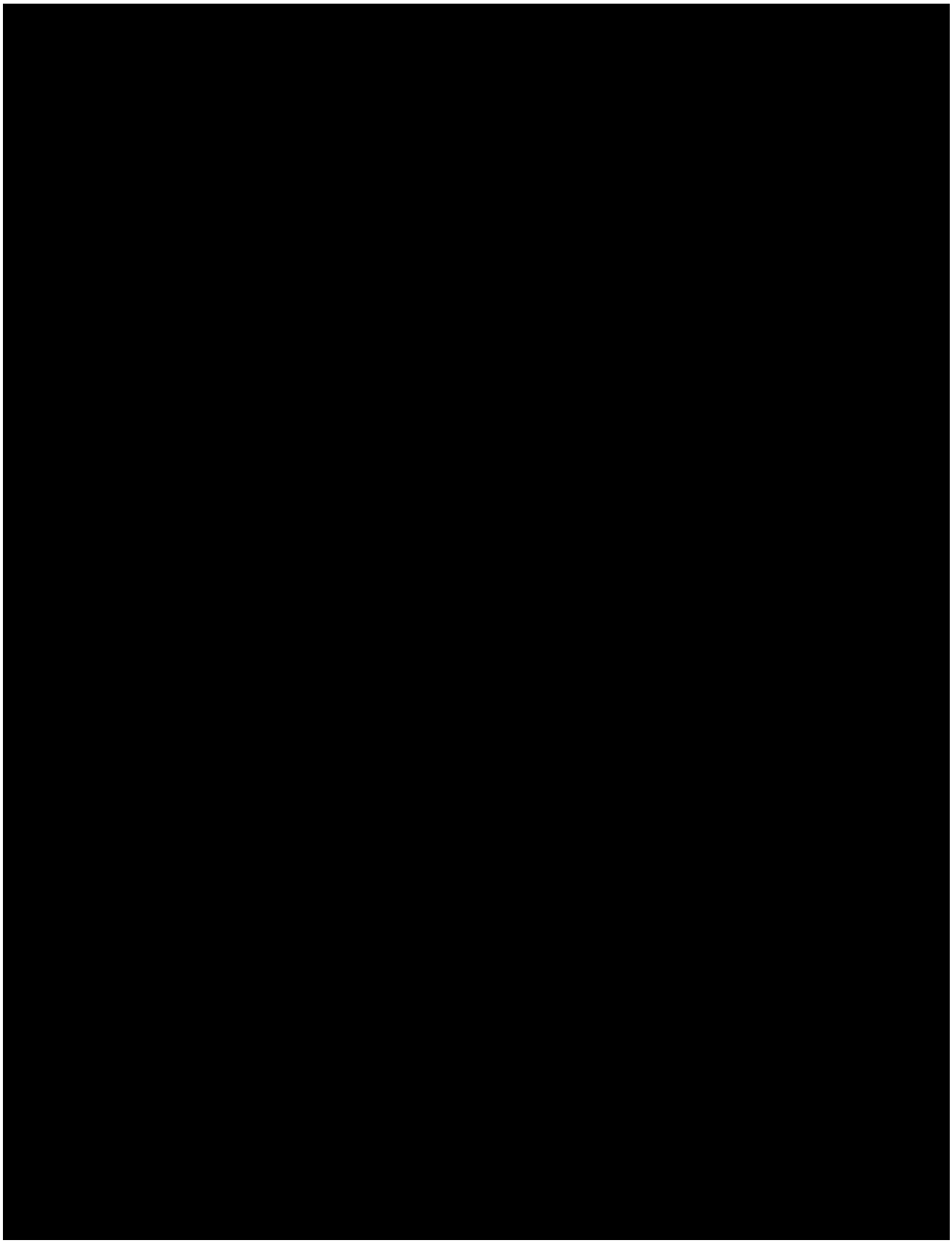
In summary, the toxicology package did not indicate any adverse systemic toxicities nor embryo-foetal toxicity with sufficient margins to the exposures expected at the dose levels in this MRD trial. Therefore, the nonclinical safety data support the chronic administration of BI 3006337 to men and women 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 (GLP-1 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 GLP-1 than to active FGF21. Monkeys showed a substantially shorter PK profile for active GLP-1 than for

active FGF21. The cause of the discrepancies in the exposure between GLP-1 and FGF21 is unknown.



1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Potential benefits of treating overweight or obese trial participants with BI 3006337 may result in the resolution of liver steatosis and may prevent the progression to NASH with significant fibrosis. This is important because NASH can eventually lead to cirrhosis, liver cancer, liver transplantation and death. Additionally, the treatment may not only reduce weight but also ameliorate insulin resistance and improve the patient lipid profile, which may directly translate into relevant improvements for patients' morbidity, mortality, and quality of life.

Trial participants may also benefit from more frequent clinical monitoring during the trial.

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.

The total volume of blood withdrawn during the entire trial per trial participant will not exceed the volume of 1050 mL. No health-related risk to the trial participants 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 30063367 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.

[redacted]

Assuming linear and dose-proportional pharmacokinetics, an accumulation of +10% with once weekly dosing (based on a half-life of 52 h) and based on the observed preliminary

single dose parameters C_{max} (1290 µg/L) and $AUC_{0-\infty}$ (80500 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 $AUC_{\tau,ss}$ = 80500 µg*h/L. Hence, these predicted exposures at the proposed dose levels in this MRD trial are covered by sufficient margins in the toxicity studies (IB Section 5.3 and 8.3).

[redacted]. 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.

It is unlikely that there will be an additional risk to trial participants with a BMI ≥25 kg/m^2 (overweight to obesity) and steatosis by the application of BI 3006337. However, due to the underlying common co-morbidities (obesity, diabetes) the NAFLD/NASH population is at increased risk for severe illness from COVID-19.

The following safety measures will be applied in this trial in order 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
- Patients 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, each dose group of 14 trial participants (10 on BI 3006337 and 4 on placebo) will be divided into 3 cohorts: cohort 1 of 3 trial participants (2 on BI 3006337 and 1 on placebo), cohort 2 of 3 trial participants (all on BI 3006337), and cohort 3 of 8 trial participants (5 on BI 3006337 and 3 on placebo). The drug administrations of these three cohorts 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
- [redacted]

[redacted]

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 who with overweight/obesity and steatosis 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. [redacted]

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 assess the safety, tolerability, PK, and PD of 3 multiple rising dose levels by s.c. injection of up to 150 mg BI 3006337 over 12 weeks in comparison with placebo in trial participants with overweight/obesity and steatosis. The primary objective is to descriptively assess the frequency (N [%]) of trial participants with drug-related AEs. Secondary objectives are to descriptively assess the PK parameters for BI 3006337 and to explore superiority of clinical efficacy vs. placebo for BI 3006337 at the highest tolerated dose.

2.1.2 Primary endpoint

The primary endpoint for the assessment of safety and tolerability of BI 3006337 is the occurrence of drug-related AEs between the first administration of trial medication (BI 3006337 or placebo) and end of study (EOS).

2.1.3 Secondary endpoints

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

- $AUC_{\tau,ss}$ (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 12
- $C_{max,ss}$ (maximum measured concentration of the analyte in serum at steady state) after the last dose in Week 12
- $t_{max,ss}$ (time from dosing to the maximum measured concentration of the analyte in serum at steady state) after the last dose in Week 12

The following efficacy endpoints will be assessed:

- Relative percentage change in liver steatosis (as measured by MRI-PDFF) from baseline after 12 weeks of treatment.

Trial participants who do not complete 12 weeks of treatment due to disruption related to COVID-19 will be replaced to achieve up to 100% sample size in each dose group; the main PoCP efficacy analysis will exclude these trial participants, [redacted]; drop-outs due to other reasons will not be replaced and will be included in all analyses.

[redacted]

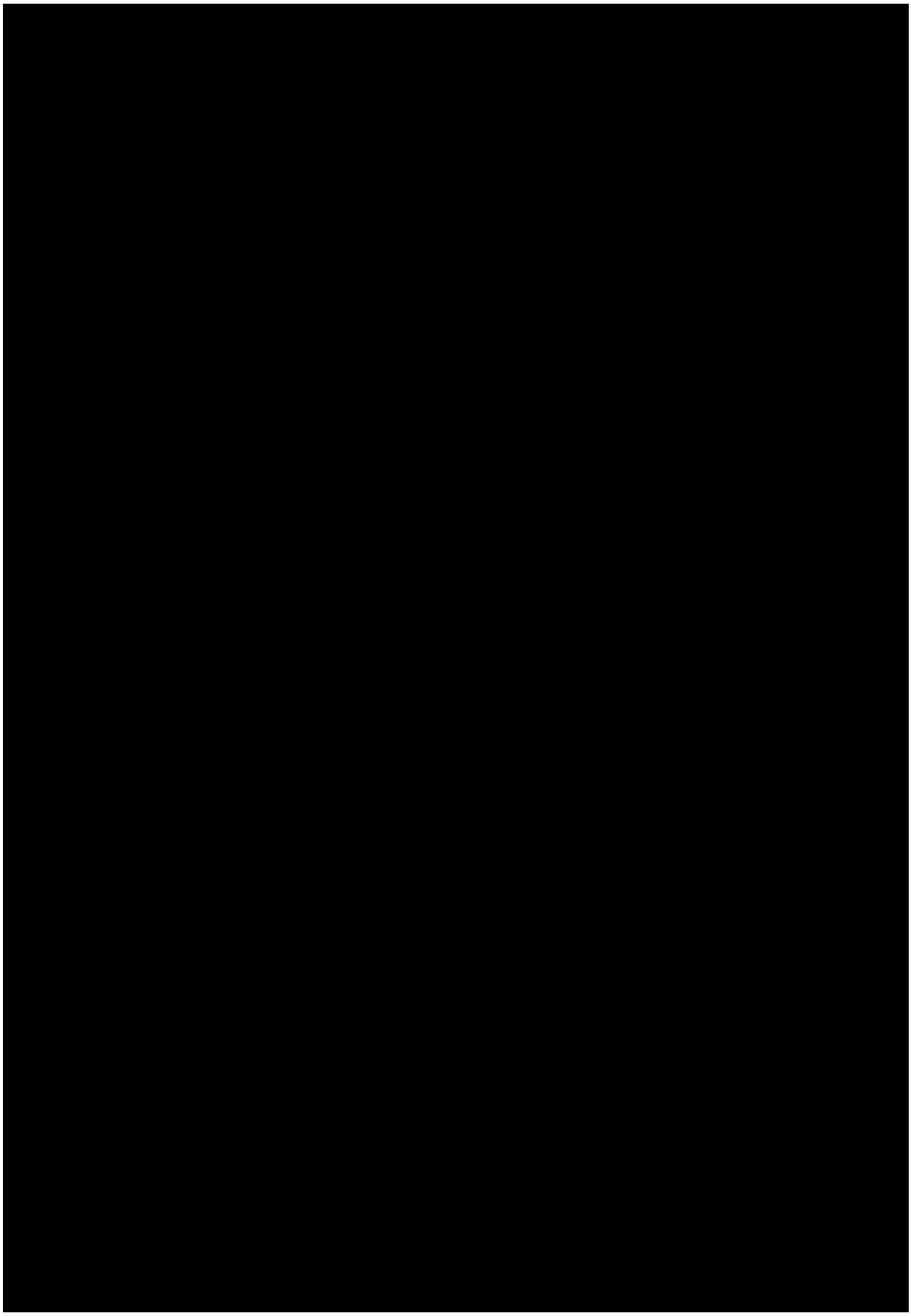
[redacted]

2.2.2.1 Safety and tolerability

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

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests including glucose
- 12-lead ECG
- Vital signs (Temperature, BP, PR)
- Local tolerability at the injection site

[redacted]



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This MRD and PoCP Phase Ib trial is designed as single-blind (within each dose group) and randomised trial with placebo matching the dose of BI 3006337 as comparator. Treatment allocation will be performed within each dose group in a 5:2 ratio (BI 3006337 to placebo).

The trial will consist of a screening period of up to 6 weeks to assess trial participant eligibility, a treatment period of 12 weeks and a follow up period of 3 weeks.

It is planned to include approximately 56 trial participants in the trial. In total the number of trial participants will not exceed 72. This sample size considers the investigation of three dose levels and the repetition of the highest tolerated dose level for the PoCP analysis with 14 trial participants per group in DG 1-3 and 14 to 30 trial participants in DG 4:

- [redacted]

Within dose group 1-3, 10 trial participants will receive BI 3006337 and 4 will receive placebo once weekly. For safety reasons, each dose group will consist of 3 cohorts. The first two cohorts are in fixed order and randomization will only be performed in Cohort 3 in a 5:3 ratio (BI 3006337 to placebo).

The trial medication will be administered in the following order:

- Cohort 1 (fixed order: ‘active – active – placebo’): 2 trial participants on BI 3006337 and 1 on placebo (in total 3 trial participants)
- Cohort 2 (fixed order: ‘active – active – active’): 3 trial participants on BI 3006337 (in total 3 trial participants)
- Cohort 3 (randomised): 5 trial participants on BI 3006337 and 3 on placebo (in total 8 trial participants)
- For cohort 3 in DG 4: At least 8 trial participants will be randomised. The number of 24 randomised trial participants in cohort 3 of DG 4 will not exceed.

In cohort 1 and 2, the 3 trial participants will be dosed sequentially. 72 h will elapse between the last trial participant of cohort 1 and the first trial participant of cohort 2, which is based on the time to reach peak concentrations of BI 3006337 (median t_{max} 7 to 61.5 h) and is expected to cover the period of highest risk/peak effect. The first 2 cohorts will be dosed in a single-blinded, fixed sequence fashion ‘active – active – placebo’ (cohort 1) and ‘active – active – active’ (cohort 2). First dosing in cohort 3 can only start after all trial participants in the previous cohorts have completed 72 h.

An overview of the trial design is presented in Table 3.

Table 3 Overview of the trial design

	Doses/Weeks											
Dose group	1	2	3	4	5	6	7	8	9	10	11	12
1	[redacted]											
[redacted]												

*Repetition of the highest tolerated dose level for PoCP analysis

A trial participant will be in the trial for up to 18 weeks in total (first screening until EOS). The overall treatment duration will be 12 weeks. A trial participant who completes the planned treatment or terminates treatment prematurely should undergo a follow-up visit (EOS examination; see Flow Chart).

Trial participants who do not complete 12 weeks of treatment due to disruption related to COVID-19 will be replaced to achieve up to 100% sample size in each dose group; the main PoCP efficacy analysis will exclude these trial participants, [redacted]; drop-outs due to other reasons will not be replaced and will be included in all analyses.

A Dose Escalation Committee (DEC), including but not restricted to Patient Safety Physician, Clinical Project Lead who is the medical expert representative with extensive hepatology expertise (CPL), Trial Statistician (TSTAT), Principal Investigators (PI), Clinical Trial Lead (CTL) and independent members experienced in treatment of liver disease or endocrine disease, will decide on the dose escalation. Target for releasing the next dose level is planned after 14 trial participants (100%) in the dose group completed 7 weeks of dosing. Two additional weeks are to be needed for preparing the DEC. The decision to proceed to the next dose group will be based upon the safety and tolerability of the preceding dose groups. The next dose group will only be treated if 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). In addition, dose group 3 will only be treated after the complete PK results of dose group 1 are available. Details will be defined in the DEC charter.

In addition to safety, tolerability and PK parameters, the trial will be performed to investigate PD parameters like fasting plasma glucose or insulin (see Section 2.2.2.4). As needed, additional safety, efficacy, and PK/PD analyses may be performed during the trial.

The end of the trial will be the date of the last visit of the last trial participant in the whole trial (at trial participant level: the date of the follow-up visit).

No formal interim analysis is planned. Unblinded exploratory analyses on the safety and tolerability will be performed during the conduct of the trial to evaluate dose escalations.

For definitions and handling of blinding, refer to Section 4.1.5.1.

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.

3.1.1 Staggered conduct of dose escalation

For safety reasons dose escalation will be performed in a staggered manner. The escalation of BI 3006337 within the escalation schedule to a higher dose level than given in the previous titration schedule will only be performed after a safety review meeting (refer to Section 3.1.2). An additional safety review will be performed when expanding the cohort on the highest dose level. Safety review meetings will start on Week 9 of treatment (see Figure 1).

3.1.2 Dose Escalation Committee (DEC) – Operations and Safety Review

A documented Safety Review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the sponsor of the trial, e.g. because of any unforeseen AEs, etc. Proceeding to the next dose group will only be permitted if no safety concerns exist in the opinion of the DEC members. In summary, the implementation of the DEC and safety monitoring measures as described in this CTP are considered adequate to ensure trial participant safety in this Phase Ib trial.

Safety review meetings are either major (at the end of each dose group) or minor (within a dose group prior to escalating to the next dose group at the time points indicated in Figure 1). In general, dose escalation decisions will be taken based on safety data (and PK data, if applicable, see Section 7.2.7).

Minimum data set for review in minor safety review meetings.

Every effort should be made to recruit a complete DG with 14 patients. At a minimum, data from a minimum dataset of 8 patients on active drug and a minimum dataset of 2 patients on placebo (in case of dropouts until Week 7, see Section 3.3.5) in each dose group need to be available for escalation to a higher dose. For the minimum dataset with regards to preliminary PK data, see Section 7.2.7. The minimum data set for review consists of the following:

- AEs in the current and preceding dose groups up to at least Week 7, 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 patient to change prior to Database Lock)
- Results from 12-lead ECG
- Vital signs in the current and preceding dose groups up to at least Week7
- Clinical laboratory tests in the current and preceding dose groups up to at least Week7
- Assessment of local tolerability
- Preliminary PK data as described in Section 7.2.7
- Check of criteria for stopping trial participant treatment as per Section 3.3.4.1

Minimum data set for review in **major** safety review meetings

Major safety meetings should take place within of 3 weeks after data cut off on week 12. For major safety review meetings, the same minimum requirements as for minor safety review meetings apply. In addition, dose group 3 will only be treated after the complete PK results of dose group 1 are available.

The decision to escalate the dose will be made by the DEC members after in-depth analysis of all available safety data, especially serious AEs (SAEs, if occurred), AEs, and out-of-range laboratory results (if considered clinically significant). For the purpose of safety evaluation and decision taking at completion of each dose level in this trial, the Principal Investigator will provide [redacted] assessment based on [redacted] direct clinical experience in the use of the investigational compound; because decisions in this Phase Ib dose escalation trial are taken based on safety observations of the trial participant cohorts, the view of the investigator on individual trial participants is considered essential for the overall safety assessment. In addition, and depending on the results and findings, suitable experts from the sponsor (e.g. TSTAT) or external institutions may be consulted on an as needed basis. In these cases, expert recommendations will be documented in the minutes of the Safety Review and considered for the decision making. Decision of the DEC must be made unanimously.

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

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

This will be an MRD trial with implementation of a DEC to decide on dose escalation, which is appropriate for the exploration of safety, tolerability, PK, and PD. The trial will be randomised and single-blind within each dose group to allow unbiased comparison with placebo.

Based on the expected mechanism of action of BI 3006337 and the studied population, the reduction of liver fat content measured by MRI-PDFF will be used as primary efficacy endpoints in this MRD trial. Liver steatosis is the main imaging and histologic finding common to all forms and stages of NAFLD/NASH. MRI-PDFF is a quantitative imaging biomarker that enables accurate, repeatable, and reproducible quantitative assessment of liver fat over the entire liver [R22-0898]. Thus, the technique has become the gold-standard for

assessing treatment response regarding liver fat reduction in NASH trials [R21-3294]. Reductions in liver fat content as measured by MRI-PDFF have been consistently associated to histologic response in subjects with NASH [R22-0900].

The trial will include an option for participants to complete questionnaires to provide feedback on their clinical trial experience (see Section 10.1). Providing this feedback is not required for trial participation, and information collected from these questionnaires will not be analysed as part of the clinical data for the trial.

3.3 SELECTION OF TRIAL POPULATION

The MRD 1466-0002 trial for BI 3006337 will include a population of participants with overweight/obesity and steatosis (i.e. without clinically significant degrees of hepatic necroinflammation or fibrosis). This MRD trial is planned to be conducted without the use of biopsies for either eligibility or efficacy assessments. The overall eligibility goal will be to include participants with a clinically sound diagnosis of NAFLD, with steatosis confirmed and quantified by MRI-PDFF, and with exclusion of participants with clinically significant degrees of hepatic necroinflammation or fibrosis made with non-invasive tests.

The trial will include approximately 56 trial participants (40 on BI 3006337 and 16 on placebo) and [redacted]

Screening of trial participants for this trial is competitive, i.e., screening for the trial will stop at all sites at the same time once a sufficient number of trial participants has been screened to deliver the required number of patients randomized into each DG. Investigators will be notified about screening completion and will then not be allowed to screen additional trial participants for this trial. Trial participants already in screening at this time will be allowed to continue to randomization if eligible.

After14 participants have been randomized into DG3, the additional patients confirmed eligible, may be randomized into DG4. The total number of participants in DG4 should not exceed 30 patients.

A log of all trial participants 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.

Even for screen failure participants, a minimum of information will be collected: participant number, visit date, demographics, eligibility criteria, information on AEs (if applicable), and concomitant treatment relevant for the AE. Re-screening is allowed once, patients will receive a new ID number. When re-screening will be performed within the screening period all tests which have been already done can be used. Every test performed outside the screening window needs to be assessed again.

If retrospectively it is found that a trial participant has been randomized in error (=did not meet all inclusion criteria or met 1 or more exclusion criteria), the sponsor or delegate should

be contacted immediately. Based on an individual benefit-risk assessment, a decision will be made whether continued trial participation is possible or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in participants with overweight/obesity and steatosis.

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

3.3.2 Inclusion criteria

Trial participants will be eligible if they meet all the following inclusion criteria at screening:

1. Male or female trial participants ≥18 years and ≤75 years of age at time of consent. Women of child-bearing potential (WOCBP[1]) must be willing and able to use 2 forms of effective contraception where at least 1 form is a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly. Male trial participants must be willing and able to use condom if their partner is a WOCBP (Section 4.2.2.3)
2. BMI ≥25-<40 kg/m^2
3. Liver fat fraction ≥8% as measured by MRI-PDFF
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

Trial participants will NOT be eligible if they meet any the following exclusion criteria:

1. Current or past significant alcohol consumption (daily alcohol consumption in women should not exceed more than one standard drink per day and two drinks per day for men, whereby one standard drink is equivalent to 12 oz beer [5% alcohol]; 5 ounces of wine [12% alcohol], 1.5 ounces of 80 proof [40% alcohol]) or inability to reliably quantify alcohol consumption based on Investigator judgement within the last 5 years. The Alcohol Use Disorders Identification Test (AUDIT) shall be used a standardized screening tool for alcohol use disorder
2. Intake of medications historically associated with liver injury, hepatic steatosis, or steatohepatitis (e.g. oral or intravenous corticosteroids, methotrexate, valproic acid, tamoxifen, tetracycline, amiodarone) for more than 14 consecutive days within 12 weeks prior to the screening visit

[1]A woman is considered of childbearing potential, i.e. fertile, following menarche, and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

3. Presence of any form of acute or chronic liver disease other than simple steatosis (e.g. viral hepatitis, autoimmune liver disease, primary biliary sclerosis, primary sclerosing cholangitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency). Chronic viral hepatitis parameters that would be considered exclusionary for the participation to this trial are (hepatitis B and C testing will be done at the screening visit):
    a. HBV: trial participants with positive HbsAg
    b. HCV: trial participants with positive HCV RNA. Trial participants treated for hepatitis C must have a negative RNA test at screening and also be HCV RNA negative for at least 3 years prior to screening in order to be eligible for the trial
4. Liver stiffness >10kPa as measured using Fibroscan. In patients with a non-valid Fibroscan measurement, a Fib-4 score >1.3 should be considered exclusionary.
5. Suspicion, confirmed diagnosis, or history of hepatocellular carcinoma
6. Treatment with vitamin E (at a minimum dose of 800 IU/day) or pioglitazone not stable (in the opinion of the Investigator) within 90 days before screening
7. History of type 1 diabetes
8. Use of GLP1-receptor agonists within last 90 days before screening
9. Use of glucose lowering or weight loss medication not stable (in the opinion of the Investigator) within 30 days before screening
10. Bariatric surgery or treatment with weight-loss device, prior to or planned during trial conduct; except gastric-band surgery more than 2 years prior to screening (including adjustments) with a stable BW within the last 12 months
11. Unstable BW (gain or loss) of more than 10% within 12 weeks before screening
12. Known history of HIV infection and/or acute SARS-CoV-2 infection at screening visit (confirmed by PCR test)
13. Abnormal laboratory values as listed below:
    a. eGFR <50 mL/min/1.73 m^2 at the screening visit (CKD-EPI formula)
    b. Bilirubin level >1.5x ULN at the screening visit (except for known Gilbert's disease with a conjugated bilirubin of <0.3 mg/dL)
    c. ALT and/or AST >5x ULN at the screening visit
    d. HbA_{1c} ≥9.5% at the screening visit
14. Diagnosis of a serious or unstable disease including hepatic (other than steatosis), renal, gastrointestinal, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, psychiatric, immunologic, or hematologic disease and other conditions that, in the clinical judgment of the Investigator, are likely to interfere with the analyses of safety and efficacy in this trial. Trial participants with an expected life expectancy of less than 2 years are also excluded.

15. 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 or *in situ* carcinoma of the uterine cervix
16. Any major surgery (major according to Investigator's assessment) performed within 12 weeks prior to randomization or planned during trial conduct
17. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, manifest hypo- or hyperthyroidism at Visit 1
18. History of chronic or acute pancreatitis or elevation of serum lipase/amylase >2x ULN, or fasting serum triglyceride levels of >500 mg/dL (>5.65 mmol/L) at screening
19. History of fracture, bone surgery (including joint or hardware replacement, bone grafting, or amputation), or clinically significant bone trauma within 12 weeks of screening.
20. 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 Visit 1
21. Resting HR >100 bpm and/or BP ≥160/95 mmHg at Visit 1. BP measurement should be repeated 10 min apart. Trial participant should be excluded only if the second measurement confirms a BP ≥160/95 mmHg.
22. A marked prolongation of QT/QTc (Fridericia) interval that is greater than 450 ms for men or 470 ms for women at Visit 1 or any other abnormal clinically significant ECG finding at Visit 1 (e.g. type 2 second-degree AV block (Type Mobitz II) or third-degree AV block)
23. History of ventricular tachycardia, type 2 second-degree AV block (Type Mobitz II), third-degree AV block or congestive heart failure NYHA III-IV
24. Heart rhythm disturbances (e.g. bradycardia with baseline HR <50 bpm, in the absence of HR lowering medications), tachycardia or tachyarrhythmia (e.g. atrial fibrillation, atrial flutter, or ventricular tachycardia), considered by the Investigator indicative of relevant cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals at Visit 1. Family history of long QT syndrome, use of prescription or over-the-counter medications known to significantly prolong the QT/QTc interval at Visit 1
25. Any of the following conditions or procedures within the last 6 months prior to Visit 1: myocardial infarction, unstable angina (e.g. CCS grading of Angina pectoris grade III and IV), artery bypass (e.g. coronary artery bypass graft, carotid bypass, peripheral artery bypass), percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischemic attack, cerebrovascular accident (stroke), or decompensated congestive heart failure
26. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
27. [redacted]

3.3.4 Discontinuation of trial participants from treatment or assessments

Trial participants may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

However, if the trial participants agree, they should stay in the trial. Even if continued trial treatment is not possible, they should attend further trial visits to ensure their safety and to collect important trial data.

Measures to control the withdrawal rate include careful trial participant selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

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

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

At the time of discontinuation, a complete EOS examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.5), the discontinued trial participant should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the trial participant.

3.3.4.1 Discontinuation of trial treatment

An individual trial participant will discontinue trial treatment if:

- The trial participant withdraws consent for trial treatment or trial participation, without the need to justify the decision

- The trial participant has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future
- An AE (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher) occurred, and the AE was assessed by the Investigator as related to the trial treatment (Section 5.2.6.1.5 and 5.2.6.1.6).
- An AE (CTCAE Grade 4 or higher) occurred, regardless of attribution to the trial treatment (Section 5.2.6.1.5 and 5.2.6.1.6).
- The trial participant needs to take concomitant medication that interacts with the investigational medicinal product or other trial treatment
- 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), or clinically relevant changes in ECG requiring intervention
- The trial participant can no longer receive trial treatment for medical reasons such as surgery, other AEs, other diseases, or pregnancy (see Section 5.2.6.2.3)
- The trial participant experiences a severe infection with SARS-CoV-2, (as confirmed by PCR test; test options outside the clinical trial to be considered if according to local requirements, see Section 5.2.3. The trial participant may resume trial treatment following recovery from SARS-CoV-2 infection if the participant is expected to derive clinical benefit, as agreed between the investigator and sponsor
- Occurrence of:
    - Systemic hypersensitivity reaction (mild/CTCAE grade 1, moderate/CTCAE grade 2 or, or and severe/CTCAE grade 3, 4) to the investigational product (Trial participants should be closely monitored for signs and symptoms of hypersensitivity reactions, please refer to Section 4.2.1)
    - DILI attributable to the trial drug (see section 5.2.6.1.4)
    - Signs of suicidal behaviour or ideation (see section 5.2.5.3)
    - Pancreatitis
    - Any injection site reaction (ISR) with ulceration, necrosis, severe tissue damage or operative intervention (CTCAE grade 3, 4, 5) should prompt permanent discontinuation. ISR classified as moderate that meets three out of the five criteria on table in section 5.2.6.1.5 should also prompt treatment discontinuation. Continue to follow the patient in the trial per the schedule of assessment and until the ISR resolves, even if the investigational agent has been discontinued.

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

If the patient becomes pregnant during the trial medication must be stopped, the patient will be discontinued from the trial and followed up until birth or otherwise termination of the pregnancy. For further information, including the process for follow-up of the outcome of the pregnancy please see Section 5.2.6.2.3.

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

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

Additional trial participants may be recruited during the trial to replace the trial participants who discontinued prematurely, please refer to Section 3.3.5 for details.

3.3.4.2 Withdrawal of consent to trial participation

Trial participants may withdraw their consent to trial participation at any time without the need to justify the decision.

If a trial participant wants to withdraw consent, the investigator should be involved in the discussion with the trial participant 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.

3.3.4.3 Discontinuation of the trial by the sponsor

BI reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Violation of GCP, or the CTP by a trial site or investigator, or the contract with BI impairing the appropriate conduct of the trial
3. The sponsor decides to discontinue the further development of the investigational product
4. New toxicological findings, SAEs, or any safety information invalidating the earlier positive benefit-risk assessment

The investigator/the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the fourth reason).

The dose escalation/staggering and trial treatment will be stopped for all patients in the ongoing dose groups once the sponsor becomes aware of one of the following 3 scenarios:

1. More than 50% of the patients at one dose level show drug-related and clinically relevant AEs of moderate (CTCAE grade 2) or severe (CTCAE grade 3 and 4) intensity
2. If at least 1 drug-related SAE is reported
3. If severe non-serious AEs considered as drug-related by the investigator in 2 patients of the same dose group (14 patients) occur.

These cases will be reviewed by the DEC considering individual patient and cumulative data, to decide on:

1. Proceeding with treatment and randomization in the ongoing dose groups
2. Further randomization and enrolment for the next dose group
3. The discontinuation of the trial

31. Details are described in the DEC charter.

32.

Further treatment and follow-up of trial participants affected will occur as described in Section 3.3.4.1.

3.3.5 Replacement of patients

If some patients do not complete the trial (including patients non-evaluable for PK), they may be replaced if considered necessary to reach the objective of the trial. The CTL together with the Trial Clinical Pharmacologist and the TSTAT are to decide if and how many patients will be replaced.

Additional trial participants may be recruited to replace trial participants who discontinue participation early for non-safety related reasons (e.g. unable to attend the protocol defined visits for personal reason) or trial disruption (e.g. measures to control the spreading of COVID 19). Trial participants may only be replaced prior to Week 7 and after an agreement with the sponsor. Trial participants who do not complete 12 weeks of treatment due to disruption related to COVID-19 will be replaced.

A replacement patient will be assigned a unique trial subject number and will be assigned to the same treatment as the patient he or she replaces. In case of patient replacement needed, previous cohort should be prioritized first, before continuing with randomization in following cohort to avoid missing patients in cohorts.

4. TREATMENTS

[redacted]

4.1.1 Identity of the Investigational Medicinal Products

Table 4 and Table 5 display the characteristics of the investigational medicinal products to be administered in this trial.

[redacted]

[redacted]

4.1.2 Selection of doses in the trial and dose modifications

[redacted] have been selected in order to assess the safety, tolerability, PK, and PD of the novel dual GLP-1 and FGF21 receptor agonist BI 3006337 in trial participants with overweight/obesity and steatosis. The selected doses cover a safe starting dose in the sub-therapeutic range, the estimated therapeutic range, and potentially supra-therapeutic doses within the levels determined by toxicological investigations (see Section 1.2).

4.1.3 Method of assigning trial participants to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be assigned to treatment groups in a 5:2 ratio with IMP or placebo administration. Randomisation will be performed at Visit 2 using a randomisation centre and Interactive Response Technology (IRT) system to allocate patients to treatment groups. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT system). If a patient withdraws from the trial, then the enrolment code cannot be re-used. For further details, refer to Section 7.4.

4.1.4 Drug assignment and administration of doses for each trial participant

The treatments to be evaluated in this trial are described in Section 3.1 and outlined in Table 3. The dose volume for placebo corresponds to the dose volume of the respective dose level.

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

On the treatment days (see Flow Chart), BI 3006337 or placebo will be administered by the investigating physician or authorised designee to the trial participant 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 s. Skin is sanitized before injection. For administration, syringe sizes dependent on the administered volume [redacted], will be used). If the volume exceeds 2 mL, the dose will be divided into 2 syringes and will be injected into 2 different injection sites on the same side of the abdomen wall. The subsequent doses should be administered on the alternate side of the abdominal wall. Following s.c. injection, the trial participant should remain in a supine position for at least 30 min. 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 1.5 h after dosing. Water may be consumed *ad libitum* except for 1 hour before and 1.5 h after drug administration. Predefined meals will be served as outlined in the Flow Chart. For restrictions with regard to diet see Section 4.2.2.2.

Trial participants will be kept under close medical surveillance until at least 48 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).

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see Section 6), physical participant visits to the sites may not be feasible or may need to be restricted to ensure participant safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue trial treatment. Where permitted by local law and regulations, trial medication may be shipped directly to the participants' home. In agreement with the sponsor, a home visit service or telemedicine may assist the participant with medication administration.

Missed doses

If a dose is missed on the planned dosing day, subjects should take the planned dose within 48 h. If more time has elapsed since the missed dose, subjects should wait to take the next planned dose.

The total number of skipped doses during the trial must not exceed 3 doses. Skipping more than 3 doses will be considered as non-compliance of trial medication, and the patient will have to discontinue the trial medication. In case of 3 consecutive skipped doses, treatment discontinuation may be considered, and the sponsor may be contacted for alternative options.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial is designed as a single-blind. The treatments administered (BI 3006337 or placebo) will be blinded to the trial participants but will be known to the investigators (outcome assessors). Only the current dose level will be known to the trial participants due to the rising dose design (see Section 3.2).

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

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

Within the central ECG lab, the staff involved with interval measurements and morphological analyses will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given trial participant will be performed by board certified cardiologists.

Also the staff of the central MRI lab will be blinded.

Access to the randomisation schedule will be controlled and documented.

4.1.5.2 Emergency unblinding and breaking the code

As this trial will be conducted in a single-blind design, the trial participants' treatment assignments will be known to investigators. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products BI 3006337 and placebo will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice.

For details of packaging and the description of the labels, 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 patient information form. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. If necessary, a temperature log must be maintained to make sure that the drug supplies are stored at the correct temperature.

If the storage conditions are found to be outside the specified range, the local CRA (as provided in the list of contacts) has to be contacted immediately.

4.1.8 Drug accountability

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

1. Approval of the CTP by the IRB/ethics committee
2. Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
3. Approval/notification of the regulatory authority, e.g. CA
4. Availability of the *curriculum vitae* of the Principal Investigator
5. Availability of a signed and dated CTP
6. Availability of FDA Form 1572 (if applicable)

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

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

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each trial participant, and 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 participants. The investigator or designee will maintain records that document adequately that the trial participants were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Except for acetaminophen administration to perform the acetaminophen absorption test (see Section 4.2.1.1), 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 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 patient should be referred to an appropriate psychiatric clinic.

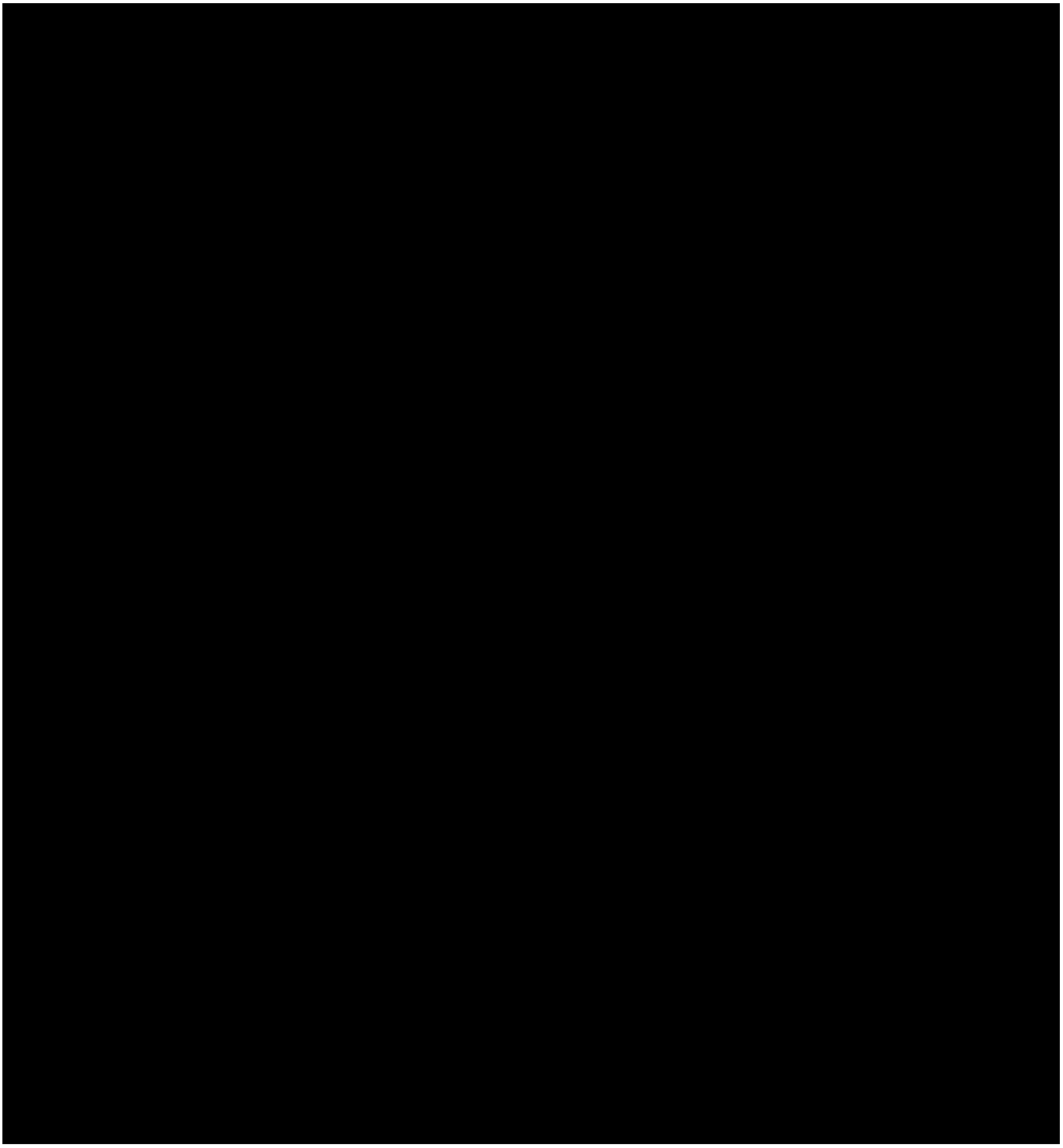
Systemic hypersensitivity

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 (eg, anaphylactic reaction), epinephrine
- Draw a blood sample for the evaluation of IgE, histamine, serum tryptase, and complement components (see laboratory manual in the ISF)
- [redacted]

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.

[redacted]



4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed, except mentioned in Section 4.2.1. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF. The following medications are prohibited during the entire duration of the trial (also during screening):

- [redacted]

While enrolled in this trial, trial participants must not participate in another investigational drug or device trial or receive other investigational treatment(s).

4.2.2.2 Restrictions on diet and lifestyle

While admitted to the trial site, the trial participants will be instructed not to consume any foods or drinks other than those provided by the staff. Predefined meals will be served at the times indicated in the Flow Chart.

For s.c. administration of the trial medication (BI 3006337 or placebo), the trial participant will be fasting for at least 10 h 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.

Additionally:

- Total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.
- Alcoholic beverages consumption and smoking is not allowed during stay 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 EOS examination.
- Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire trial.

4.2.2.3 Contraception requirements

WOCBP (for definition refer Section 3.3.2) and their male sexual partner must use two medically approved methods of birth control during the treatment period and for a period of at least 3 weeks after last trial drug intake. Male partner of a WOCBP trial participant who is able to father a child must use a condom.
WOCBP (trial participant) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and

correctly.

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- If male partner of a trial participant is vasectomised with documented absence of sperm, no further contraception methods are required

Male trial participants must refrain from donating sperm and use condom if their sexual partner is a WOCBP during the treatment period and until 3 weeks after the last dose of trial medication. As BI 3006337 is non-genotoxic, a time interval of the REP is considered sufficient. No contraception is required for the male participant's partner.

Or

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

4.3 TREATMENT COMPLIANCE

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 serum concentrations of trial medication will provide additional confirmation of compliance.

Trial participants 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

5.1.1 Magnetic Resonance Imaging for Proton Density Fat Fraction

MR imaging will be used to assess the liver fat content in the whole liver by way of proton density fat fraction (PDFF) at the time points specified in the Flow Chart. Therefore, sites must be equipped or collaborating with a site equipped with an MRI scanner from the following manufacturers: [redacted] Ideally the MRI scanner should be equipped with a manufacturer specific MRI-PDFF package also known as multi-echo, multi-peak Dixon techniques. All imaging sites will undergo a quality assessment process prior to trial initiation based on a review of MRI hardware and software.

[redacted]

Data transfer
All MR images will be transferred electronically to the central MR images lab [redacted] for evaluation. For the screening visit the transfer has to be made as soon as possible to allow for a timely evaluation of the core lab. [redacted] will conduct quality control to ensure adherence to the imaging protocol and sufficient image quality (e.g., correct MR sequences, appropriate liver coverage). If the images fail to meet the required standard, the site will be informed, and the participant will be asked to undergo a repeat scan within a reasonable timeframe. If the second MR scan fails quality control or the participant declines a repeat scan, the MR scan from that visit will be deemed unusable for analysis. It is essential to obtain MR scans correctly and promptly.
Data transfer from the central MR images lab to the sponsor and the CRO is described in the ECG data transfer agreement (see TMF).

[redacted]

[redacted]

5.2 ASSESSMENT OF SAFETY

At screening, 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, and PR), 12-lead ECG, laboratory tests, a physical examination and C-SSRS completion. At the EOS examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical examination including determination of BW and potential injection site reactions as well as recording of AEs and concomitant therapies, and C-SSRS completion.

5.2.1 Physical examination

A complete physical examination will include at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. The results must be included in the source documents available at the site. For the time points of the physical examination, refer to the Flow Chart.

5.2.2 Vital signs

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

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

At dosing visits for subcutaneous drug administration, vital signs evaluations (BP, PR) will be performed pre-dose and at 30 min after the end of drug administration. Additional measurements will be also performed after the end of drug administration at the dosing visits. Any new clinically relevant abnormal findings should be recorded as AEs or SAEs and should be followed up and/or treated as medically appropriate per local standards.
See Sections 4.1.4 and 4.2.1 for the monitoring for signs and symptoms of hypersensitivity reactions

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 trial participants have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not

required. The parameters that will be determined are listed in Table 7 and Table 8 ranges will be provided in the ISF, Section 10 for parameters listed in Table 7.

Manual differential WBC 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.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1) and the DILI Checklist provided in the ISF or eDC system. The amount of blood taken from the trial participant concerned will be increased due to this additional sampling. Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the Laboratory Manual.

The central laboratory will transfer the results of the analysis to the sponsor or delegate.

Table 7 Routine laboratory tests

Functional lab group	Test name	A	B	C	D	E	F
Haematology	Haematocrit	X	X	X	--	X	--
	Haemoglobin	X	X	X	--	X	--
	RBC Count/Erythrocytes	X	X	X	--	X	--
	Reticulocytes, absol.	X	X	X	--	X	--
	WNC/Leucocytes	X	X	X	--	X	--
	Platelet Count/Thrombocytes (quant)	X	X	X	--	X	--
Automatic WBC differential (relative and absolute)	Neutrophils	X	X	X	--	X	--
	Eosinophils	X	X	X	--	X	--
	Basophils	X	X	X	--	X	--
	Monocytes	X	X	X	--	X	--
	Lymphocytes	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	--
Coagulation	Activated partial thromboplastin time	X	X	X	--	X	--
	Prothrombin time – (Quick and INR)	X	X	X	--	X	--
Enzymes	AST/GOT, SGOT	X	X	X	--	X	--
	ALT/GPT, SGPT	X	X	X	--	X	--
	ALP	X	X	X	--	X	--
	GGT	X	X	X	--	X	--
	CK	X	X	X	--	X	--
	CK Isoenzyme MB [only if CK is elevated]	X	X	X	--	X	--
	Lactate Dehydrogenase	X	X	X	--	X	--
	Lipase	X	X	X	--	X	--
	Amylase	X	X	X	--	X	--
	Calcitonin	X	X	X	--	X	--
Hormones	TSH	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	--

Functional lab group	Test name	A	B	C	D	E	F
	Urine WBC/Leucocytes (qual)	X	X	X	--	X	--
	Urine pH	X	X	X	--	X	--

Table 7 (cont'd) Routine laboratory tests

Functional lab group	Test name	A	B	C	D	E	F
Substrates	Glucose (NaF plasma)	X	X	X	X	X	--
	Insulin	X	X	X	X	X	--
	HbA_{1c}	X	X	X	--	X	--
	Creatinine	X	X	X	--	X	--
	Bilirubin, Total	X	X	X	--	X	--
	Bilirubin, Direct	X	X	X	--	X	--
	C-Peptide	X	X	X	--	X	--
	Protein, Total	X	X	X	--	X	--
	C-Reactive Protein (Quant)	X	X	X	--	X	--
	Uric Acid	X	X	X	--	X	--
	Cholesterol, total	X	X	X	--	X	--
	Triglyceride	X	X	X	--	X	--
	High density lipoprotein (HDL) cholesterol	X	X	X	--	X	--
	Low density lipoprotein (LDL) cholesterol	X	X	X	--	X	--
Electrolytes	Calcium	X	X	X	--	X	--
	Sodium	X	X	X	--	X	--
	Potassium	X	X	X	--	X	--
	Inorganic phosphate	X	X	X	--	X	--
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	X	X	X	--	X	--
PCR Test	SARS-CoV-2	X	--	--	--	--	--
Serum pregnancy test (only for female participants of childbearing potential at Visit 1 and if urine pregnancy test is positive at other visits	Human Serum Chorionic Gonadotropin	X	--	--	--	--	--
Urine pregnancy test	Urine Chorionic Gonadotropin	--	--	--	--	--	X

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

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

C: parameters to be determined at Visit 2 on Day 1, Day 2 and Day 3, Visit 3 on Day 4, Visit 4 on Day 8, Visit 5 on Day 15 and Day 17, Visit 7 on Day 22, Visit 8 on Day 29, Visit 9 on Day 36, Visit 11 on Day 50, Visit 13 Day 64, Visit 15 Day 79 and Day 80 (for time points refer to Flow Chart)

D: parameters to be determined at Visit 2 on Day -1, Visit 3 on Day 4, Visit 5 on Day 15, Visit 6 on Day 18, Visit 7 on Day 22, Visit 10 on Day 43, Visit 12 on Day 57, Visit 14 on Day 71, Visit 16 on Day 81 (for time points refer to Flow Chart)

E: parameters to be determined at Visit 18 (EOS examination)

F: parameters to be determined at Visit 2 on Day-1, Visit 7 on Day 22, Visit 12 on Day 57, Visit 15 on Day 79 and Visit 18 (EOS examination)

In case of systemic hypersensitivity including anaphylactic reaction emerging during or the investigator should consider in accordance with severity of the reaction and local standard of

care to evaluate IgE, histamine, serum tryptase, and complement components (see Section 4.2.1).

A bedside glucose test will be performed for safety reasons as indicated in the Flow Chart. For quantification of blood glucose, 1 drop (50 µL) of blood taken from a fingertip will be sufficient. The results will be listed in the trial report but will not enter statistical analysis.

The tests listed in Table 8 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. Except for drug screening, it is planned to perform these tests at SCR only. Drug screening will be performed at SCR and at the beginning of Visit 2, Visit 3, Visit 5 and Visit 15.

The investigator will use the exclusionary lab test results for the assessment of the participants' eligibility for the trial. The lab results will not be reported to the sponsor.

Table 8 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody and HIV-1 p24 Antigen (qualitative)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 65107410 or 55106810, [redacted] will be performed prior to the 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.

The laboratory tests listed in Table 7 and Table 8 will be performed at the central lab except for drug screening. Urine drug screening will be performed at central lab and either by local lab or the trial site. The SARS CoV 2 virus PCR test will be performed in the central lab or at local lab or trial site according to local requirements.

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting electrocardiogram

Recording
Single standard twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (ELI 150c, [redacted]) at the time points given in the Flow Chart.

Electrode placement will be performed according to the method of Wilson, Goldberger, and Einthoven at same locations within the subjects throughout the trial to allow proper comparisons of the ECGs.

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

All ECGs will be recorded for a 10-second duration after trial participants 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 point to avoid compromising ECG quality.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation.

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

Storing
All ECGs will be stored electronically at the ECG core lab for a minimum of 30 years.

Data transfer
All ECGs will be transferred electronically to the central ECG lab [redacted] for evaluation. For the screening and D-1 visits the transfer has to be made as soon as possible to allow for a timely evaluation of the core lab.

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 and the CRO is described in the ECG data transfer agreement (see TMF).

Evaluation

a. Central ECG lab

The digital ECG recordings will be transmitted to the core lab for central reading by board certified cardiologists. This will include a semi-automated measurement of the cardiac intervals and a morphological interpretation.

The intervals RR, PR, QRS, and QT will be measured semi-automatically and on screen using the global superimposed 12 lead median beats in which each median beat is mathematically derived from the available 10 second-recording of the corresponding lead. The individual median beats are graphically displayed as temporally aligned and overlapped (or superimposed on) one on another. Global interval measurements are subsequently defined as the interval from the earliest onset of any viable lead to the latest offset of any viable lead.

A mean RR interval will be assessed automatically from all the sinus node triggered complexes recorded over the 10 s of the ECG. The cardiac QRS-axis will be assessed by the ECG machine's algorithm.

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 for details).

The morphological interpretation of the ECGs will also be performed per ECG recording, independently of the quantitative measurement of the ECG parameters, and according to the coded list used by the ECG core lab and will include the following main categories rhythm analysis, ST segment morphology characterization, T and U wave morphology characterization.

The ECG recordings will be evaluated and rated as normal, abnormal clinically significant / non clinically significant, or unable to evaluate, and the results will be reported to the site. The results will be made available for screening ECGs within 24 h after receipt of the ECGs at the core lab.

For blinding arrangements, see Section 4.1.5.1.

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

V1 and V2/D-1 visits

At the screening visit V1 and at the visit V2/D-1, the investigator must perform a complete review of the ECG results from core lab to ensure the patient has met all the entry criteria for the study exclusion (see Section 3.3). Any pre-existing conditions should be recorded as baseline conditions. If the ECG is rated as abnormal, the investigator will have to determine if the abnormal findings are clinically significant. At the visit V2/D-1 an eligibility decision may be made based on the local reading of the ECG if the results of the central ECG have not been received, prior to randomisation visit.

V2/D1 pre dose visits

ECG recorded at the randomization visit V2/D1/pre dose should be evaluated by the investigator before the patient receives the first dose. If abnormalities are observed by the investigator for this ECG, it is strongly recommended that the investigator will wait until the results from central reading are available (after 24 h of receipt of the ECG), and the randomization visit should be rescheduled. To receive a fast feedback on this ECG it, again should be transferred to the core lab as soon as possible.

All other visits

All ECGs at the other scheduled visits should be also evaluated by the investigator who will have the responsibility of following up with the patient if there are any clinically significant findings present. It is strongly recommended to repeat 12-lead ECG recording and/ or a referral to a cardiologist and/or perform additional cardiac tests (e.g. cardiac enzymes) if there is an indication of significant abnormalities or in case of doubts.

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator.

Any ECG abnormalities will be monitored carefully and, if necessary, the trial participant will be removed from the trial and will be asked to see a medical specialist to receive the appropriate medical treatment.

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

Assessment of the injection site should be performed after each s.c. drug administration as indicated in the 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" and will be captured in the eSource local tolerability page. Injection site reactions with clinically relevant findings must be recorded as AEs; specially, injection site reactions deemed as moderate as per the table in section 5.2.6.1.5 should be always recorded as AEs. For the severity of the AE please refer to Section 5.2.6.1.5. The diameter of the affected area will be measured. Digital photography (including a ruler to show the size in cm) should be used by the investigator to document clinically relevant injection site reactions.

5.2.5.2 Monitoring for hypersensitivity reactions

Trial participants will be kept under close medical surveillance until at least 48 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).

5.2.5.3 Suicidal risk assessment and reporting

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

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

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the "baseline/screening" version) with the aim to exclude subjects with a lifetime history of suicidal ideation and behavior. After the baseline visit, the assessment "since last visit" will be performed at clinic visits as specified in the

Flow Chart. The Investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated, or reports may be validated by a consulting psychiatrist. If there is a positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the Investigator is to immediately interview the patient during the clinic visits and advise the patient to consult with a psychiatrist. If the positive report is confirmed, appropriate actions for the patient's safety must be initiated. Treatment with trial medication should be stopped, and patient should be discontinued from the trial (refer to section 3.3.4.1). Additionally, all C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior must be reported as separate SAEs by the Investigator. For 'Self-injurious behavior, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied. For each negative report (suicidal ideation type 1, 2 or 3) after start of the trial, the Investigator is to decide based on clinical judgment whether it represents an AE as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.2.6 Assessment of adverse events

Data and information necessary for the thorough assessment of AEs, SAEs, and AESIs will be reported to the sponsor via eCRF. This may include specific data and information not prospectively specified in this protocol.

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

The following should also be recorded on the appropriate eCRF(s) and BI SAE form (if applicable):

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

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

5.2.6.1.2 Serious adverse event

An SAE is defined as any AE, which fulfils at least 1 of the following criteria:

- Results in death
- Is life-threatening, which refers to an event in which the trial participant 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 on appropriate medical judgement which may jeopardise the trial participant and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 Adverse events considered "Always Serious"

In accordance with the EMA initiative on Important Medical Events, BI 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 described in Section 5.2.6.1.2.

The latest list of 'Always Serious AEs' can be found in the eDC system. A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.2.

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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:

For participants with **abnormal** aminotransaminase at baseline (defined as ALT or AST >1.5x ULN):

A) Any one of the following alerts should **trigger the DILI Checklist:**

1. AST or ALT ≥2x baseline or ≥300 U/L (whichever occurs first); and concomitant TB >2x baseline
2. AST or ALT ≥2x baseline or ≥300 U/L (whichever occurs first); and concomitant INR >1.2x baseline
3. AST or ALT ≥2x baseline or ≥300 U/L (whichever occurs first) and any new or worsening signs and/or symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

4. AST or ALT ≥3x baseline

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the DILI Checklist provided in the eDC system.

B) The following events should lead to **immediate discontinuation of trial treatment** (active or comparator) in trial participants with abnormal AST and ALT at baseline:

- Hepatic injury alerts number 1, 2 or 3
- AST or ALT >5x baseline or >500 U/L (whichever occurs first)
- Any magnitude of ALT or AST elevation above baseline and any new or worsening signs and/or symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

For participants with **normal/near normal** levels of ALT and AST at baseline:
A) **DILI checklist will be triggered** by the following alterations of hepatic laboratory parameters:

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the DILI Checklist provided in the eDC system.

B) The following events should lead to **immediate discontinuation of trial treatment** (active or comparator) in trial participants with normal AST and ALT at baseline:

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

For participants with **normal/near normal or abnormal** aminotransaminase at baseline:

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

C) Further important considerations

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Additionally, **with participants having a normal AST and ALT at baseline**, the emergence of an isolated AST or ALT elevation between ≥3-fold and <5x ULN requires repeat testing within 72 h (AST, ALT, Total Bilirubin and INR). DILI Checklist is not required unless repeat testing triggers alerts 1, 2, 3, or 4.

Systemic hypersensitivity reactions including anaphylactic reaction

Any suspicion of severe systemic hypersensitivity reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.4; [R11-4890]). See Section 4.2.1 for procedures in case of systemic hypersensitivity.

5.2.6.1.5 Intensity (severity) of adverse events

The intensity (severity) of adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 released on 27 November 2017 [R18-1357].

The assessment of the injection site as per section 5.2.5.1 should be based on the following criteria:

Injection site reactions: (adapted from R08-1466 and R22-4429):

Injection site reaction	mild	moderate	severe
Erythema/redness[1]	2.5-5cm	5.1-10 cm	>10 cm
Induration/swelling[1]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity
Pruritus	itching localized to the injection site that is relieved spontaneously or in <48 h of treatment	itching beyond the injection site that is not generalized or itching localized to the injection site requiring >48 h treatment	generalized itching causing inability to perform usual social and functional activities
Pain	does not interfere with activity	repeated use of non-narcotic pain reliever >24 h or interferes with activity	any use of narcotic pain reliever of prevents daily activity
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest

[1]Measured local reaction should be done at the greatest single diameter

5.2.6.1.6 Causal relationship of adverse events

Medical judgement should be used to determine the relationship between the AE and the BI investigational compound, 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 trial 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 trial drug concerned)
- Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- 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 Adverse event collection

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

Trial participants will be required to report any AEs and their time of onset and end, and intensity of these events. In addition, each trial participant will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. At a minimum, trial participants 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 in order 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:

- From signing the informed consent onwards until the individual trial participant's EOS (please see Section 6.2.3):
  all AEs (serious and non-serious) and all AESIs
- After the individual trial participant's EOS:
  the investigator does not need to actively monitor the trial participant for new AEs but should only report any occurrence of cancer of new histology and trial drug related SAEs and trial drug 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 Adverse event 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 immediately (within 24 h of becoming aware of the event, the country specific process will be described in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone in addition. This does not replace the requirement to complete and fax the BI SAE form.

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

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a trial participant has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 h) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

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 Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Studies is to be completed. However, an SAE and/or AESI associated with the pregnancy must be reported as described in Section 5.2.6.2.2.

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

Date and clock times of drug administration and PK sampling will be recorded in the CRFs. PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK data), including addition of samples and visits, as long as the total blood volume taken per trial participant does not exceed 1050 mL. Such changes would be implemented via non-substantial CTP Amendments.

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

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

After completion of the trial, the samples may be used for further methodological investigations (e.g. for stability testing). However, only data related to the analyte (including [redacted], 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 final CTR is archived.

[redacted]

[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKERS

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in Sections 5.1 and 5.2. Further, [redacted]

[redacted]

[redacted]

5.4.2 Methods of sample collection

For the measurement of the exploratory biomarkers, 13 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.

Detailed instructions for biomarker blood sampling, processing, storage, 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.

All left over samples will be stored and used for not yet specified explorative investigations. Samples may be used for not yet specified biomarker analyses or method development. Results of these assessments will not be part of the CTR. The trial samples will be discarded after completion of any additional investigations but not later than 2 years after the CTR has been archived.

PD sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK/PD data), including addition of samples and visits, as long as the total blood volume taken from each trial participant does not exceed 1050 mL. Such changes would be implemented via non-substantial CTP Amendments.

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, 10 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 in countries where all applicable local regulatory and ethics approvals have been obtained for biobanking.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects and to determine efficacy, PK, and PD markers of BI 3006337 in an appropriate way.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the execution of the investigational plan as per this CTP may not be feasible. With the consent of the trial participant, the sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual trial participant visits and assessments, home healthcare nurse visits, direct-to-participant/direct-from-participant shipments of trial treatment or bio-sample pick up from the participant's home. The implementation of these measures will depend on the trial participant's consent, operational feasibility, local law, and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

The acceptable time window for the screening visit is provided in the Flow Chart. Exact times of measurements outside the permitted time window will be documented.

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

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min with exception for Visit 17 and EOS when a deviation from the scheduled time for all the planned trial activities of ± 120 min is acceptable.

The acceptable deviation from scheduled ambulatory and site admission visits will be ± 1 day.

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

For planned individual serum and plasma concentration 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 PK parameters.

If a trial participant misses an appointment (e.g. ambulatory visit), it will be rescheduled if possible. A time window of ± 1 day would be acceptable. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting. Remote visits may be performed in exceptional cases, please refer to Section 4.1.4 for details.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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.

6.2.1 Screening period

After having been informed about the trial at Visit 1, all trial participants will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the trial. Additionally, a PCR test on SARS-CoV-2 will be performed. For information regarding physical examination, vital signs, laboratory tests (including drug and virus screening), and 12-lead ECGrefer to Sections 5.2.1 to 5.2.4.

During the screening visit, demographics information will be collected. This includes:

- Age on the day of informed consent (in years)
- Sex (male, female in order to describe the trial participant`s sex at birth)
- Gender identity (male, female, non-binary, not answered, or other in order to describe how the trial participant self-identifies, regardless of their genotypic or phenotypic sex) if 1) locally accepted (i.e. based on HA/EC/IRB acceptance, independent of acceptance by investigators or participants), 2) investigators are willing to ask, and 3) participants are willing to reply
- For women of childbearing potential, yes/no in order to characterize the trial participant population and as a basis for contraception

6.2.2 Treatment period

On Day -1 of Visit 2, the trial participants will be admitted to the trial site and a urine drug screening will be done at this time point. [redacted] and examination of laboratory parameters, 12-lead ECG as well as vital signs for the generation of baseline values will be performed.

In the morning of Day 1 (i.e. the day with first administration of BI 3006337 or placebo), each trial participant will undergo the examination of laboratory parameters, 12-lead ECG, and vital signs prior to administration of BI 3006337 or placebo.

Each trial participant will receive weekly doses of trial medication (BI 3006337 or placebo) on Day 1 of Visit 2 (during hospitalization), Day 8 of Visit 4 (during ambulatory visit), Day 15 of Visit 5 (during hospitalization), Day 22 of Visit 7 (during ambulatory visit), Day 29 of Visit 8 (during ambulatory visit, Day 36 of Visit 9 (during ambulatory visit), Day 43 of Visit 10 (during ambulatory visit), Day 50 of Visit 11 (during ambulatory visit), Day 57 of Visit 12 (during ambulatory visit), Day 64 of Visit 13 (during ambulatory visit), Day 71 of Visit 14 (during ambulatory visit), and Day 78 of Visit 15 (during hospitalization days) according to the randomized allocation.

The 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.

Trial participants will be kept under close medical surveillance for at least 48 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 o [redacted] designee.

For details on time points and procedures for collection of blood samples for PK analysis, [redacted] analysis [redacted], refer to the Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Trial completion

For physical examination, recording of vital signs, laboratory tests, recording of 12-lead ECGs, assessment of local tolerability at the injection site, and AE assessment during the EOS examination on Day 99 of Visit 18 (corresponding to the REP 3 weeks after the last administration of trial medication), see Sections 5.2.1 to 5.2.6.

Trial participants who discontinue before the end of the planned treatment period should undergo the EOS examination, see Flow Chart and Section 3.3.4.1.

A trial participant is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period (= EOS visit completed)
- Lost to follow-up
- Refusal to be followed-up
- Death

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary objective of this trial is to descriptively assess the frequency [N (%)] of trial participants with drug-related AEs. The primary endpoint is defined in Section 2.1.2.

The secondary objectives are to descriptively assess the PK parameters for BI 3006337 and to explore superiority of clinical efficacy versus placebo for BI 3006337 at the highest tolerated dose. Endpoints as specified in Section 2.1.3 will be analysed by descriptive statistics.

7.1 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of different dose groups of BI 3006337 are to be determined on the basis of the investigated parameters in comparison with placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

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

7.2 PLANNED ANALYSES

7.2.1 General considerations

The statistical analyses will be based on the following analysis sets.

- Randomized set (RS): This trial participant set includes all randomised trial participants, whether treated or not.
- Treated set (TS): The treated set includes all trial participants who were enrolled or randomised and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the trial participants received. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all trial participants in the treated set (TS) who provide at least one primary or secondary 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 trial participant will be included in the PKS, even if he contributes only one primary or secondary PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

Further analysis sets will be defined in the TSAP, if needed.

All individual efficacy, safety, and PK data will be listed.

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with trial medication, treatment errors, prohibited concomitant medication, completeness, and consistency of data) will be assessed by the trial team. Important protocol deviation (IPD) will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are restricted to the Treatment Period and are defined as:

- Premature treatment discontinuation of BI 3006337

The strategies for handling intercurrent events in this trial are as follows:
Treatment Policy: This is the effect of randomizing patients to a treatment arm regardless of treatment actually being taken. All intercurrent events will be handled according to the treatment policy approach as defined in ICH E9 (R1).

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

Handling of the intercurrent events that are not listed above will be decided by the review and will be documented in the TSAP.

7.2.3 Primary objective analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. Inferential statistics is not planned here. The analysis will be based on the treated set (TS) and will be descriptive in nature. Refer to Section 7.2.6 for a description of the analysis of safety and tolerability, which are the primary objectives of this trial.

7.2.3.1 Sensitivity Analyses

Not applicable.

7.2.3.2 Subgroup Analyses

Not applicable.

7.2.3.3 Supplementary Analyses

Not applicable.

7.2.4 Secondary objective analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively.

Pharmacokinetic (PK)
The PK parameters listed in Section 2.1 and 2.2 for BI 3006337 will be calculated using non-compartmental analysis (see also Section 7.2.7). Noncompartmental PK parameters will be calculated based on actual sampling times using a validated PK software (e.g. Phoenix® WinNonlin®).

Plasma concentration data and parameters of a trial participant will be included in the statistical 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 Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a trial participant's data will be documented in the CTR.

Relevant protocol deviations may be

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

Plasma concentrations and/or parameters of a trial participant will be considered as non-evaluable, if for example

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

Analysis will be evaluated of Pharmacokinetic parameter analysis set (PKS). Trial participants who are considered as not eligible for the PKS will be listed with their individual plasma concentrations and individual PK parameters, however, will not be included in descriptive statistics for plasma concentrations, PK parameters, or other statistical assessment.

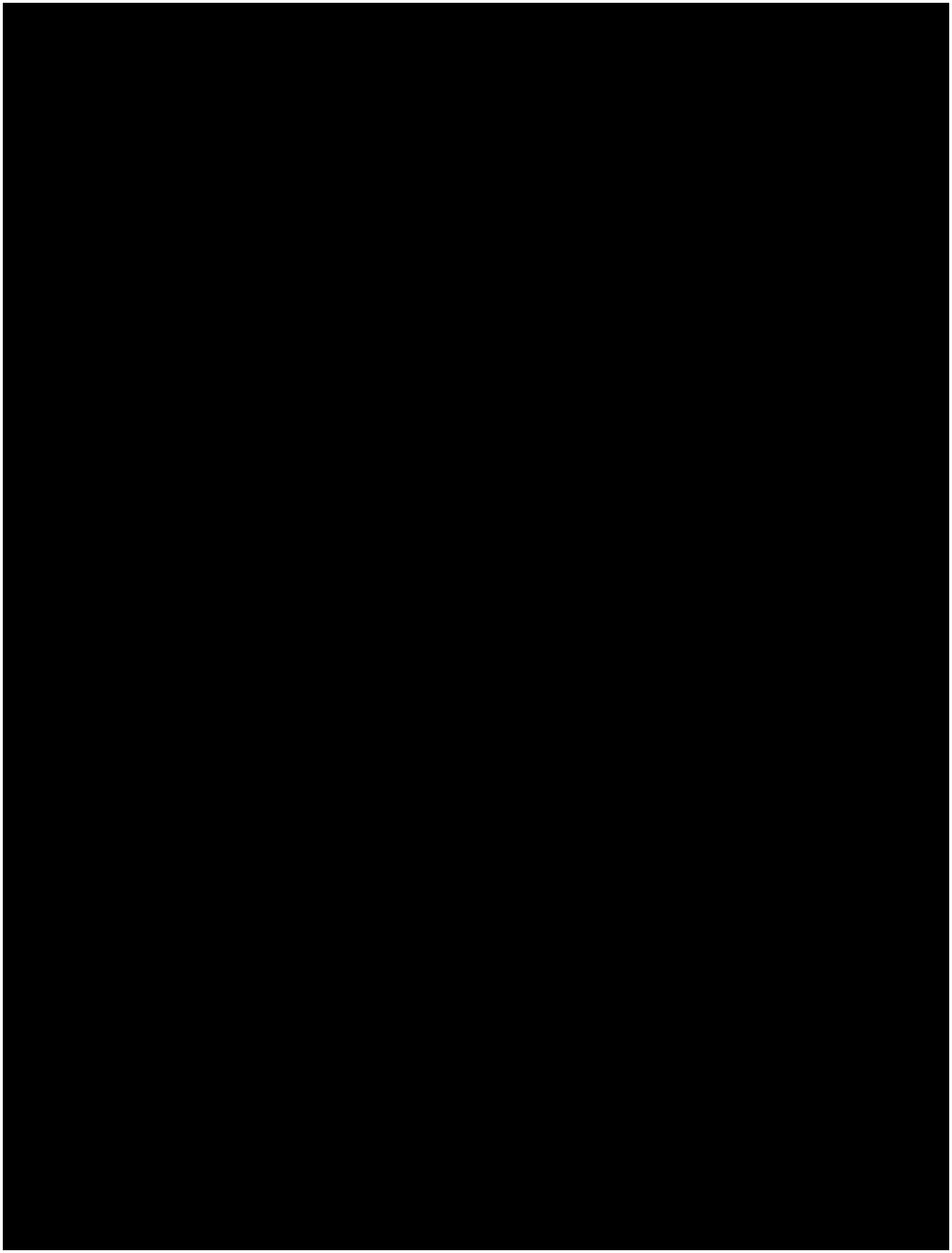
Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Only concentrations within the validated concentration range will be used for the calculation of PK parameters. Plasma concentrations will be plotted graphically versus time for all evaluable trial participants as listed in the drug plasma concentration timetables. For the presentation of the mean profiles, the arithmetic mean and the planned blood sampling times will be used.

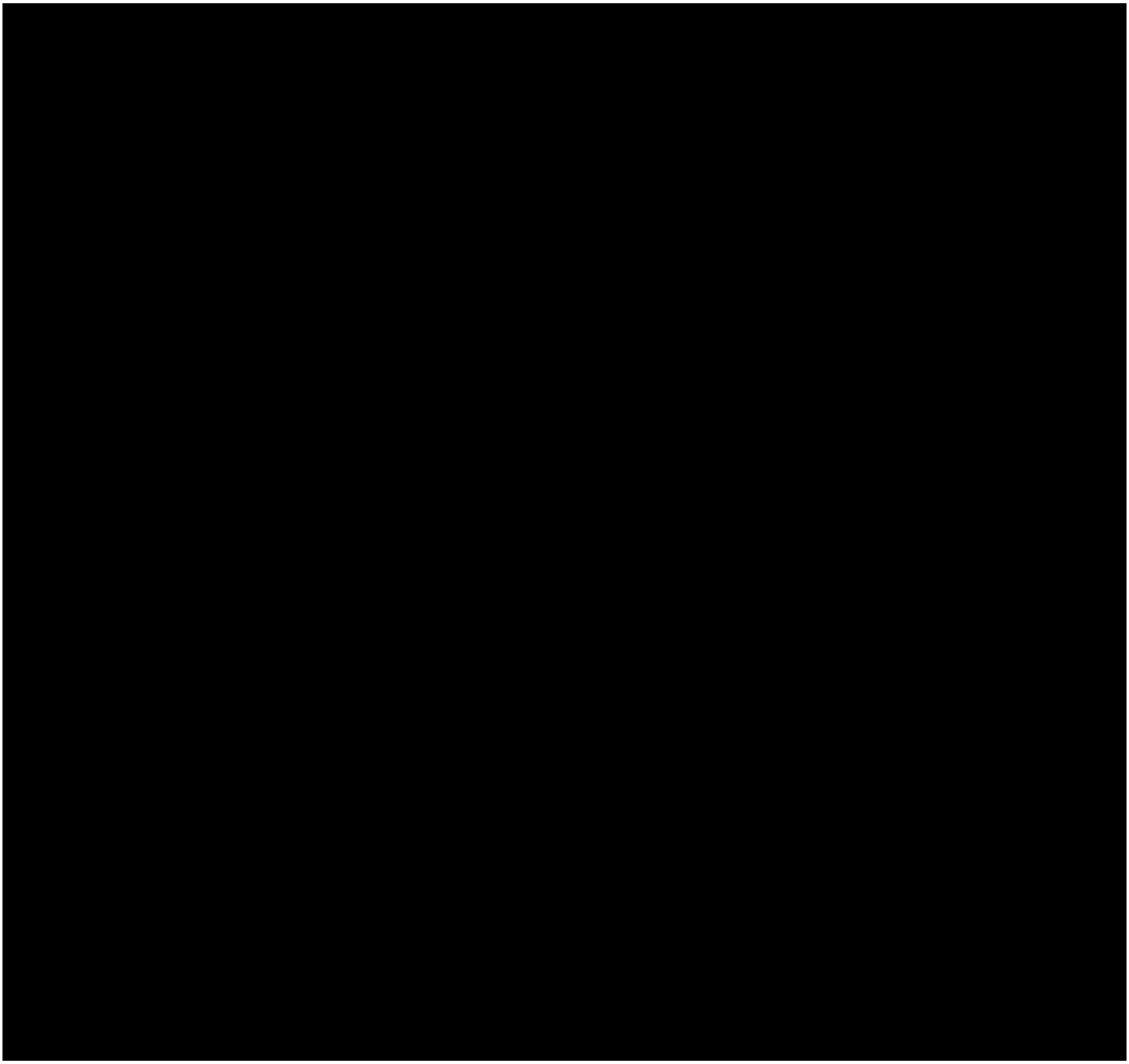
The following descriptive statistics will be calculated for analyte concentrations as well as for all PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the

evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Efficacy
Efficacy endpoints will be assessed: [redacted].
Trial participants who do not complete 12 weeks of treatment due to disruption related to COVID-19 will be replaced to achieve up to 100% sample size in each dose group; the main PoCP efficacy analysis will exclude these trial participants, [redacted]; drop-outs due to other reasons will not be replaced and will be included in all analyses

[redacted]





7.2.6 Safety analyses

Safety will be assessed from the further endpoints and parameters of interest listed in Section 2.2.2.1 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 to the trial participant will be used (any deviations from the randomised treatment will be discussed in the minutes of the Report Planning Meeting).

Treatments will be compared in a descriptive way. Placebo group in the safety evaluation will consist of all trial participants treated with placebo, regardless of the dose group in which they were treated. The BI 3006337-treated groups will be compared with 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 planned time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs). Therefore, measurements planned, or AEs recorded prior to first injection of trial medication will be assigned to the 'screening' period, those between the first trial medication injection and end of REP (see Section 1.2.5) will be assigned to the treatment period. Events occurring after the REP but prior to next injection or end of 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 database lock 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-trial intervals).

AEs will be coded using MedDRA. All treated trial participants will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent adverse events, i.e. all AEs occurring between start of treatment and end of the REP. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by primary system organ class and preferred term. SAEs, AESIs (see Section 5.2.6.1.4) and other significant AEs (according to ICH E3) will be listed separately.

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

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

7.2.7 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Sections 2.1.3 and 2.2.2 for drug BI 3006337 will be calculated using non-compartmental analysis. Trial participant s who are not included in

the PKS (refer to Section 7.3.2) will be reported with their individual plasma and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma pharmacokinetic parameters or other statistical assessment.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Noncompartmental PK parameters will be calculated based on actual sampling times using a validated PK software (e.g. Phoenix® WinNonlin®). Preliminary analysis will be based on planned sampling times (see Section 7.2.9). Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

The concentration taken before the first dose is generally below lower limit of quantification (BLQ). To perform a noncompartmental analysis, this concentration at time zero is set to zero. BLQ values in the lag-phase are also set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values are ignored, i.e. those occurring after a concentration above BLQ.

If a predose concentration value is greater than 5% of C_{max}, the trial participant's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidance. The individual pharmacokinetic parameters of such a trial participant will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of the trial participant's C_{max} value, the trial participant's data without any adjustments will be included in all pharmacokinetic measurements and calculations. The area under the curve will be calculated using the linear up/log down algorithm: if a drug concentration is equal to or higher than the preceding concentration, the linear trapezoidal method is used. If the drug concentration is smaller than the preceding concentration, the logarithmic method is used.

The $AUC_{\tau,ss}$ is calculated based on actual sampling times according to the following rules. If the dosing interval lies within the time frame of scheduled samplings but does not coincide with an observed sampling point, then a linear or logarithmic interpolation is done to estimate the corresponding drug plasma concentration at time t_τ, according to the trapezoidal rule that applies. The prerequisite for this rule is plasma concentrations above the quantification limit. If the dosing interval goes beyond the time of the last quantifiable data observation and λz cannot be estimated, various options may apply.

(1) No $AUC_{\tau,ss}$ value is reported for this subject (not calculated = NC)
(2) If reasonable, the pre-dose concentration at steady state may be used as concentration at the end of the dosing interval in order to determine $AUC_{\tau,ss}$.
(3) Alternatively, $AUC_{0\text{-}tz,ss}$ should be given instead (if reasonable for all subjects), where $AUC_{0\text{-}tz,ss}$ is the area under the concentration-time curve from the time point 0 after the last dose at steady state to the last quantifiable drug plasma concentration within the dosing interval τ. However, $AUC_{\tau,ss}$ and $AUC_{0\text{-}tz,ss}$ should be considered as different parameters and should not be merged for combined descriptive statistics.

Every effort should be made to include all concentration data in the PK and/or PD analysis. If not possible, a case-by-case decision is required whether the value should only be excluded from half-life estimation, descriptive statistics or the complete analysis. The excluded concentration will be listed in the PK/PD exclusion file and displayed in the concentration listings of the CTR with the respective flag. The following rules generally apply:

- If a concentration is excluded from half-life determination only, it will be used for all parameter calculations, except the half-life determination, and it will be included for the calculation of descriptive statistics and for graphical presentation,
- If a concentration value is excluded from descriptive statistics, it is used for parameter calculation, but not included for calculation of descriptive statistics. The value may be presented graphically in displays that only show individual data based on actual times (timescale is based on planned time).,
- If a concentration value is excluded from further calculations, it is neither used for the calculation of parameters and descriptive statistics nor presented graphically in the CTR.

The decision to exclude a concentration value from the analysis should be justified in the CTR, and only the derived parameters obtained without the excluded concentration value should be presented throughout the CTR. However, in case of sensitivity analysis, derived parameters obtained with excluded concentration value may be presented as well with an appropriate flag.

Descriptive statistics of concentrations at specific time points are calculated by default when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled is based on the total number of samples that were drawn at the specific time point (i.e. BLQ, NOR, NOA and NOS are included).

$$\frac{number\ of\ concentrat\ ion\ values}{total\ number\ of\ samples} \geq 2/3 \quad \text{(At a specific time point)}$$

For assessment of dose proportionality, Linearity index and attainment of steady state, see Sections 7.2.4 and 7.2.5.

Graphical displays

To support the analyses of dose proportionality, linearity and attainment of steady state, graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of trough plasma concentrations and the (geometric) mean plasma concentration time profiles.

Biomarker analysis

Intra-individual differences from baseline (Day -1 of Visit 2) will be calculated for all PD endpoints (see Section 5.4). Data will be compared descriptively between DGs and placebo. The placebo group will consist of all subjects treated with placebo, regardless of the DG in which they were treated.

Additionally, for estimation purposes model-based analyses may be applied as appropriate:

- [redacted]
- [redacted]

More details will be provided in the TSAP.

[redacted]

7.2.9 Interim analysis

No interim analysis is planned. Unblinded exploratory analyses on the safety and tolerability, will be performed during the conduct of the trial to evaluate dose escalations.

A preliminary analysis of selected PK parameters of BI 3006337 (e.g. $AUC_{\tau,ss}$ and $C_{max,ss}$ after Week 3) as well as nausea/vomiting and HR provided as individual values and appropriate summary measures, will be performed for dose before proceeding to the next dose level or expanding the dose group on the highest tolerated dose level. Available concentration data up to at least Visit 6 will be used.

In contrast to the final PK/PD calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results. The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without trial participant identification information. The preliminary results will be distributed to the investigator and the trial team. Depending on the results of available preliminary PK/PD analyses and the tolerability and safety of the compound, changes to the dosing schedule (e.g. additional intermediate doses), and additional PK/PD preliminary analyses may be performed if requested by the Clinical Trial Lead, the investigator or Trial Clinical Pharmacologist. Preliminary PK/PD results will not be reported in the CTR.

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

It is not planned to impute missing values for PK parameter calculations.

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

7.4 RANDOMIZATION

Within each dose group, randomization will only be performed in Cohort 3 in a 5:3 ratio (BI 3006337 to placebo). The first two cohorts will follow fixed dosing.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. Specific parameters used for the creation of the randomization schedule (e.g. block size or biasing coin probabilities) will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enrol approximately 56 trial participants in this trial (the maximum number of trial participants will not exceed 72): the size of at least 14 trial participants per dose group (10 on BI 3006337 and 4 on placebo) is generally considered reasonable for the exploratory evaluation of multiple dose safety and PK.

Trial participants who cannot complete 12 weeks of treatment due to disruption related to COVID-19 will be replaced to achieve up to 100% sample size in each dose group.

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

The trial will be carried out in compliance with the CTP, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Guideline for GCP, relevant BI SOPs, the US Code of Federal Regulations, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the CTP, 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 treating physician of the trial participant.

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

The trial participant must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the trial participant's own free will with the ICF after confirming that the trial participant understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the ICF. 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 participant 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, 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 the 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 trial participants 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 that include all observations and other data pertinent to the investigation on each trial participant. Source data as well as reported data should follow the 'ALCOA principles' and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal, and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the trial participant may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least 1 documented attempt to retrieve previous medical records. If this fails, a verbal history from the trial participant, documented in their medical records, would be acceptable.

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

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

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

- Trial participant identification: sex, year of birth (in accordance with local laws and regulations)

- Trial participant participation in the trial (substance, trial number, trial participant number, date the trial participant was informed)
- Dates of trial participant'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 trial participant's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a trial participant 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 trial participant or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the trial participant eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

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

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war; please see Section 6), site access may be restricted, thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY

Data protection and data security measures are implemented for the collection, storage, and processing of trial participant data in accordance with the principles 7 and 12 of the World Health Organization GCP handbook.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a trial participant identification number instead of the trial participant's name. The code is only available at the site and must not be forwarded to the sponsor. In case trial participant's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the trial participant will be redacted by the site prior to forwarding. Access to the trial participant files and clinical data is strictly limited: personalised treatment data may be given to the trial participant's personal physician or to other appropriate medical personnel responsible for the trial participant'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.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs, and trial participants will be informed as appropriate.

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

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

- Sample and data usage must be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials

- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to the ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **first act of recruitment** representing the **start of the trial** is defined as the date when the first trial participant in the whole trial signs informed consent.

The **end of the trial** is defined as the 'date of the last visit of the last trial participant in the whole trial' ('Last Trial Participant Completed'). At the trial participant level, this is the date of the follow-up visit. The "**Last Trial Participant Last Treatment"** (LPLT) date is defined as the date on which the last trial participant in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this CTP.

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.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by BI Pharma GmbH & Co. KG, Germany.

A DEC will be established to decide on dose escalation (see Section 3.1).

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

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial

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

The trial will be conducted in 10 to 25 Phase I sites with access to MRI-PDFF measurements in the USA under the supervision of the Principal Investigators. The centres manage the trial in accordance with applicable regulations and internal SOPs.

Safety laboratory tests will be performed in a central laboratory and/or a dedicated CRO appointed by BI using validated assays.

The analyses of BI 3006337 concentrations and ADAs/NAbs in serum will be performed at [redacted]

The analyses of acetaminophen will be performed at [redacted]

For investigation of PDs, serum adiponectin (HMW and total) and the bone biomarkers in serum will be measured in a central laboratory and/or a dedicated CRO appointed by BI using validated assays.

MR imaging to assess the liver fat content in the whole liver using proton density fat fraction (PDFF) will be performed at [redacted]

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

On-site monitoring will be performed by the CRO.

Data management responsibility is with an CRO according to BI´s FOT model and agreed contract with CRO. Statistical tasks and programming will be performed by a CRO. CRO works according CRO´s SOPs and BI´s SOPs/documents which are available in the BI procedural document list.

Tasks and functions assigned 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. Responsibilities of the TSTAT will be filed in the TMF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P13-02280 Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2012; 10(8); 837-858.

R07-4722 Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), 2005.

R08-1466 Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (September 2007). Website: fda.gov/cber/guidelines.htm; 2007.

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R11-4890 Sampson HA *et al.* Second symposium on the definition and management of anaphylaxis: summary report - second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol; 117(2), p. 391-397; 2006.

R15-5365 Weston CJ, Shepherd EL, Claridge LC, et.al. Vascular adhesion protein-1 promotes liver inflammation and drives hepatic fibrosis. J Clin Invest 2015; 125(2); 501-520.

R15-6057 Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. Natl Vital Stat Rep 2013; 61(4); 1-117.

R15-6070 Dharel N, Fuchs M. Nonalcoholic fatty liver disease - a major public health challenge for the 21 st century. JSM Gastroenterol Hepatol 2014; 2(2); 1018.

R16-0366 E14 Implementation Working Group. ICH E14 guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions & answers (R3) (current version dated 10 December 2015). Website: ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1 4/E14_Q_As_R3__Step4.pdf (access date: 29 January 2016); Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2015).

R16-3177 Armstrong MJ, Gaunt P, Aithal GP, *et al.* Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled Phase II study. Lancet 2016; 387(10019); 679-690.

R18-1357 U.S. Department of Health and Human Services - Common terminology criteria for adverse events (CTCAE) version 5.0

R18-2829 Murphy KG, Bloom SR. Nonpeptidic glucagon-like peptide 1 receptor agonists: a magic bullet for diabetes? Proc Natl Acad Sci USA; 104(3), p. 689-690; 2007.

R19-2360 Sonoda J, Chen MZ, Baruch A. FGF21-receptor agonists: an emerging therapeutic class for obesity-related diseases. Horm Mol Biol Clin Invest 2017; 30(2).

R19-2365 Wei W, Dutchak PA, Wang X, *et al.* Fibroblast growth factor 21 promotes bone loss by potentiating the effects of peroxisome proliferator-activated receptor gamma. Proc Natl Acad Sci USA; 109(8), p. 3143-3148; 2012.

R20-0498 Xu P, Zhang Y, Liu Y, *et al.* Fibroblast growth factor 21 attenuates hepatic fibrogenesis through TGF-beta/smad2/3 and NF-kappaB signaling pathways. Toxicol Appl Pharmacol 2016; 290; 43-53.

R20-0504 Xu J, Lloyd J, Hale C, *et al.* Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. Diabetes; 58, p. 250-259; 2009.

R20-0506 Sarruf DA, Thaler JP, Morton GJ, *et al.* Fibroblast growth factor 21 action in the brain increases energy expenditure and insulin sensitivity in obese rats. Diabetes; 59, p. 1817-1824; 2010.

R20-0507 Sanyal A, Charles ED, Neuschwander -Tetri BA, *et al.* Pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analogue, in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, Phase IIa trial. Lancet 2018; 392; 2705-2717.

R20-0508 Kharitonenkov A, Shiyanova TL, Koester A, *et al.* FGF-21 as a novel metabolic regulator. J Clin Invest; 115(6), p. 1627-1635; 2005.

R20-0509 Kim AM, Somayaji VR, Dong JQ, *et al.* Once-weekly administration of a long-acting fibroblast growth factor 21 analogue modulates lipids, bone turnover markers, blood pressure and body weight differently in obese people with hypertriglyceridaemia and in non-human primates. Diabetes Obes Metab 2017; 19; 1762-1772

R21-3294 Causs C, Reeder SB, Sirlin CB, *et al.* Noninvasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology; 68(2), p. 763-772; 2018.

R22-0898 Bonekamp S, Tang A, Mashhood A, *et al.* Spatial distribution of MRI-determined hepatic proton density fat fraction in adults with nonalcoholic fatty liver disease. J Magn Reson Imaging; 39, p. 1525-1532; 2014.

R22-0899 Harrison SA Ruane PJ Freilich BL Neff G Patil R Behling CA Hu C Fong E Temple B_de Tillman EJ Rolph TP Cheng A Yale K. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, Phase IIa trial. Nature Med; 27, p. 1262-1271; 2021.

R22-0900 Patel J, Bettencourt R, Cui J, *et al.* Association of noninvasive quantitative decline in liver fat content on MRI with histologic response in nonalcoholic steatohepatitis. Ther Adv Gastroenterol; 9(5), p. 692-701; 2016.

R22-4307 Harrison SA Ruane PJ Freilich B Neff G Patil R Behling C *et al.* A randomized, double-blind, placebo-controlled Phase IIa trial of efruxifermin for patients with compensated NASH cirrhosis. JHEP Rep; 2022.

R22-4429 National Institutes of Health. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events (version 2.0, November 2014). Website: rsc.niaid.nih.gov/sites/default/files/daids-ae-grading-table-v2-nov2014 .pdf (access date: 2022-12-16); 2014.

R23-0438 Trulicity (dulaglutide) injection, for subcutaneous use (Eli Lilly) (U.S. prescribing information, revised: 11/2022). 2022.

R23-0766 TYLENOL For Children Plus Adults - acetaminophen suspension; product information. Website: accessdata.fda.gov/spl/data/702a808 d-9376-4f67-89f8-d5dd43d5d793/702a808 d-9376-4f67-89f8-d5dd43d5d793.xml (access date: 28 February 2023)

R23-1948 U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015-2020 Dietary Guidelines for Americans (8th ed, December 2015);

R23-2478 Loomba R, Sanyal AJ, Kowdley KV, Bhatt DL, Alkhouri N, Frias JP, *et al.* Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. N Engl J Med 2023.

R23-4413 Zepbound (tirzepatide) Injection, for subcutaneous use (Eli Lilly) (U.S. prescribing information, revised: 11/2023). 2023.

R23-4564 Wegovy (semaglutide) injection, for subcutaneous use (Novo Nordisk) (U.S. prescribing information, revised: 07/2023). 2023.

R24-0206 Ozempic (semaglutide) injection, for subcutaneous use (Novo Nordisk) (U.S. full prescribing information, revised: 9/2023). 2023.

R24-0207 Victoza (liraglutide) injection, for subcutaneous use (Novo Nordisk) (U.S. prescribing information, revised: 07/2023). 2023.

R24-0208 Saxenda (liraglutide) injection, for subcutaneous use (Novo Nordisk) (U.S. prescribing information, revised: 04/2023). 2023.

R24-0209 Mounjaro (tirzepatide) injection, for subcutaneous use (Eli Lilly and Company) (U.S. prescribing information, revised: 07/2023). 2023.

R24-0216 Trulicity 0.75 mg, 1.5 mg, 3 mg, 4,5 mg solution for injection in prefilled pen (Eli Lilly) (summary of product characteristics, manufacturers of the biological active substance and manufacturer responsible for batch release, conditions or restrictions regarding supply and use, other conditions and requirements of the marketing authorisation, conditions or restrictions with regard to the safe and effective use of the medicinal product, labelling and package leaflet, last updated: 16/03/2023). 2023.

9.2 UNPUBLISHED REFERENCES

[redacted]

10. APPENDICES

10.1 TRIAL PARTICIPANT FEEDBACK

Optional Trial Participant Feedback Questionnaires:
This trial will include an option for participants to complete anonymized questionnaires, 'Trial Participant Feedback Questionnaire', to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval and after consent of the trial participant. Providing feedback is optional and not required for participation in the trial.

Optional Caregiver Feedback Questionnaires:
If applicable, this trial will include an option for caregivers to complete anonymized questionnaires, 'Caregiver Feedback Questionnaire', to provide feedback on the clinical trial experience. Individual caregiver level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval and after consent of the caregiver. Providing feedback is optional and not required for participation in the trial.

10.2 INSTRUCTIONS FOR USE

Not available.

10.3 COVID-19 RISK ASSESSMENT

Potential risks for trial participants due to the COVID-19 pandemic have been evaluated together with the Coordinating Investigator. The mode of action, available pharmacological, non-clinical and clinical data do not indicate an increased risk of contracting SARS-CoV-2 or aggravated clinical courses due to the treatment with BI 3006337 (e.g. effects on impaired or over- active immune-response). However, participants with NAFLD are at higher risk for severe illness from COVID-19 due to the underlying common co-morbidities (obesity, diabetes, CV disease).

Participants with active SARS-CoV-2 infection at the screening (e.g. confirmed by PCR test) will be excluded from the trial (see Section 3.3.3). Rescreening of patients following the resolution of symptoms may be possible at the investigator´s discretion. In case of a diagnosed severe SARS-CoV-2 infection, trial treatment might be discontinued immediately and appropriate measures for monitoring, treatment and quarantine will be implemented. Trial treatment may be resumed after recovery as per Investigator´s discretion based on individual benefit-risk assessment on a case-by-case basis.

Based on current data, the mode of action of BI 3006337 should not interfere with the immune system. Hence, effects of BI 3006337 on either the safety or efficacy of COVID-19 vaccines are considered unlikely.

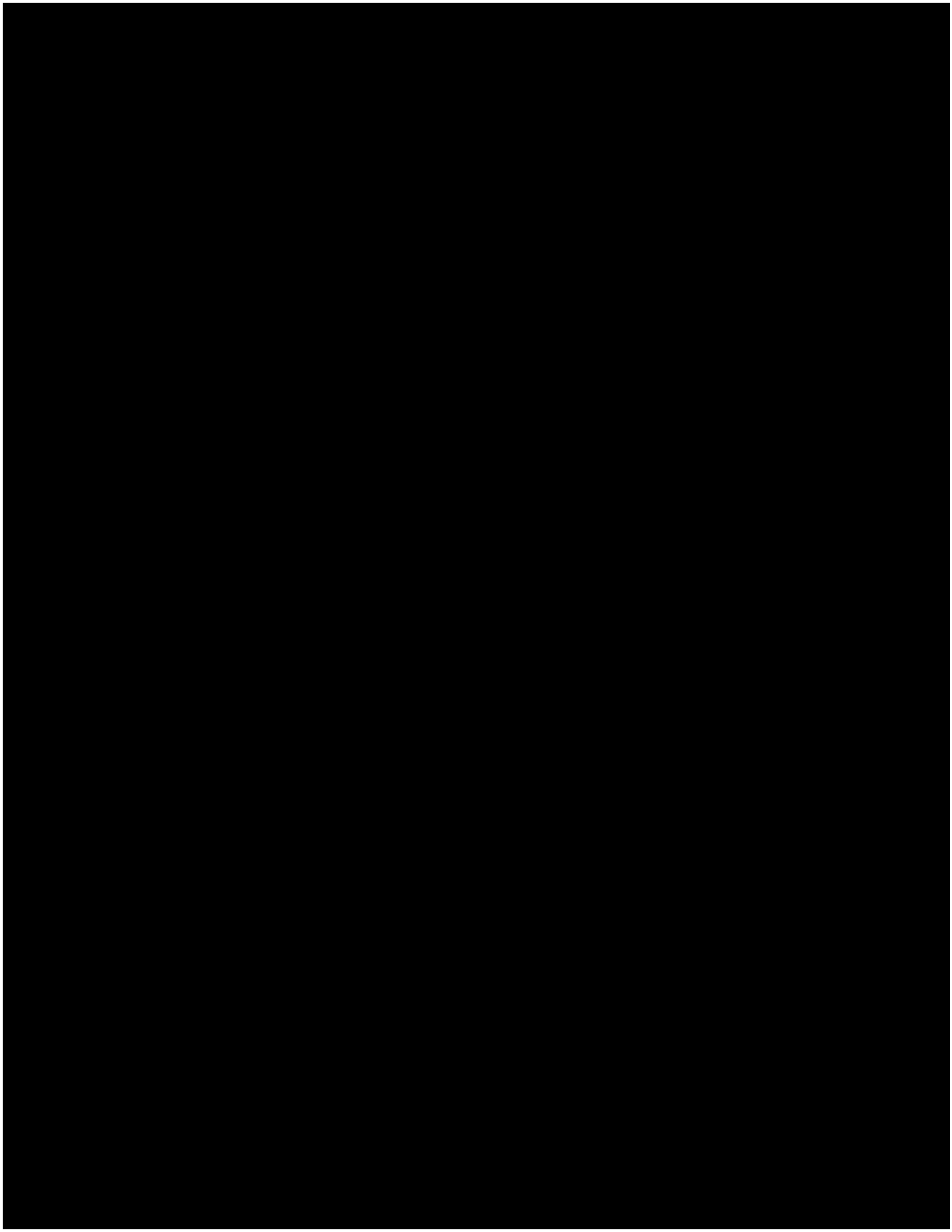
The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the planned trials. BI as the sponsor, if required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the patient.

10.4 DIAGNOSIS OF ANAPHYLAXIS

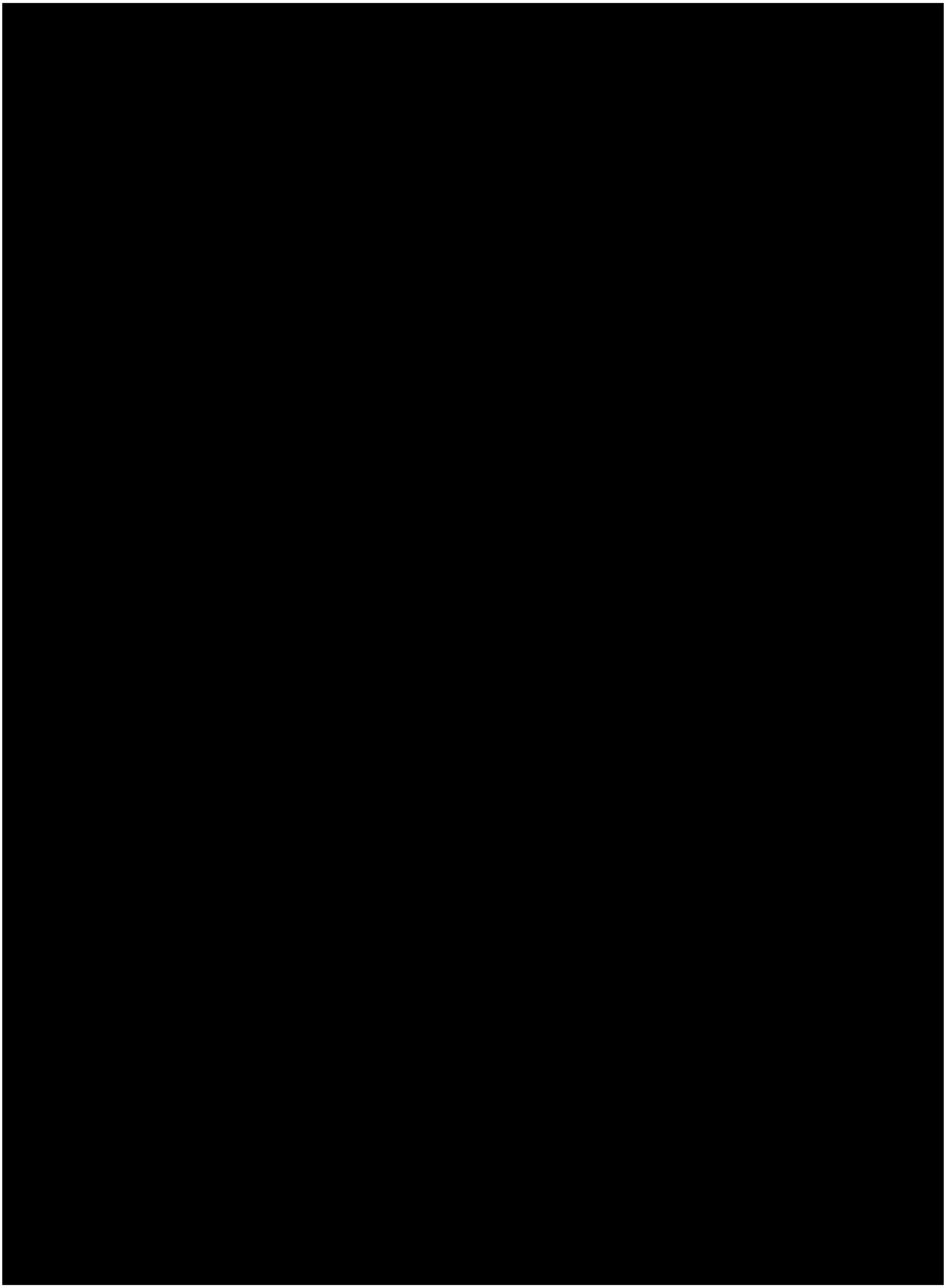
Clinical Criteria for diagnosing anaphylaxis [R11-4890]

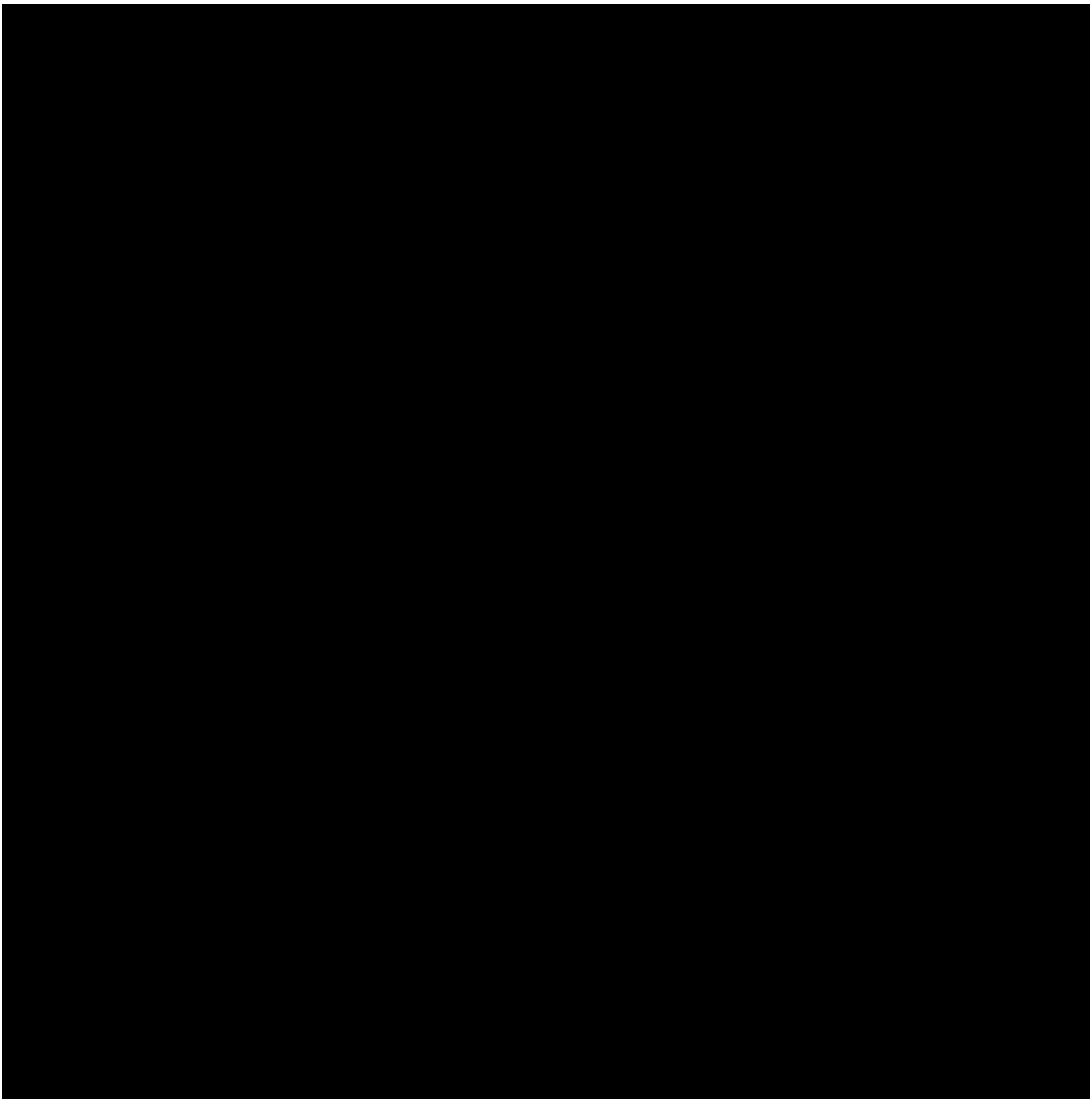
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

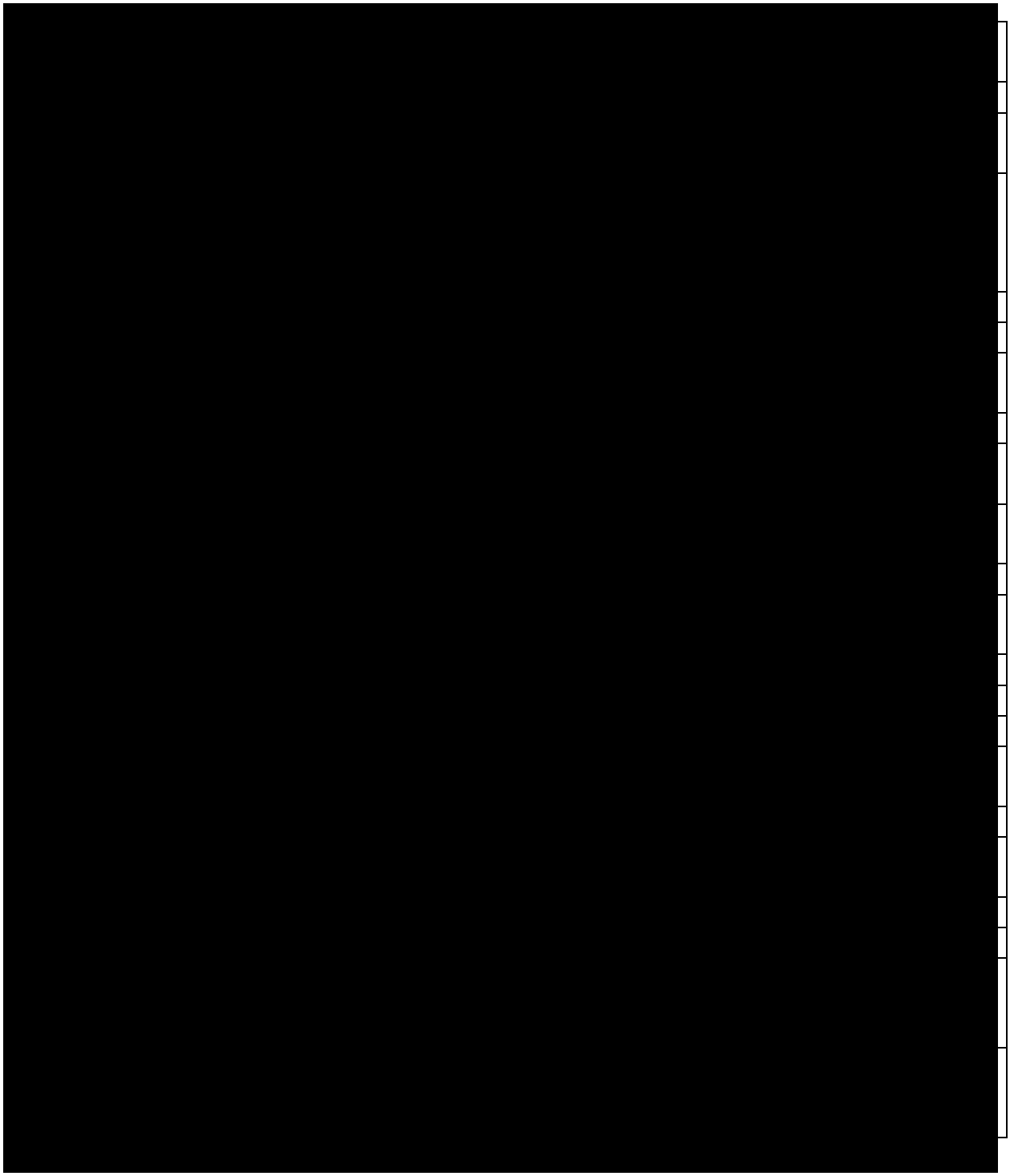
PEF, Peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg +[2 x age] from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.



[redacted]







APPROVAL / SIGNATURE PAGE

Document Number: c39013879 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-05

Title: Phase Ib trial to assess safety and tolerability of multiple subcutaneous doses of BI 3006337 in patients with overweight or obesity and hepatic steatosis

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	08 Feb 2024 21:06 CET
Approval-Clinical Program [redacted]		09 Feb 2024 10:15 CET
Approval-Biostatistics		09 Feb 2024 16:27 CET
Verification-Paper Signature Completion		14 Feb 2024 07:48 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed