Boehringer Ingelheim

Clinical Trial Protocol

	Document Number: **c40535128-02**
EU Clinical Trial No.	2022-502424-43-00
BI Trial No.	1509-0001
BI Investigational Medicinal Product	BI 3000202
Title	A randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, and pharmacokinetics of single rising doses of BI 3000202 administered as tablet to healthy male subjects, and a randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 3000202 as tablet with and without food in healthy male subjects
Lay Title	A study in healthy men to test how different doses of BI 3000202 are tolerated and how food influences the amount of BI 3000202 in the blood
Clinical Phase	I
Clinical Trial Leader	[redacted]
Principal Investigator	[redacted]
Current Version, Date	Version 2.0, 25 May 2023
Original Protocol Date	21 Mar 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	21 March 2023
Revision date	25 May 2023
BI trial number	1509-0001
Title of trial	A randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, and pharmacokinetics of single rising doses of BI 3000202 administered as tablet to healthy male subjects, and a randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 3000202 as tablet with and without food in healthy male subjects
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	This trial starts the clinical development of BI 3000202. The single rising dose (SRD) part of the trial investigates safety, tolerability, and pharmacokinetics of a range of single doses of BI 3000202 as basis for further development. The food effect (FE) part is conducted to assess the effect of food on the relative bioavailability of the BI 3000202 [redacted].
Trial objectives	SRD part: To investigate safety, tolerability, and pharmacokinetics following single rising doses of BI 3000202 as [redacted]. FE part: To investigate the influence of food on the relative bioavailability of the BI 3000202 [redacted]
Trial endpoints	SRD part: • Primary endpoint: Occurrence of any treatment-emergent adverse event assessed as drug-related by the investigator. This is expressed as the percentage of subjects treated with investigational drug who experience such an event. • Secondary endpoints: AUC_{0-24} and C_{max} of BI 3000202 in plasma FE part: • Primary endpoints: AUC_{0-24} and C_{max} of BI 3000202 in plasma • Secondary endpoint: $AUC_{0-\infty}$ of BI 3000202 in plasma
Trial design	SRD part: Single-blind, randomised within dose groups, placebo-controlled parallel-group design. FE part: Open-label, randomised, single-dose, two-way cross-over design investigating the two treatments: [redacted] fasted and [redacted] fed

Number of subjects	
total entered	68*
on each treatment	SRD part: 56* (6 receiving BI 3000202 and 2 receiving on placebo at each of 7 dose levels) FE part: 12 subjects (all on active) * Additional subjects may be entered in the SRD part to allow testing of additional doses based on experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered in the SRD part may exceed 56 but is not to exceed 80. The addition of further dose groups exceeding the already tested dose levels for the evaluation of safety findings will be subject to a substantial CTP amendment requiring approval.
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test products	SRD part: [redacted] BI 3000202 FE part: [redacted] BI 3000202
Dose	SRD part:* [redacted] as single dose * Based on experience gained during the trial conduct (e.g. preliminary PK data), intermediate doses may be tested provided the planned and approved highest dose will not be exceeded. FE part:** [redacted] as single dose ** The FE part will only be started if in the SRD part a dose at least 4-fold the dose selected for the FE part has shown acceptable safety and tolerability. This means, that a dose of [redacted] to be used in the FE part requires a safe and tolerable dose of at least [redacted] in the SRD part.
mode of administration	SRD part: [redacted] an overnight fast of at least 10 h FE part: [redacted] an overnight fast of at least 10 h (Treatment R) and following a high calorie, high fat breakfast (Treatment T)
Comparator products	SRD part: Placebo to BI 3000202 [redacted] FE part: Not applicable
Dose	SRD part: [redacted] (placebo [redacted] matching to active dose groups) FE part: Not applicable
mode of administration	SRD part: [redacted] after an overnight fast of at least 10 h FE part: Not applicable
Duration of treatment	SRD Part: 1 single dose FE part: 2 single doses separated by a washout period of at least 3 days

Statistical methods	Descriptive statistics will be calculated for all endpoints. SRD part: Dose proportionality will be explored under fasting conditions using a regression model. A 95% confidence interval for the slope will be computed. FE part: Relative bioavailability will be estimated by the ratios of the geometric means (tablet fed / tablet fasted) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for sequence, subjects nested within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA.

FLOW CHART – SRD PART

Visit	Day	Planned time (relative to drug administration) (h:min)	Approximate clock time of actual day (h:min)	Event and comment	Safety laboratory [8]	PK blood [10, 12]	PK urine [10,13]	PD blood [10]	12-lead ECG [9]	Continuous ECG monitoring	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -1			Screening (SCR)[1]	x[A]				x		x	
2	-3 to -1	-74:00[7]	06:00	Ambulatory visit	x[B,7]							x
	1	-1:30	06:30	Admission to trial site[2]								
		-1:00	07:00		x[5]				x[2,9]	x[2]	x[2]	x[2]
		-0:45	07:15						x[2,9]			
		-0:30	07:30	Allocation to treatment[2]	x[C,2]	x[2]	x[2]	x[2]	x[2,9]			
		0:00	**08:00**	**Drug administration**			▲			▲		
		0:15	08:15			x	|			|		
		0:30	08:30			x	|		x[9]	|	x	x
		0:45	08:45			x	|			|		
		1:00	09:00			x	|	x	x[9]	|	x	x
		1:30	09:30			x[11]	|		x[9]	|		
		2:00	10:00	240 mL fluid intake		x	|	x	x[9]	|	x	x
		2:30	10:30			x	|			|		
		3:00	11:00			x	|		x[9]	|	x	x
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	┼	x	x[9]	▼	x	x
		5:00	13:00			x	|					
		6:00	14:00			x	|	x	x[9]			
		7:00	15:00	Snack (voluntary)[3]			|					
		8:00	16:00			x	┼	x	x[9]		x	x
		10:00	18:00	Dinner[3]			|					
		12:00	20:00			x	┼		x[9]		x	x
	2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	x[C]	x	▼	x	x[9]		x	x
	3	48:00	08:00	Ambulatory visit		x		x[14]	x[9]		x	x
4	4 to 14			End of study (EoS) examination[4]	x[D]				x		x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, 12-lead ECG and rhythm strip over at least 15 min, safety laboratory (including drug screening and infectious serology), demographics (including determination of body height and weight, smoking status and alcohol history), medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; procedures are to be performed and completed within the 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action..
4. At the end of study (synonym for End of Trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. Urine drug screening and alcohol breath test only
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this safety laboratory assessment can be omitted if the screening examination is performed on Days -3, -2 or -1.
8. Letters A, B, C, and D describe different sets of safety laboratory examinations (see Table 5.2.3: 1)

9. The ECG recording must be performed in triplicate ECGs at this time. At baseline (Day 1 predose) 3 triplicate ECGs are recorded within approximately 1 h. The baseline recordings should be separated by about 15 min. The resulting ECGs will be transferred electronically to the central ECG lab.
10. Sampling times and periods may be adapted based on information obtained during the trial (e.g., due to preliminary PK or PD data) including addition of samples and ambulatory appointments if the total blood volume removed does not exceed 500 mL per subject
11. In dose group [redacted], one additional blood sample for stability testing will be taken at this time (refer to Section 5.3.2.4)
12. In dose group [redacted], including blood sample for metabolite identification (refer to Section 5.3.2.2)
13. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24h.
14. For dose groups 6 and 7 only.

FLOW CHART – FE PART

Visit	Period	Day	Planned time (relative to drug administration) (h:min)	Approximate clock time of actual day (h min)	Event and comment	Safety laboratory [8]	PK $_{blood}$ [9]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1		-21 to -1			Screening (SCR)[1]	x[A]		x	x	
2	1	-3 to -1	-74:00[7]	06:00	Ambulatory visit	x[B,7]				x[7]
2/3 *	1/2 *	-1	-14:00	18:00	Admission to trial site[10]	x[5]				x
		1	-1:00	07:00	Allocation to treatment (visit 2 only)[2]	x[C,2]	x[2]	x[2]	x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast (treatment T only)					
			0:00	**08:00**	**Drug administration**					
			0:15	08:15			x			
			0:30	08:30			x			
			0:45	08:45			x			
			1:00	09:00			x			
			1:30	09:30			x	x	x	x
			2:00	10:00	240 mL fluid intake		x			
			2:30	10:30			x			
			3:00	11:00			x			
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	x	x	x
			5:00	13:00			x			
			6:00	14:00			x			
			7:00	15:00	Snack (voluntary)					
			8:00	16:00			x			x
			10:00	18:00	Dinner[3]					
			12:00	20:00			x			x
		2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	x[C]	x	x	x	x
		3	48:00	08:00	Ambulatory visit		x			x
4		4 to 14			End of study (EoS) examination[4]	x[D]		x	x	x

*Two identical treatment periods separated by a wash-out phase of at least 3 days between BI 3000202 administrations

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, 12-lead ECG, safety laboratory (including drug screening and infectious serology), demographics (including determination of body height and weight, smoking status and alcohol history), medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; procedures are to be performed and completed within 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (synonym for End of Trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. Urine drug screening and alcohol breath test only.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Visit 2 only; safety laboratory to be taken and to be medically evaluated within 3 days prior to first administration of study drug; this assessment can be omitted if the screening examination is performed on Days -3, -2 or -1.
8. Letters A, B, C, and D describe different sets of safety laboratory examinations (see Table 5.2.3: 1)

9. Sampling times may be adapted based on information obtained during the trial (e.g., due to preliminary PK data in the SRD part) including addition of samples and ambulatory appointments if the total blood volume removed does not exceed 500 mL per subject
10. The time is approximate; all procedures are to be completed no later than 10 h prior to drug administration.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse events of special interest
Ae_{t1-t2}	Amount of analyte eliminated in urine over the time interval t_1 to t_2
AMP	Auxiliary Medicinal Product
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-24}	area under the concentration-time curve of the analyte in plasma over the dosing interval 0 to 24 hours
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
$CL_{R,\ t1-t2}$	Renal clearance of the analyte in plasma from the time point t_1 to t_2
C_{max}	Maximum measured concentration of the analyte in plasma
C_{min}	Minimum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)
EUCT No.	EU Clinical Trial No.
FE	Food effect
fe_{t1-t2}	Fraction of administered drug excreted unchanged in urine over the time

	interval from t_1 to t_2
GCP	Good Clinical Practice
gMean	Geometric mean
HPC	Human Pharmacology Centre
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
PR interval	ECG interval from the onset of P wave to the beginning of the QRS complex
QRS duration	Duration of the QRS complex, i.e. the combination of the Q, R, and S waves in an electrocardiogram
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
REP	Residual effect period
SAE	Serious adverse event
SOP	Standard operating procedure
SRD	Single-rising dose
SSc	Systemic sclerosis
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

BI 3000202 is a [redacted] is developed for [redacted]

1.1 MEDICAL BACKGROUND

Systemic sclerosis (SSc) is an immune-mediated, multi-organ, and heterogeneous rheumatic disease with high mortality, characterized by extensive fibrosis, vasculopathy, and autoantibodies against various cellular antigens. It is a rare and orphan disease with high unmet medical need, with a European prevalence rate of approximately 100 to 200 per million, a United States (US) prevalence rate of 50 to 300 per million, and an Asian prevalence rate of 20 to 50 per million (R14-4918). Except for the recent approval of rituximab in Japan, there are no approved disease-modifying drugs in SSc.

SSc patients have been classified into two major disease subsets based on the extent of skin involvement. Those with generalized involvement are classified as diffuse cutaneous systemic sclerosis (dcSSc), whereas those with restricted involvement affecting the limbs distal to the elbows or knees, with or without face and neck involvement, are classified as limited cutaneous systemic sclerosis (lcSSc) (R17-0149). These skin-based subsets have other distinguishing clinical associations, as well as specific serum autoantibody profiles. dcSSc patients tend to have renal, cardiac, and lung fibrosis, while lcSSc patients frequently have late-stage complications, especially pulmonary arterial hypertension (PAH) and severe gut disease. However, some cases fall within the subsets less clearly, which has prompted a reassessment of the heterogeneity of this disease using molecular criteria (P17-04969). Extensive gene expression analyses of SSc skin samples and use of hierarchical clustering algorithms have indicated that there are four "intrinsic" gene expression subsets (molecular phenotypes) termed fibroproliferative, inflammatory, limited and normal-like, which appear to be stable in patients longitudinally (P20-07220, P20-00650). Data from small studies suggests that changes in modified Rodnan skin score (mRSS) in response to immune-modulating drugs correlate with the molecular phenotypes and may relate to [redacted]

SSc appears to share a genetic landscape with other systemic autoimmune diseases (i.e. systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), multiple sclerosis (MS), and primary biliary cholangitis (PBC); (R17-0314), (R18-3144). [redacted]

[redacted]

(R22-3708).

[redacted]

For more details on medical background refer to the Investigator's Brochure (IB) [c40070068]

1.2 DRUG PROFILE

BI 3000202 is a [redacted]

Nonclinical pharmacology, pharmacokinetics in animals and toxicology results are described in the IB [c40070068].

1.2.1 Prediction of human pharmacokinetics

A human clearance of [redacted] was predicted using *in vitro* human hepatocyte data and a correction factor from *in vitro/in vivo* correlations across mouse, rat, dog, minipig and cynomolgus monkey. A human volume of distribution at steady state of [redacted] was predicted based on mean over species. These parameters resulted in a predicted human disposition mean residence time and effective half-life [redacted], respectively [n00298647].

After oral dosing a human bioavailability, total mean residence time and absorption rate constant [redacted] were estimated, respectively.

[redacted]

1.2.2 Residual Effect Period

The Residual Effect Period (REP) of BI 3000202, when measurable drug levels and/or pharmacodynamic effects are still likely to be present, is not known for this first-in-human trial. [redacted]

1.2.3 Drug product

Please refer to Section 4.1. For a more detailed description of the BI 3000202 profile, please refer to the current Investigator's Brochure [c40070068].

1.3 RATIONALE FOR PERFORMING THE TRIAL

This trial starts the clinical development of BI 3000202. The SRD part of the trial investigates safety, tolerability, and pharmacokinetics of a range of single doses of BI 3000202 as basis for further development.

The food effect (FE) part is conducted to assess the influence of food on the relative bioavailability of the BI 3000202 [redacted]

1.3.1 Selection of starting dose (SRD part)

1.3.1.1 Derivation of safe starting dose

The maximum recommended starting dose (MRSD) was estimated following FDA Guidance for Industry 'Estimating the Maximum Recommended Safe Starting Dose in Initial Clinical Trials for Therapeutics in Healthy Volunteers' (R06-1037) based on toxicity data. Using the NOAEL in the 4-week repeat dose toxicity studies and converting these animal NOAELs to Human Equivalent Doses (HEDs):

[redacted]

Monkey: [redacted]

A detailed description of the derivation of the maximum safe starting dose can be found in the IB [c40070068].

1.3.1.2 Safety margins of starting dose to the NOAEL in rat and monkey GLP toxicity studies

[redacted]

- [redacted]
- [redacted]

* BI 3000202 plasma exposure in [redacted] exposure in [redacted] used for safety margin calculations.
** [redacted]

These safety margins of expected exposure at the starting dose to the relevant exposures at NOAEL are considered sufficient.

1.3.2 Dose escalation (SRD part)

Escalation scheme has been chosen such that escalation factors are decreasing with increasing doses. Table 1.3.2: 1 shows the planned dose escalation, the escalation factors, and the predicted systemic exposures.

Predictions are from simulations performed using R software (version 3.5.2) and are based on preclinical data. Concentration profiles were predicted after a single oral administration, from

a 2-compartment model with first-order absorption and first-order elimination, where parameter values originated from several animal species fits [n00298647].

Table 1.3.2: 1 Dose escalation scheme, escalation factors and BI 3000202 exposure in plasma predicted based on [redacted]

Dose level *	Dose of BI 3000202 (mg)	Escalation factor from previous dose level	Predicted C_{max} (nM)	Predicted AUC_{0-24} (nM*h)	C_{max} / AUC_{0-24} safety factors based on NOAEL exposure** (corrected for potency differences)***
[redacted]					

* A dose level (= dose group) will only be administered if the treatment in the preceding dose group(s) was safe and showed acceptable tolerability and if the systemic exposure of the next dose (gMean values for AUC_{0-24} and C_{max}, guided by preliminary PK analysis) is expected to not exceed the maximum acceptable exposure. For more information see Sections 1.3.3, 3.3.4, and 7.2.7.

[redacted]

1.3.3 Maximum dose and maximum exposure (SRD part)

The maximum dose in the SRD part of this trial is [redacted], and this dose will not be exceeded in this trial. Dose escalation will be guided by assessment of safety in the preceding dose group(s). The selected dose range in this trial [redacted] is expected to cover subtherapeutic, anticipated therapeutic and supratherapeutic doses.

[redacted]

Hence, it is planned to explore higher doses and exposures to account for uncertainties in translation from preclinical data to human experience, i.e. actual PK parameters may deviate from predicted values, for any or all of the following reasons:

- Bioavailability may be less than predicted
- Clearance may be higher than predicted
- Half-life and mean residence time may be shorter than predicted
- Pharmacokinetics may be non-linear with less than dose-proportional increase
- Account for uncertainties associated with PK/PD model in SSc

Further, even if the therapeutic dose turns out to be as low as [redacted] higher than therapeutic doses and exposures are typically explored in the well-controlled clinical environment of first-in-human trials if supported by non-clinical safety data, to provide a sufficient safety margin for subsequent trials, e.g.

- To cover exposures possibly be reached in trials with multiple dosing and accumulation
- To cover exposures possibly be seen in trials in patients with impaired excretion function, such as renal / hepatic impairment, where substantial increases in exposure may be seen
- To cover exposures that may possibly be achieved in subsequent drug-drug interaction trials
- To derive a safe supra-therapeutic dose for a tQT trial or achieve high enough exposures during SRD trial to waive a tQT trial
- To cover future clinical trials in case higher doses are needed to assess efficacy, including development for other indications than SSc

[redacted]

[redacted]

For a complete report of toxicity findings refer to the IB [c40070068]. In summary, the results of BI 3000202 safety pharmacology assessments demonstrated an acceptable profile for Phase I clinical trials in healthy volunteers.

[redacted]

This exposure cap is defined for the expected (predicted) gMean values of a dose level as estimated based on preliminary PK data of preceding dose group(s). That means, a dose level will only be administered if expected gMean values for C_{max} and AUC_{0-24} do not exceed these exposure values (see dose escalation stopping criteria in Section 3.3.4.3).

In addition, due to inter-individual variability, actual systemic exposure in individual subjects may exceed these values. However, as soon as the actual observed exposure in one subject exceeds the maximum acceptable exposure, dose escalation will be stopped (see Section 3.3.4.3).

[redacted]

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 3000202 as an [redacted] treatment of adults with Systemic Sclerosis.

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication. An overview on trial-related risks is given in Table 1.4.2: 1.

Table 1.4.2: 1 Overview of trial-related risks for this trial

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 3000202		
QT/QTc prolongation	Pro-arrhythmic potential as indicated by nonclinical data (refer to IB [c40070068])	Subjects with marked baseline prolongation of QT/QTc interval at screening or subjects with additional risk factors for Torsade de Pointes arrhythmia (see Section 3.3.3) are excluded from trial participation. Definition of dose escalation or treatment stopping criterion based on QT/QTc increase (see Section 3.3.4.2). Continuous ECG monitoring and frequent ECG recordings (see Flow Chart – SRD Part).
Increased bilirubin	See chapter 1.3.3	Subjects will undergo clinical laboratory testing to monitor potential changes of total and direct bilirubin
Decrease in mean number and percentage of B cells	See chapter 1.3.3	Clinical laboratory testing to monitor potential changes of lymphocyte count
Drug-induced liver injury (DILI)	At this moment, this risk is hypothetical in nature and it is a general safety consideration. DILI is a rare but severe event, thus under constant surveillance by sponsors and regulators (refer to Section 5.2.6.1.4).	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety.
Theoretical risk of increasing susceptibility to infection, the duration or severity of infection, malignancy or decreased cellular senescence	See chapter 1.3.3	Close monitoring for adverse events

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Phototoxicity potential	[redacted]	Protection measures such as sunscreen, avoiding ultraviolet light and medication with phototoxic potential (ref. Section 4.2.2.2)
Trial procedures		
Skin irritation, redness, itching	General risk by ECG electrodes, acceptable in the framework of trial participation.	Exclusion of subjects from trial participation with known clinically relevant hypersensitivity reactions to adhesive tapes.
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site

In addition, the following general safety measures will be applied in order to minimize the risk to the healthy volunteers:

- Dose selection is based on the expected pharmacologically active dose, expected systemic exposures after single-dose administration, and toxicity findings in preclinical studies. Escalation factors between dose steps decrease at higher doses. For details see Sections 1.3.1, 1.3.2, and 1.3.3.
- A maximum acceptable human exposure has been defined based on toxicity findings (see Section 1.3.3). Dose escalation is guided by preliminary analysis of BI 3000202 PK (C_{max} and AUC_{0-24}).
    - A dose level will only be administered if estimated (predicted) gMean values for C_{max} and AUC_{0-24} do not exceed the maximum acceptable human exposure (see Section 1.3.3 and Section 3.3.4.3).
    - Moreover, dose escalation will be stopped in case observed exposure in one subject who has been dosed with BI 3000202 has exceeded the maximum acceptable exposure (see Section 3.3.4.3)
- A documented Safety Review takes place prior to each dose escalation (for details, refer to Section 3.1)
- For safety reasons, each dose group of 8 subjects (6 on active and 2 on placebo) will be divided into two cohorts of 2 subjects each (1st and 2nd cohort) and one cohort of 4 subjects (3rd cohort). Further details are provided in Section 3.1.
- Stringent in- and exclusion criteria define a relatively homogenous population and exclude subjects that might be at increased risk for adverse events (see Section 3.3).
- Safety laboratory examinations will be performed at pre-defined time points (see Flow Chart - SRD Part and Flow Chart – FE Part) before and 24 hours after drug administration. These examinations include extensive standard safety laboratory examinations (see Section 5.2.3).

- A thorough ECG and heart rate monitoring including continuous ECG monitoring in the SRD part for 4 h post dose and in addition frequent 12-lead ECG and vital signs measurements at time points as described in the Flow Charts for SRD and FE part are planned.
- Subjects will be confined for at least 24 h after study drug administration. During in-house confinement the subjects are under medical observation and are monitored for both expected and unexpected adverse events. They will only be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted]. If required, in-house observation period may be prolonged.
- The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

1.4.3 Discussion

Based on the mode of action, the pharmacological target, the relevance of animal species and models and nonclinical toxicology data, BI 3000202 is not considered a high-risk compound.

In the context of the unmet medical need and anticipated benefit of BI 3000202, the benefit risk evaluation of the compound, based upon the available preclinical information for BI 3000202, is favourable.

Considering the medical need for the development of a better tolerated and more effective treatment for patients with Systemic Sclerosis, the expected benefit outweighs the potential risks

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

SRD part

The main objectives of the SRD part of this trial are to investigate safety, tolerability and pharmacokinetics (PK) of BI 3000202 in healthy male subjects following [redacted] of single rising doses.

FE part

The main objective of the FE part is to investigate the relative bioavailability of a BI 3000202 [redacted]

2.1.2 Primary endpoint

SRD part

The primary endpoint to assess safety and tolerability of BI 3000202 is the occurrence of any treatment-emergent adverse event assessed as drug-related by the investigator. This is expressed as the percentage of subjects treated with investigational drug who experience such an event.

FE part

The following pharmacokinetic parameters will be determined for BI 3000202:

- AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over the dosing interval 0 to 24 hours)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoints

The following pharmacokinetic parameters will be determined for BI 3000202, if feasible:

SRD part

- AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over the dosing interval 0 to 24 hours)
- C_{max} (maximum measured concentration of the analyte in plasma)

FE part

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives in the SRD part are the exploration of the pharmacokinetics including dose proportionality, explorative analysis of metabolites as well as investigation of exploratory biomarkers (pharmacodynamics, PD) of BI 3000202 after single dosing and the assessment of the PK/PD relationship.

2.2.2 Further endpoints

2.2.2.1 Safety and tolerability

Safety and tolerability of BI 3000202 will be assessed based on:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring (SRD part only)
- Vital signs (blood pressure, pulse rate)

2.2.2.2 Further pharmacokinetic endpoints

SRD part

The following pharmacokinetic parameters will be determined for BI 3000202, if feasible:

- t_{max} (time from dosing to the maximum measured concentration of the analyte in plasma)
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- $\%AUC_{tz-\infty}$ (the percentage of $AUC_{0-\infty}$ obtained by extrapolation)
- AUC_{t1-t2} (area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2)
- λ_z (terminal rate constant in plasma)
- $t_{1/2}$ (terminal half-life of the analyte in plasma)
- MRT_{ex} (mean residence time of the analyte in the body, extravascular)
- CL/F (apparent clearance of the analyte in the plasma after extravascular administration)

- V_z/F (apparent volume of distribution during the terminal phase after extravascular administration)
- Ae_{t1-t2} (amount of analyte that is eliminated in urine from the time interval t_1 to t_2)
- fe_{t1-t2} (fraction of administered drug excreted unchanged in urine from time point t_1 to t_2)
- $CL_{R, t1-t2}$ (renal clearance of the analyte in plasma from the time point t_1 to t_2)

Further pharmacokinetic parameters might be calculated as appropriate.

FE part

The following pharmacokinetic parameters will be determined for BI 3000202, if feasible:

- t_{max} (time from dosing to the maximum measured concentration of the analyte in plasma)
- AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- $\%AUC_{tz-\infty}$ (the percentage of $AUC_{0-\infty}$ obtained by extrapolation)
- λ_z (terminal rate constant in plasma)
- $t_{1/2}$ (terminal half-life of the analyte in plasma)
- MRT_{ex} (mean residence time of the analyte in the body, extravascular)
- CL/F (apparent clearance of the analyte in the plasma after extravascular administration)
- V_z/F (apparent volume of distribution during the terminal phase after extravascular administration)

Further pharmacokinetic parameters might be calculated as appropriate.

2.2.2.3 Exploratory biomarkers

SRD part

Percent change of INFα from *ex vivo* stimulated whole-blood will be used for the exploratory evaluation of the pharmacodynamics of BI 3000202.

Further pharmacodynamic parameters might be determined as appropriate.

FE part

No sampling of biomarkers will be done.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

[redacted]

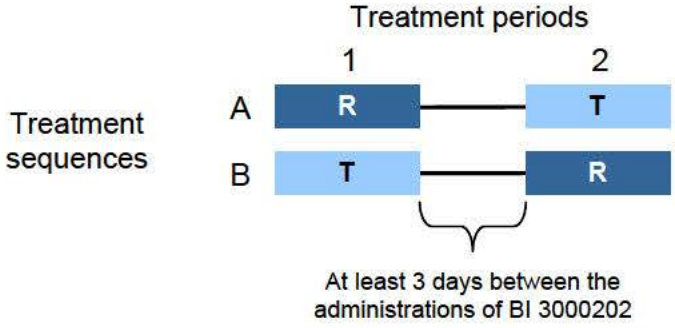

Figure 3.1: 1 Overview of trial design

SRD part: 7 doses will be tested, maintaining an interval of at least 3 days between the last drug administration in the previous dose group and the first drug administration in the subsequent dose group. Each dose group will include 8 subjects, with 6 subjects receiving BI 3000202 and 2 subjects receiving matching placebo. A safety review must take place prior to each dose escalation.

FE part: In each treatment period (1 and 2), the subjects will receive 1 dose of BI 3000202 under fed (T) or fasted (R) conditions. A washout period of at least 3 days will separate the two treatments and can be modified based on preliminary PK data from the SRD part. One dose of BI 3000202 will be tested.

SRD part

This part of the trial is designed as blinded to subjects (refer to Section 4.1.5), randomised, and placebo-controlled within parallel dose groups.

It is planned to include a total of 56 healthy male subjects in the SRD part of the trial. The subjects will be assigned to 7 groups consisting of 8 subjects per group; the groups will be dosed sequentially (see Table 3.1: 1). The investigator is allowed to add dose levels below the highest approved dose (e.g., add low and/or intermediate dose groups) on the basis of experience gained during the trial (for instance, based on preliminary PK data). Thus, the actual number of subjects entered may be more than 56 but is not to exceed 80. If required for the further evaluation of pharmacokinetics and / or pharmacodynamics, such changes may be implemented via non-substantial CTP amendments. However, the addition of further dose groups for the evaluation of safety findings is subject to a substantial CTP amendment and requires approval by the IEC/competent authority.

Within each dose group, 6 subjects will receive BI 3000202 and 2 will receive placebo. Only one dose is tested within each dose group. For safety reasons, each dose group will consist of at least 3 cohorts. The administration of trial medication is planned in the following order:

- Cohort 1: 1 subject to receive active treatment and 1 subject to receive placebo (in total 2 subjects)
- Cohort 2: 2 subjects to receive active treatment (in total 2 subjects)
- Cohort 3: 3 subjects to receive active treatment and 1 subject to receive placebo (in total 4 subjects); subjects in cohort 3 are randomly allocated to treatment.

Cohort 1 and cohort 2 as well as cohort 2 and cohort 3 will be separated by at least 22 hours each, which based on an anticipated effective half-life of BI 3000202 of approximatel [redacted]

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

Table 3.1: 1 Dose groups

Dose Group	1	2	3	4	5	6	7
Dose (mg)	[redacted]						
Number of subjects	8	8	8	8	8	8	8
Subjects to receive placebo	2	2	2	2	2	2	2
Subjects to receive BI 3000202	6	6	6	6	6	6	6

The groups will be dosed consecutively in ascending order, and a time interval of at least 3 days will be maintained between the last drug administration to subjects in the previous dose group and the first drug administration to subjects in the subsequent dose group. The decision to treat the next dose group will be based upon safety and tolerability data of all the preceding dose groups. Preliminary PK analysis will be performed regularly throughout the study (see Section 7.2.7). The next dose group will only be treated if, in the opinion of the investigator

and sponsor, no safety concerns have arisen in the preceding dose groups (i.e. no dose-limiting events occurred), and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.3).

A documented safety review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime by the Principal Investigator (or an authorised deputy) or the sponsor of the trial (for instance, due to the occurrence of any unforeseen adverse events).

Although no formal safety review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.2).

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

- AEs in the current and preceding dose groups up to at least 48 h post dosing, including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to database lock)
- Results from 12-lead ECG at the site in the current and preceding dose groups up to at least 24 h post dosing
- Vital signs in the current and preceding dose groups up to at least 24 h post dosing
- Clinical laboratory tests in the current and preceding dose groups up to at least 24 h post dosing
- Preliminary PK data as detailed in Section 7.2.7
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the Clinical Trial Leader (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs, and out-of-range laboratory results (if considered clinically significant). In addition, and depending on the results and findings, suitable experts from the sponsor 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 decision making. Dose escalation will only be permitted if no safety concerns exist neither in the opinion of the Principal Investigator (or an authorised deputy) nor the Clinical Trial Leader (or an authorised deputy).

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

FE part

A total of 12 healthy male subjects is planned to participate in this randomised, open-label, two-way crossover trial part with two treatment periods in order to assess the relative

There will be a washout period of at least 3 days between the treatments. The duration of the washout period may be modified, based on preliminary SRD data.

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

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

SRD part

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

Blinding conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, subjects will be aware of the dose of drug administered. The disadvantage of the trial design is a possible observer bias with regard to dose-dependent effects; in addition, the sequential dosing of groups could potentially result in time-related effects. However, as such effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in single rising dose trials involving healthy volunteers to include a placebo group to control for safety of the trial medication. Each dose group consists of 8 subjects, with 6 randomised to active treatment, and 2 randomised to placebo. For data analysis purposes, the placebo control group will include all subjects of all dose groups treated with placebo. Six subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of safety and pharmacokinetics.

FE part

For relative bioavailability trials, the crossover design is preferred due to its efficiency: since each subject serves as his own control, the comparison between formulations or treatments is based on a comparison within subjects rather than between subjects. This trial design therefore removes inter-subject variability from the comparison between formulations or treatments (cf. R94-1529).

3.3 SELECTION OF TRIAL POPULATION

It is planned that 68 healthy male will enter the trial. The actual number of subjects entered may exceed the total of 68 if additional intermediate doses are tested in the SRD part of the trial (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

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

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

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests without any clinically significant abnormalities
2. Age of 18 to 45 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
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

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders

6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. 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
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients and including intolerance or allergy to standardised meals)
12. Use of drugs within 21 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation) or vaccination of any kind within 21 days of planned administration of trial medication or any vaccination requiring re-vaccination during the course of the trial
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 24 g per day)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. Prior history of jaundice excluding neonatal jaundice
25. ALT (alanine transaminase) or AST (aspartate transaminase) or serum creatinine above upper limit of normal range at screening examination, confirmed by a repeat test
26. Total bilirubin above 1.5 upper limit of normal range at screening examination, confirmed by a repeat test.

27. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of administration of trial medication until 30 days thereafter

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.2), the subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he is not willing or able to adhere to the trial requirements in the future
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events (AEs), or diseases)
5. An AE or clinically significant laboratory change or abnormality occurs that the investigator assesses as warranting discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg), clinically relevant changes in ECG requiring intervention, or unexplained hepatic enzyme elevations at any time during the trial

6. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor and dose stopping criteria

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational product
3. Deviation from GCP or the CTP impairing the appropriate conduct of the trial
4. New toxicological findings, serious AEs, or any safety information invalidating the earlier positive benefit-risk assessment (see Section 1.4)

Dose escalation of BI 3000202 in the SRD part or treatment in the FE part will be stopped if:

1. More than 50% of the subjects at one dose level show drug related and clinically relevant adverse events of moderate or severe intensity, or if at least two subjects of the same dose group in the SRD part or 3 subjects in the FE part have drug-related severe non-serious adverse events, or if at least one drug-related serious adverse event is reported
2. At least 2 subjects who received active treatment at one dose level in the SRD part or 3 subjects in the FE part have relevant individual QT prolongations, i.e. a QTc increase of greater than 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording
3. The C_{max} or AUC_{0-24} of at least 1 subject of one dose group increases above the following exposure thresholds or if the estimated gMean exposure in the next dose group is expected to exceed a [redacted] Estimation will be done based on preliminary PK results of preceding dose groups (see Section 7.2.7)

3.3.5 Replacement of subjects

In general, subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced, i.e. no additional subject will be recruited to be dosed with the same treatment as the subject he replaces. Note, data from the subject to be replaced will be included in the safety analysis. The Clinical Trial Leader together with the Trial Pharmacologist and the Trial Statistician are to decide if and how many subjects will be replaced.

SRD part: If data from less subjects on active treatment than the required number of subjects needed for escalation to a subsequent dose group (see Section 3.1) are considered evaluable (including subjects evaluable for PK), enrolment of additional subjects to the current dose group will be considered in order to support the benefit-risk assessment and to achieve the required number of evaluable subjects before dose group escalation. At maximum 2 additional subjects may be recruited per dose group.

FE part: In case more than 3 subjects do not complete the trial (including subjects non-evaluable for PK), subjects may be replaced if considered necessary to reach the objective of the trial. The total number of replacements may not exceed 4 subjects (1/3 of the total number of evaluable subjects required to complete the trial). A replacement subject will be assigned a unique trial subject number and will be assigned to the same treatment sequence as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test and reference products are given below (for treatments and doses refer to Section 4.1.4):

Test product 1 (for use in SRD part)

Substance:	BI 3000202
[redacted]	[redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
[redacted]	[redacted]
Duration of use:	Single dose

Test product 2 (for use in SRD part)

Substance:	BI 3000202
[redacted]	[redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
[redacted]	[redacted]
Duration of use:	Single dose

Test product 3 (for use in SRD and FE part)

Substance:	BI 3000202
[redacted]	[redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
[redacted]	[redacted]
Duration of use:	Single dose

Test product 4 (for use in SRD part)

Substance:	BI 3000202
[redacted]	[redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
[redacted]	[redacted]
Duration of use:	Single dose

Reference product (Placebo matching to test product 1 - 4, for use in SRD part only)

Substance:	Placebo to BI 3000202 film-coated tablets
[redacted]	[redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
[redacted]	[redacted]
Duration of use:	Single dose

* For numbers of [redacted] refer to Table 4.1.4: 1 (SRD part) and Table 4.1.4:2 (FE part).

4.1.2 Selection of doses in the trial

For the SRD part, the doses selected for this trial cover the range of sub-therapeutic, anticipated therapeutic, and supra-therapeutic doses and include a safety margin (see Section 1.2).

The dose selected for the FE part is expected to be in the therapeutic range and used in further clinical development (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. Subjects willing to participate in the SRD part will be recruited to dose

groups and respective dose cohorts according to their temporal availability. As soon as enough subjects are allocated to a dose cohort, the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. Because the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects will be assigned to treatments (active treatment or placebo, SRD part) or to treatment sequences (FE part) prior to the (first) administration of trial medication. For this purpose, the randomisation scheme will be provided to the trial site in advance. Numbers of the randomisation scheme will be allocated to subjects by drawing lots. Subjects are then assigned to treatment (sequence) according to the randomisation scheme.

The randomisation procedure is described in Section 7.4.

4.1.4 Drug assignment and administration of doses for each subject

The investigator (or authorised designee) will administer the trial medication as an [redacted] together with about 240 mL of water to subjects who are in an upright position. The so-called four-eye principle (two-person rule) should be applied for administrations: 1 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.

During the first 4 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination) or to sleep.

Subjects will be kept under close medical surveillance for at least 24 hours after drug administration (SRD and FE part).

For restrictions with regard to diet, see Section 4.2.2.2.

SRD part

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

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing.

Table 4.1.4: 1 BI 3000202 and placebo treatments in SRD part

Dose group	Substance
1	BI 3000202
2	BI 3000202
3	BI 3000202
4	BI 3000202
5	BI 3000202
6	BI 3000202
7	BI 3000202
1-7	Placebo*

* Subjects receiving pl

FE part

Table 4.1.4: 2

Treatment	Substance
R	BI 3000202
T	BI 3000202

For treatment T, a high-fat, high-calorie meal will be served 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 3; this meal is in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' (R03-2269).

Table 4.1.4: 3 Composition of the high-fat, high-calorie meal

Ingredients	kcal
2 chicken eggs (whole content) for scrambled eggs	192
10 g butter for frying scrambled eggs	75
35 g fried bacon	186
2 toasted slices of wheat bread	130
15 g butter for buttering toast slices	113
115 g hash brown potatoes	132
240 mL whole milk (3.5% fat)	156
Sum[1]	984

[1] The total caloric content was supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

For treatment R, administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing.

For restrictions with regard to diet, see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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

Table 4.1.5.1: 1 Blinding level of individual functions

Role/function	Timing of Unblinding / receiving access to the treatment information (including rationale)
Subject/Participant	SRD part This trial part is blinded to treatment but not to dose level. The dose level will be known to the subject/participant. FE part This open label trial part will provide the subject treatment information as soon as treatment has been assigned.
Investigator/Site Staff	As requested to prepare trial site prior to first subject entered. The randomisation scheme will be provided to the trial site prior to randomisation for preparation of medication.
Sponsor trial team and data	As requested during trial conduct.
Bioanalytical Staff	As requested for analysis of bioanalytical samples.
Pharmacologist/ Biomarker expert/ Pharmacometrician	As requested for preliminary, interim analysis of pharmacokinetic, pharmacodynamic data or pharmacometric modelling.
Drug metabolism scientist	As requested for analysis of drug metabolites.
ECG laboratory	Within the central ECG lab, the staff involved with interval measurements will be blinded with respect to subject, treatment, recording date and time as well as planned time points of the ECGs. The staff involved with the morphological analyses will be blinded with respect to treatment. For the quality control of the measurements, certain members of the ECG evaluation team will review the entire portfolio of ECG measurements for each subject blinded to date, time, and time point.

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

4.1.5.2 Unblinding and breaking the code

As this trial will be conducted open label (FE part) / single blind (SRD part), subjects' treatment assignments will be known to investigators. Therefore, no emergency envelopes will be provided. The SAE/AESI Individual Case Safety Report (ICSR) in the safety database will be open and treatment/dosage known.

4.1.6 Packaging, labelling, and re-supply

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

The label will be prepared according to Regulation (EU) No. 536/2014, Annex 6, omitting certain particulars with the following justifications:

- The investigator name was omitted from the label because it is included on the Trial Identification Card (TIC), which will be issued to each trial subject.
- The "keep out of reach of children" statement was omitted from the label because the product will remain at the clinical site.

The visit number is not relevant for the label (SRD part) because there is only one visit.

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EU Clinical Trial Number is indicated on the title page of this protocol as well as on the subject information and informed consent forms. Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol

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

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products. These

records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of 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 Clinical Trial Leader. 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

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart – SRD Part and Flow Chart – FE Part. No food is allowed for at least 4 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the milk served with breakfast prior to treatment T in the FE part (see Table 4.1.4: 2), the water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects).

During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the (first) administration of trial medication until after the last PK sample of the trial is collected.

Alcoholic beverages must not be consumed from 3 days before the (first) administration of trial medication until after the last PK sample of the trial is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 10 h before until 24 h after administration of trial medication.

Smoking is not allowed during in-house confinement.

Excessive physical activity (such as competitive sport) should be avoided from 7 days before the first administration of trial medication until the end of trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire trial. Trial subjects are advised to apply protective measures such as sunscreen and sunglasses while outdoors Contraception requirements.

Subjects whose sexual partner is a WOCBP must use male contraception (sexually abstinent or use of condoms) during the study and for at least 30 days after the last dose of BI 3000202.

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

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

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, determination of height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG (including rhythm strip of at least 15 minutes in the SRD part), laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

Demographics information includes trial subject`s age on the day of informed consent, subject's sex at birth, and ethnicity and race in order to sufficiently characterize the trial population and to support possible subgroup analyses if needed.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap Pro 100, GE Medical Systems, Freiburg, Germany) at the times indicated in the Flow Chart – SRD Part and Flow Chart – FE Part, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

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 – SRD Part and Flow Chart – FE Part after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required. The parameters to be assessed are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name (comment/abbreviation)	A	B	C	D
Haematology	Haematocrit	X	X	X	X
	Haemoglobin	X	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X	X
	Reticulocytes, absol.	X	--	X	X
	Reticulocytes/Erythrocyte	X	--	X	X
	White Blood Cells/Leucocytes	X	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.				
Coagulation	Activated Partial Thromboplastin Time	X	--	X	X
	Prothrombin time (Quick)	X	--	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	--	X	X
Enzymes	AST (Aspartate aminotransferase) /GOT, SGOT	X	X	X	X
	ALT (Alanine aminotransferase) /GPT, SGPT	X	X	X	X
	Alkaline Phosphatase	X	--	X	X
	Gamma-Glutamyl Transferase	X	--	X	X
	Creatine Kinase (CK)	X	X	X	X
	Creatine Kinase Isoenzyme MB (only if CK is elevated)	--	--	--	--
Hormones	Thyroid Stimulating Hormone	X	--	--	--
Substrates	Glucose (Plasma)	X	--	X	X
	Creatinine	X	--	X	X
	Bilirubin, Total	X	X	X	X
	Bilirubin, Direct	X	X	X	X
	Protein, Total	X	--	X	X
	Albumin	X	--	--	X
	C-Reactive Protein (Quant)	X	X	X	X
	Uric Acid	X	--	--	--
	Cholesterol, total	X	--	--	--
	Triglyceride	X	--	--	--
Electrolytes	Sodium	X	--	X	X
	Potassium	X	--	X	X
	Calcium	X	--	X	X

A: parameters to be determined at the screening examination
B: parameters to be determined at Visit 2 on Days -3, -2 or -1 (laboratory assessment can be omitted if screening examination is performed on Days -3, -2 or -1), for time point refer to Flow Chart – SRD Part and Flow Chart – FE Part)
C: parameters to be determined on Day 1 (predose) and Day 2 of each treatment period (see Flow Chart - SRD Part and Flow Chart – FE Part)
D: parameters to be determined at the end of trial examination

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name (comment/abbreviation)	A	B	C	D
Urinalysis (Stix)	Urine Nitrite (qual)	X	--	X	X
	Urine Protein (qual)	X	--	X	X
	Urine Glucose (qual)	X	--	X	X
	Urine Ketone (qual)	X	--	X	X
	Urobilinogen (qual)	X	--	X	X
	Urine Bilirubin (qual)	X	--	X	X
	Urine HGB (qual)	X	--	X	X
	Urine Leucocyte esterase (qual)	X	--	X	X
	Urine pH	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)				

A: parameters to be determined at the screening examination
B: parameters to be determined at Visit 2 on Days -3, -2 or -1 (laboratory assessment can be omitted if screening examination is performed on Days -3, -2 or -1), for time point refer to Flow Chart – SRD Part and Flow Chart – FE Part)
C: parameters to be determined on Day 1 (predose) and Day 2 of each treatment period (see Flow Chart - SRD Part and Flow Chart – FE Part)
D: parameters to be determined at the end of trial examination

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests at screening only. Drug screening will be performed at screening and prior to drug administration(s).

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. AlcoTrue® M, Bluepoint Medical GmbH & Co. KG) will be performed prior to drug administration(s), 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.

[redacted]

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

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

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the time points given in the Flow Chart – SRD Part and Flow Chart – FE Part. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). For the SRD part, precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the treatment period

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

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

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart – SRD Part. In exceptional cases where technical issues occur the window may be expanded to 240 sec.

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

Additional (unscheduled) ECGs may be recorded for safety reasons.

Storing

[redacted]

Data transfer

[redacted]

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded. Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

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

Evaluation

a) Central ECG lab (SRD part only)

Central ECG lab evaluation will be performed starting from after the first dose group of the SRD part for the first of three replicate ECGs per time point. The remaining second and third ECGs per triplicate ECG will be stored for additional analysis if required. This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically.

For statistical analyses, heart rate (HR) and the QT interval corrected for HR (QTc e.g., QTcF and QTcB) will be determined by the sponsor (see TSAP for details).

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

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

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

b) Trial site

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

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the trial, the QT and QTcF values generated by the computerised ECG system or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront (i.e., prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

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

Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.4.2 Continuous ECG monitoring

SRD part only: cardiac rhythm (including heart rate) will be monitored by means of continuous 3-lead ECG recording using the CARESCAPE Monitor B450 (GE Healthcare, Freiburg, Germany) for at least 15 min before drug administration (for baseline assessment) and for 4 h following drug administration). This continuous ECG monitoring supports the early detection of adverse events such as clinically relevant bradycardia, tachycardia, or arrhythmia at the trial site. Beyond this clinical evaluation at the trial site, no further data collection or analyses are performed based on continuous ECG monitoring.

ECG data from continuous ECG recording will not be transferred to the clinical trial database. Abnormal findings during continuous ECG recording will be recorded as AEs if judged clinically relevant by the Investigator.

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,

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

5.2.6.1.3 AEs considered 'Always Serious'

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

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

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
  - Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the

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

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g., pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g., after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger

- There is an alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned)

Disappearance of the event even though the trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

Subjects will be required to report spontaneously any AEs. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart – SRD Part and Flow Chart – FE Part. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

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

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

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
    - All AEs (serious and non-serious) and all AESIs

- The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g., phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point immediately (without undue delay). The country specific reporting process (contact details) will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

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

5.2.6.2.3 Pregnancy

Potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point. 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 Clinical Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and Part B).

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood and urine samples will be collected at the time points / time intervals indicated in the Flow Chart – SRD Part and Flow Chart – FE Part. The actual sampling times will be used for determination of pharmacokinetic parameters.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g., because of preliminary PK data), including addition of samples and visits, as long as the total blood volume taken per subject does not exceed 500 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 pharmacokinetic analysis

For quantification of BI 3000202 concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube by means of either an indwelling venous catheter or by venipuncture with a metal needle. Samples will be mixed gently and kept in ice water or on ice until centrifugation

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at 2000-4000 x g and at 4°- 8°C. After centrifugation the plasma fraction needs to be diluted exactly with 1M citric acid in a ratio of 1+1 (v/v). Therefore, an of 300 µL plasma will be transferred to amber/brown tubes (e.g., Sarstedt Screw cap micro tube, 1.5 ml) containing 300 µL 1M citric acid. The polypropylene tubes should either be vortexed for a couple of seconds or well waved back and forth (e.g. 10 times) to ensure a thorough mixing of citric acid and plasma. Two plasma aliquots will be obtained. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min, with interim storage of blood samples in ice water or on ice. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -70°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -70°C or below until analysis.

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

5.3.2.2 Blood sampling for metabolism analysis

Additional K_2-EDTA plasma samples for the identification of drug metabolites will be investigated in [redacted]. Based on the knowledge gained during the trial conduct, e.g. from preliminary PK results, the dose group may be modified to a different one. The change will be implemented via a non-substantial CTP amendment.

The blood samples will be drawn at the same time points as PK samples (see Flow Chart – SRD Part). At each of these times, 2.7 mL blood will be needed for metabolite analysis. The blood samples will be processed in the same way as the PK samples (see Section 5.3.2.1). In particular, after centrifugation the plasma fraction will be diluted with 1M citric acid in a ratio of 1+1 (v/v). However, the plasma obtained (approximately 1 mL) will be transferred into a single polypropylene tube. Samples will be stored at approximately -70°C or below until transfer to the metabolism laboratory.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, planned sampling time and 'MetID'.

Plasma samples dedicated to metabolism investigation are transferred to:

[redacted].

At the analytical laboratory, samples will be stored at approximately -70°C or below until analysis. Only data related to the parent compound and its metabolites will be acquired. Evaluation of drug metabolism will be reported separately and will not be included in the CTR. The trial samples will be discarded after completion of the experiments but not later than 5 years after the CTR has been archived.

5.3.2.3 Urine sampling for pharmacokinetic analysis

Only SRD part:

A blank urine sample will be collected before administration of trial medication (see the Flow Chart – SRD Part) and two 1.0 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart – SRD Part will be collected in 2 L polyethylene (PE) containers and stored at 2° - 8° C, protected from the light. Subjects are told to empty their bladders at the end of each sampling interval.

Due to the known instability of the drug (its metabolites) in urine, citric acid will be added to each 2 L PE collection container prior to the start of urine sampling. To avoid nonspecific binding of the drug to the container surface an anti-adsorptive agent will be added to each 2 L PE collection container prior to the start of urine sampling. Details about sample collection, citric acid and anti-adsorptive agent concentration and required tubes will be provided in a separate laboratory manual.

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

Until transfer on dry ice to the analytical laboratory, the urine samples will be stored at approximately -70°C or below at the trial site. The second aliquot will be transferred after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the urine samples will be stored at approximately -70°C or below until analysis.

After analysis, the urine samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites) or to address Health Authority questions

regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR has been archived.

5.3.2.4 Additional blood sample for stability-testing

To assess the stability of the analyte in whole blood, one additional blood sample will be obtained in the SRD part from all [redacted]. Based on the knowledge gained during the trial conduct, e.g., from preliminary PK results, the chosen timing or dose group may be changed to a different one. The change will be implemented via a non-substantial CTP amendment.

Approximately 2.4 mL blood will be drawn from an antecubital or forearm vein into two 1.2 mL K_2-EDTA-blood drawing tubes at the time indicated in the Flow Chart – SRD Part (immediately after the drawing of a regular blood PK sample, which means that no additional venous puncture will be necessary).

From each K_2-EDTA tube, one aliquot will be generated:

- One aliquot ('stability reference') will be centrifuged for approximately 10 min at approximately 2000-4000 x g and at 4°-8° C. After centrifugation the plasma fraction needs to be diluted with 1M citric acid in a ratio of 1+1 (v/v). Therefore, an exact volume of 300 µL plasma will be transferred to an amber/brown polypropylene tube containing 300 µL 1M citric acid and transferred into a freezer.
- The second aliquot ('stability test') will be stored for about 4 h at room temperature and protected from the light (storage time must be documented) and will then be centrifuged and stored as described for the first aliquot.

At a minimum, the aliquots should be labelled with BI trial number, administered drug, subject number, planned sampling time, and whether the sample is the 'stability reference' or 'stability test' sample.

Until transfer to the analytical laboratory, both aliquots will be stored at approximately -70 °C or below at the trial site. Both aliquots will be provided to the responsible bioanalyst together with the information about sample handling (i.e., storage time of stability test sample at room temperature). After receipt, the aliquots will be stored at the bioanalytical laboratory at approximately -70°C or below until analysis.

The results of the analysis of these samples will not be reported in the CTR but will be used for bioanalytical assay validation and therefore included in the corresponding method validation report. The remaining sample volume will be discarded at latest upon completion of the method validation report.

5.3.3 Analytical determinations

As described in Section 4.1.5, the bioanalyst may be unblinded during sample analysis. The analysis will be performed under [redacted]

[redacted]

5.3.3.1 Analytical determination of BI 3000202 plasma concentration

BI 3000202 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry). All details of the analytical method will be available prior to the start of sample analysis. Samples from placebo treated subjects are not intended to be analysed.

As described in Section 4.1.5, the bioanalyst may be unblinded during sample analysis.

5.3.3.2 Analytical determination of BI 3000202 urine concentration

Analyte concentrations in urine will be determined by a fit for purpose validated LC-MS/MS assay with extended acceptance criteria. All details of the analytical method will be available prior to the start of sample analysis. Samples from placebo treated subjects will not be analysed.

As described in Section 4.1.5, the bioanalyst may be unblinded during sample analysis.

5.3.3.3 Further use of PK samples

After completion of the trial analysis, remaining plasma and urine samples taken for PK analysis (ref. Section 5.3.2.1 and 5.3.2.3) may be used for further methodological investigations (e.g., for stability testing, assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR has been archived.

5.3.4 **Pharmacokinetic - pharmacodynamic relationship**

The relationship of BI 3000202 plasma concentrations and the percent [redacted]

5.4 ASSESSMENT OF BIOMARKERS

5.4.1 **Drug-Drug Interaction Biomarkers**

Not applicable.

5.4.2 **Pharmacodynamic biomarkers**

[redacted]

5.4.2.1 Methods of sample collection

Blood will be drawn from an antecubital or forearm vein into a 4.3 mL sodium citrate-anticoagulant blood drawing tube by means of either an indwelling venous catheter or by venepuncture with metal needle. Samples have to be carefully inverted (no shaking) after blood drawing and be kept at room temperature until they arrive at the analytical lab.

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 subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

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

After completion of the trial, the samples may be used for further biomarker investigations. The trial samples will be discarded after completion of any additional investigations but not later than 5 years after the CTR has been archived.

5.4.2.2 Analytical determinations

[redacted]

5.4.3 Pharmacogenomic biomarkers

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.6.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be obtained at the screening examination from each subject whose genotype has not been previously determined. Separate informed consent for genotyping will be obtained from each volunteer prior to sampling.

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by

the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the CTR. However, the data may be part of the CTR, if necessary.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

Each subject entered in the SRD part is expected to participate in a screening visit, one treatment period of 3 trial days and an end-of-study visit (maximum duration of trial participation approximately 5 weeks).

Subjects entered in the FE part are expected to participate in a screening visit, two treatment periods of 3 trial days, 2 drug administrations separated by at least 3 days, and in an end-of-study visit (maximum duration of trial participation approximately 6 weeks).

Details are provided in the Flow Chart – SRD Part and Flow Chart – FE Part.

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening, measurements and assessments scheduled to occur 'before' trial medication administration on Day 1, and the end of trial examination are provided in the Flow Chart – SRD Part and Flow Chart – FE Part.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration, ± 30 min until 24 h post-dose, ± 60 min until 48 h after drug administration.

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

For planned blood sampling times and urine collection intervals, refer to the Flow Chart – SRD Part and Flow Chart – FE Part. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic and pharmacodynamic (exploratory biomarker) parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the trial. For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5. Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.6).

6.2.2 Treatment periods

SRD part

Each subject will receive one single dose of trial medication (BI 3000202 or placebo) at Visit 2. Trial subjects will be admitted to the trial site in the morning of Day 1 and kept under close medical surveillance for at least 24 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted].

FE part

Each subject will receive a single dose of BI 3000202 on Day 1 of Visits 2 and 3. Drug administrations will be separated by a washout period of at least 3 days (ref. Flow Chart – FE Part). Trial subjects will be admitted to the trial site in the evening of Day -1 and kept under close medical surveillance for at least 24 h following drug administration in each period. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted].

Both parts

Trial medication will be [redacted] supervision of the investigator or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

For details on time points and procedures for collection of plasma and urine samples for PK and biomarker analysis, refer to Flow Chart – SRD Part and Flow Chart – FE Part, Sections 5.3.2 and 5.4.2.

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

For details on times of all other trial procedures, refer to the Flow Chart – SRD Part and Flow Chart – FE Part.

6.2.3 Follow-up period and trial completion

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

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoS Visit. If needed in the opinion of the investigator, additional visits may be scheduled after the EoS Visit 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 subject's EoS Visit must be followed until they have resolved, have been sufficiently characterized, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

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

SRD part

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

FE part

To assess the food effect [redacted], the relative bioavailability of BI 3000202 will be estimated by the ratios of the geometric means (T/R), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

For the SRD part, the following analysis set will be created in addition:

- Pharmacodynamic parameter analysis set (PDS): This set includes all subjects in the treated set (TS) who provide at least one PD endpoint (see Section 2.2.2.3) that was not excluded due to a protocol deviation relevant to the evaluation of PD or due to PD non-evaluability (as specified in the subsection 7.2.1.3 'Biomarkers'). Descriptive analyses of PD endpoints will be based on the PDS.

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

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

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 3000202 will be calculated according to the relevant BI internal procedure.

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

Important protocol deviations may be

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

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

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

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

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

7.2.1.3 Biomarkers

Biomarker data and parameters of a subject will be included in the statistical biomarker analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of biomarkers (to be decided no later than in the Report Planning Meeting) or due to non-evaluability (as revealed during data analysis, based on the criteria specified below).

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

Exclusion of a subject's data will be documented in the CTR. Biomarker data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

7.2.2 Primary endpoint analyses

SRD part

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

FE part

Primary analyses:

The statistical model used for the analysis of the primary endpoints as specified in Section 2.1.2 will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, where

y_{ijkm} = logarithm of response measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2,

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, m = 1, 2, ..., n_i

π_j = the j^{th} period effect, j = 1, 2,

τ_k = the k^{th} treatment effect, k = 1, 2 (i.e. R, T)

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratios of the geometric means (T/R) for the primary endpoints and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means).

Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Further exploratory analyses:

The same statistical model as stated above will be repeated for the primary endpoints but with all sources of variation ('sequence', 'subjects within sequences', 'period', 'treatment') considered as fixed effects.

In addition to the model-based approach all parameters will be calculated and analysed descriptively.

7.2.3 Secondary endpoint analyses

SRD part

Primary analyses:

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

Further exploratory analyses

Dose proportionality will be explored via graphical checks and if applicable via the power model stated below. The analysis will be performed for the pharmacokinetic endpoints specified in Section 2.1.3.

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

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

where

- y_{km} logarithm of response (PK parameter) measured on subject m receiving dose k,
- μ the overall mean,
- β slope parameter of linear regression line,
- D_k level of dose k, k=1,…,7,
- e_{km} the random error associated with the m^{th} subject who was administered dose k ($e_{km} \sim N(0, \sigma^2)$ iid).

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

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

FE part

The secondary endpoint (refer to Section 2.1.3) will be calculated according to the relevant SOP of the Sponsor and will be assessed statistically using the same methods as described for the primary endpoints.

7.2.4 Further endpoint analyses

7.2.4.1 Pharmacokinetic analyses

Further PK endpoints will be analysed descriptively for both parts separately.

7.2.4.2 Biomarker analyses

Analysis of pharmacodynamics parameters is only applicable for the SRD part.

The PD endpoint listed in Section 2.2.2 as well as possible further PD endpoints specified in the TSAP will be analysed descriptively by dose group over time. The placebo group will consist of all subjects treated with placebo in the SRD part.

7.2.5 Safety analyses

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

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

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

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs). Therefore, measurements performed or AEs recorded prior to intake of trial medication will be assigned to the screening period, those between the trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before unblinding the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

treatments, on-treatment totals, or periods without treatment effects (such as screening and post-study intervals).

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

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

Laboratory data will be compared to their reference ranges. Values outside the reference range will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

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

The ECG variables QT, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints with regard to QT/QTc interval, HR, PR interval and QRS duration. These endpoints and their analyses will be described in the TSAP.

7.2.6 Other analysis

SRD part

An exploratory analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned.

A population PK and/or PK/PD analysis may be performed at the project level using a nonlinear mixed effects modelling approach. Further details will be specified in an appropriate pharmacometric analysis plan; this analysis will not be part of the CTR.

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

7.2.7 Interim analyses

No formal interim analysis is planned.

Prior to each dose escalation a documented safety review will be performed as described in Section 3.1. To support dose escalations a preliminary analysis of PK parameters (at least AUC_{0-24} and C_{max} of BI 3000202), provided as individual values and geometric means, will be performed for

- Dose levels 1, 2 and 3 (n) before proceeding to dose level 3, 4 and 5 (n+2)
- Dose levels 5 and 6 (n) before proceeding to the next dose level 6 and 7 (n+1)

(Note: Data from the first cohorts of the above-mentioned dose levels will be sufficient as long as the data from at least 3 subjects on active treatment were available.)

The pharmacokinetic parameters C_{max} and AUC_{0-24} for BI 3000202 will be calculated according to the relevant BI internal procedure. In contrast to the final PK calculations, the preliminary, exploratory analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations may occur between preliminary and final results.

The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without subject identification information.

Available information on dose linearity from preceding dose groups will be considered when estimating C_{max} and AUC_{0-24} values to be expected for the next higher dose to be administered.

Additional PK preliminary analysis may be performed if requested by the Clinical Trial Leader, the investigator, or Trial Clinical Pharmacologist.

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

A preliminary, exploratory analysis of the PD parameters may be performed based on evaluable data prior to database lock to inform other activities during the development of substance.

A preliminary, exploratory analysis of the PK parameters (AUC_{0-tz}, $AUC_{0-\infty}$ and C_{max} of substance) may be performed based on all evaluable data after last subject out and prior to data base lock. This may be necessary, e.g., in case the information is needed to inform other activities during the development of substance such as concomitant treatment restrictions in other studies. In contrast to the final PK calculations, the preliminary, exploratory analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. Results will be provided as individual values and geometric means as well as the adjusted gMean ratios determined according to the planned primary analysis. The preliminary, exploratory results will be distributed to the trial team. No formal preliminary PK report will be written.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

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

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

7.3.3 Biomarkers

It is not planned to impute missing values for biomarker data, i.e. pharmacodynamic parameters.

7.4 RANDOMISATION

In the SRD part, subjects will be randomised within cohort 3 of each dose group in a 3:1 ratio (test treatment to placebo). Trial medication in cohorts 1 and 2 of each dose group will be administered in a fixed order (active - placebo - active - active; see Section 3.1).

In the FE part, subjects will be randomised to one of the 2 treatment sequences in a 1:1 ratio. The block size will be documented in the CTR.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation scheme will be generated using a validated system that uses a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

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

7.5 DETERMINATION OF SAMPLE SIZE

SRD part
It is planned to include a total of 56 subjects in this part of the trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics.

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded and none of the stopping criteria apply. Thus, the actual number of subjects entered may exceed 56, but will not exceed 80 subjects entered.

The sample size of a specific dose group may increase by up to 2 subjects to enable dose escalation decision (see Section 3.3.5).

FE part
It is planned to enter a total of 12 subjects in this part of the trial, because this sample size is considered sufficient for the exploratory investigation of relative bioavailability.

In total, 56 + 12 = 68 subjects are planned to be included in this trial.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. As a rule, no trial results should be published prior to finalisation of the CTR.

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

ClinBase™
In the Human Pharmacology Centre (HPC) – Boehringer Ingelheim's Phase I unit – the validated ClinBase™ system is used for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as database. Instead of being entered into CRFs, selected data are directly entered into the ClinBase™ system.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

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

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

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

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

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

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date (mandatory), and end date (if available))
- SAEs (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

Data directly entered into ClinBaseTM (that is, without prior written or electronic record) are considered to be source data. The place where data are entered first will be defined in a trial specific Source Data Agreement. The data in ClinBaseTM are available for inspection at any time.

8.3.2 Direct access to source data and documents

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

described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 7 and 12 of the WHO GCP handbook.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a 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 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 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, storage and future use of biological samples and clinical data, in particular

- Sample and data usage must be in accordance with the informed consent

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

8.6 TRIAL MILESTONES

The first act of recruitment represents the start of the trial and is defined as the date when the first trial participant (subject) in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ('Last Subject Completed').

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

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the Human Pharmacology Centre (HPC) of BI Pharma GmbH & Co. KG, Biberach, Germany, under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

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

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

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

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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P17-04969 Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685-1699.

P20-00650 Acosta-Herrera M, Kerick M, Gonzalez-Serna D, et al. Genome-wide meta-analysis reveals shared new loci in systemic seropositive rheumatic diseases. Ann Rheum Dis 2019;78(3):311-319.

P20-07220 Kim KJ, Moon SJ, Park KS. Network-based modeling of drug effects on disease module in systemic sclerosis. Sci Rep 2020;10(1):13393..

R03-2269 Guidance for industry: food-effect bioavailability and fed bioequivalence studies. In: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2002:1-9.

R06-1037 Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. 2005.

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)

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

R14-4918 Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Curr Opin Rheumatol 2012;24(2):165-170.

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). http://www.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)

R17-0149 LeRoy EC, Black D, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15(2):202-205.

R17-0314 Ramos PS, Silver RM, Feghali-Bostwick CA. Genetics of systemic sclerosis: recent advances. Curr Opin Rheumatol 2015;27(6):521-529.

[redacted]

R18-3144 Angiolilli C, Marut W, Kroef M, et al. New insights into the genetics and epigenetics of systemic sclerosis. Nat Rev Rheumatol 2018.

[redacted]

R19-2732 Khanna D, Spino C, Johnson S, et al. Abatacept in early diffuse cutaneous systemic sclerosis - results of a phase 2 investigator-initiated, multicenter, double-blind randomized placebo-controlled trial. Arthritis Rheumatol 2020;72(1):125-136.

[redacted]

R22-3698 Dou Z, Ghosh K, Vizioli MG, et al. Cytoplasmic chromatin triggers inflammation in senescence and cancer. Nature 2017;550(7676):402-406.

[redacted]

[redacted]

R22-3705 Svegliati S, Cancello R, Sambo P, et al. Platelet-derived growth factor and reactive oxygen species (ROS) regulate ras protein levels in primary human fibroblasts via ERK1/2: amplification of ROS and Ras in systemic sclerosis fibroblasts. J Biol Chem 2005;280(43):36474-36482

[redacted]

R94-1529 Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. New York: Marcel Dekker Inc. 1992.

9.2 UNPUBLISHED REFERENCES

n00298647 Prediction of BI 3000202 Pharmacokinetics and Therapeutic Dose in Human Human. B7752. 13 Fev 2023.

c40070068 [redacted] BI 3000202. Current Version.

10. APPENDIX

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT

11.1 GLOBAL AMENDMENT 1

Date of amendment		25 May 2023
EU number		2022-502424-43-00
BI Trial number		1509-0001
BI Investigational Medicinal Product(s)		BI 3000202
Title of protocol		A randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, and pharmacokinetics of single rising doses of BI 3000202 administered as tablet to healthy male subjects, and a randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 3000202 as tablet with and without food in healthy male subjects

Substantial Global Amendment due to urgent safety reasons To be implemented immediately in order to eliminate hazard – IEC / Competent Authority to be notified of change with request for approval.	☐
Substantial Global Amendment e.g. changes in safety or physical or mental integrity of trial subjects, or in inter-pretation of scientific documents/value of the trial, or in conduct/management of the trial, or change/addition of principal investigators, co-ordinating investigators, or trial sites – implementation only after IEC / Competent Authority approval.	☒
Non-substantial Global Amendment e.g. changes that involve logistical or administrative aspects, or exploratory endpoints only – can be implemented without IEC / Competent Authority approval	☐

Section to be changed		1. Section 1.3.1.1 2. Section 1.3.2 Table 1.3.2:1 3. Section 1.3.2 Table 1.3.2:1 4. Section 1.3.3 5. Section 1.3.3 6. Section 1.3.3 7. FLOW CHART – FE PART 8. Section 3.3.4.3
Description of change		1. Addition of text "and to [redacted] to Derivation of safe starting dose. 2. [redacted] 3. [redacted]

		4. Addition of Text "and adjusted [redacted] for BI 3000202 [redacted] 5. Addition of Text "[redacted] 6. Redefining the [redacted] of the clinical trial. 7. Correction of the planned time (~~08~~ to 7) 8. Redefining the [redacted]
Rationale for change		1. Request from Competent Authority / EMA 2. Request from Competent Authority / EMA 3. Request from Competent Authority / EMA 4. Request from Competent Authority / EMA 5. Request from Competent Authority / EMA 6. Request from Competent Authority / EMA 7. Correction of typo 8. Request from Competent Authority / EMA

APPROVAL / SIGNATURE PAGE

Document Number: c40535128 **Technical Version Number:2.0**

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

Title: A randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, and pharmacokinetics of single rising doses of BI 3000202 administered as tablet to healthy male subjects, and a randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 3000202 as tablet with and without food in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Verification-Paper Signature Completion	[redacted]	25 May 2023 13:14 CEST
Approval		25 May 2023 13:17 CEST
Approval-Clinical Program [redacted]		25 May 2023 13:18 CEST
Author-Trial Statistician		25 May 2023 13:30 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed