Clinical Trial Protocol

	Document Number:	**c31414158-03**
EudraCT No.	**2020-004262-19**	
BI Trial No.	1450-0001	
BI Investigational Medicinal Product	BI 765080	
Title	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising intravenous doses of BI 765080 in healthy male subjects (single-blind, randomised, placebo-controlled, parallel-group design)	
Lay Title	A study in healthy men to test how the body takes up and tolerates different doses of BI 765080	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: Fax: [redacted]	
Principal Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 10 May 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	22 October 2020
Revision date	10 May 2021
BI trial number	1450-0001
Title of trial	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising intravenous doses of BI 765080 in healthy male subjects (single-blind, randomised, placebo-controlled, parallel-group design)
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	In this first-in-human trial, the effects of single rising doses of BI 765080 on safety, tolerability, pharmacokinetics, and pharmacodynamics will be assessed as the basis for further development in patients with chronic kidney disease.
Trial objectives	To investigate safety, tolerability, pharmacokinetics, and pharmacodynamics following single rising intravenous doses of BI 765080
Trial endpoints	Primary endpoint to assess safety and tolerability of BI 765080 is the percentage of subjects with drug-related adverse events Secondary endpoints: – $AUC_{0-\infty}$ of BI 765080 – C_{max} of BI 765080
Trial design	Single-blind, randomised within dose groups, placebo-controlled, parallel-group design
Number of subjects **total entered** **each treatment**	 48* 8 per dose group (6 on BI 765080 and 2 on placebo) * Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 48, but is not to exceed 80.
Diagnosis	Not applicable

Main criteria for inclusion	Healthy male subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product	BI 765080 powder for solution for injection/infusion, 50 mg/vial
dose	Single doses of 1 mg, 10 mg, 25 mg, 50 mg, 100 mg, and 200 mg
mode of admin.	Intravenous as 30 min infusion
Comparator product	Matching placebo for BI 765080 concentrate for infusion solution
dose	Not applicable
mode of admin.	Intravenous as 30 min infusion
Duration of treatment	Single dose
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[16]	PK blood [9]	[redacted]	Body temperature	12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -3			Screening (SCR) [1]	A			x	x		x	
2	-2	-48:00	08:00	Ambulatory visit[14]	B[7]			x				x
	-1	-12:00	20:00	Admission to trial site	x[5]			x				x
	1	-3:00	06:00	Allocation to treatment[2]	B [13]	x[2]		x[2]	x[2,10]		x[2]	x[2,17]
		0:00	**08:00**	**Drug administration start of infusion**						▲		
		0:30	08:30	end of infusion		x		x	x[8]	|	x	x[17]
		1:00	09:00			x			x[8]	|	x	x
		1:30	09:30						x[8]	|	x	x
		2:00	10:00	light breakfast[3]		x		x	x[8]	|	x	x[17]
		3:00	11:00			x			x[8]	|	x	x
		4:00	12:00	lunch[3]	x[13]	x			x[8]	▼	x	x
		6:00	14:00			x		x	x[8]		x	x
		8:00	16:00	Snack (voluntary)[3]		x			x[8]		x	x
		10:00	18:00	Dinner[3]		x						
		12:00	20:00			x		x	x[8]		x	x
	2	24:00	08:00	Breakfast[3]	B[13]	x		x	x[8]		x	x
		34:00	18:00	Dinner[3]		x		x	x[8]		x	x
	3	48:00	08:00	Breakfast[3] discharge from trial site (confirmation of fitness[15])		x			x[8]		x	x
	4	72:00	08:00	Ambulatory visit	B	x			x		x	x
	7	144:00	08:00	Ambulatory visit	B	x		x				x
	14	312:00	08:00	Ambulatory visit		x		x				x
	21	480:00	08:00	Ambulatory visit	B	x		x				x
	28	648:00	08:00	Ambulatory visit		x		x				x
	56	1320:00	08:00	Ambulatory visit	B	x[11]		x				x
	84	1992:00	08:00	Ambulatory visit		x[11]		x				x
3	84-87			End of trial (EoTrial) examination[4]	B			x	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 and body temperature, ECG, safety laboratory (including drug screening), demographics (including determination of body height, weight, smoking status, alcohol history, relevant medical history, concomitant therapy, and review of inclusion/exclusion criteria).
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 (first) 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 trial visit the EoTrial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies. EOT to be performed not before last PK sampling.
5. Only urine drug screening and alcohol breath test will be done at this time.
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 -5 to Day -3.
8. The ECG recording has to be performed in triplicate ECGs at this time
9. Sampling times and periods may be adapted based on information obtained during the trial (e.g., due to preliminary PK data) including addition of samples and visits as long as the total blood volume removed does not exceed 500 mL per subject
10. At baseline (i.e. Day 1, prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
11. In case blood levels still exceed LOQ, additional PK samples may be collected beyond Day 28.

14. SARS-CoV-2 PCR test will be performed.
15. Confirmation of fitness includes physical examination.
16. Letters A and B describe different sets of safety laboratory examinations (see Section 5.2.3).
17. Local tolerability inclusive.

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS

ACE	Angiotensin-converting-enzyme
[redacted]	
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	Attributable, legible, contemporaneous, original, accurate
ALT	Alanine amino transferase
[redacted]	
ARB	Angiotensin-receptor blocker
AST	Aspartate amino transferase
AUC	area under the concentration
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity
[redacted]	
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CKD	Chronic kidney disease
[redacted]	
C_{max}	Maximum measured concentration of the analyte in serum
CML	Clinical Monitor Local
COVID-19	Corona virus disease 2019
[redacted]	
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTM	Clinical Trial Manager

CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial/EoT	End of trial
ESRD	End-stage renal disease
EudraCT	European Clinical Trials Database
[redacted]	
FDA	Food and Drug Administration
[redacted]	
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HD	Hemodialysis
HIV	Human Immunodeficiency Virus
HR	Heart rate
HUVEC	Human umbilical vein endothelial cells
IB	Investigator's brochure
IEC	Independent Ethics Committee
iPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
i.v.	Intravenous
[redacted]	
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
MTD	Maximum tolerated dose
NKcell	Natural killer cell
NOAEL	No-observed-adverse-effect level
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)

PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
Q2W	Every 2 weeks
Q3W	Every 3 weeks
REP	Residual effect period
RR	Respiratory rate
SAE	Serious adverse event
SCR	Screening
SGLT2	Sodium-glucose co-transporter-2
SOP	Standard operating procedure
SRD	Single-rising dose
TMDD	Target mediated drug disposition
TMF	Trial master file
[redacted]	
TS	Treated set
[redacted]	
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
[redacted]	
WFI	Water for Injection
WHO	World Health Organization
XTC	Ecstasy

1. INTRODUCTION

BI 765080 is intended for the treatment of chronic kidney disease (CKD). This is the first trial in humans.

1.1 MEDICAL BACKGROUND

The incidence and prevalence of CKD can vary as a result of the underlying aetiology [R19-0901]. Overall, around 12% of the general population in Europe has CKD stages 3–5 [R19-1388], with considerable variation across European countries, ranging from 4.1% to 25.5% [R19-1184]. In developed countries, CKD is generally associated with diabetes, hypertension, old age, obesity, and cardiovascular disease. Diabetic glomerulosclerosis and hypertensive nephrosclerosis are the presumed pathological entities; however, exact diagnosis is often difficult. It has been shown that both reduced GFR and increased albuminuria are independent predictors of mortality [R17-2621, R17-2619].

Current treatment of CKD is based on clinical diagnosis and staging of GFR decline and severity of albuminuria. The current standard of care is angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) [P11-14681], usually in association with diuretic drugs in patients with high concentrations of albuminuria [R19-0901]. Selective nonsteroidal mineralo-corticoid receptor antagonists such as finerenone and sodium-glucose co-transporter-2 (SGLT2) inhibitors may be considered as standard of care in the future [P18-03010, R19-1139, R19-1356].

Although ACE inhibitors and ARBs have demonstrated efficacy in slowing the progression of diabetic nephropathy, it should be acknowledged that the relative risk reduction was small (16% in RENAAL and 19% in IDNT) for the triple composite primary endpoint of all-cause death, ESRD, or doubling of serum creatinine [R02-0327, R02-2101]. The residual risk is still considerably high. Therefore, there are high unmet needs for an effective and safe treatment that can further slow, halt, or reverse the progression of CKD.

1.2 DRUG PROFILE

For a comprehensive description of the BI 765080 profile, please refer to the current Investigator's Brochure (IB) [c30981435].

1.2.1 Nonclinical pharmacology

[redacted]

The core safety pharmacology (neurological, cardiovascular, and respiratory functions) was evaluated as part of the 4-week (rat) and 13-week (monkey) GLP repeat dose toxicity studies (see Section 1.2.2.3). [redacted]

1.2.2 Toxicology

Rationale for Toxicology Species Selection

[redacted]

1.2.2.1 Genotoxicity

Genetic toxicity studies are generally not applicable to therapeutic antibodies, as they are not expected to interact directly with DNA. Therefore, genetic toxicity studies were not conducted per ICH S6 (R1): 'Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals' [R11-1428].

1.2.2.2 Single dose toxicity

No single-dose toxicity assessments have been conducted with BI 765080

1.2.2.3 Repeated dose toxicity

4-Week study in rats, GLP [n00277285]

[redacted]

13-Week study in cynomolgus monkeys, GLP [n00277281]

[redacted]

[redacted]

In summary, BI 765080 administered to monkeys intravenously once weekly for 13 consecutive weeks at [redacted]eek was well tolerated in animals surviving until scheduled necropsy. [redacted]

[redacted]

1.2.2.4 Special studies

Local tolerance

There was no evidence of local BI 765080-related effects at the injection sites during the 4-week repeat dose toxicity study in rats [n00277285].

In the 13-week repeat dose toxicology study in monkeys [n00277281], one monkey given a [redacted] dose showed localized injection site reactions with clinical signs including swelling, exudate, and/or discharge at right and left cephalic vein dose sites. [redacted]

[redacted]

1.2.2.5 Reproductive and developmental toxicity

Developmental and reproductive toxicity studies have not been conducted with BI 765080.

[redacted]

1.2.2.6 Phototoxicity

Therapeutic antibodies are not generally expected to be phototoxic unless related to the mechanism of action. Therefore, no phototoxicity studies were conducted. There were no toxicities in the skin or eyes related to light exposure observed in the repeat dose toxicity studies [n00277285, n00277281].

1.2.3 Nonclinical pharmacokinetics

[redacted]

1.2.4 Prediction of human pharmacokinetics

[redacted]

1.2.5 Clinical experience in humans

This will be the first clinical trial in humans with BI 765080.

[redacted]

[redacted]

1.2.6 Residual Effect Period

The residual effect period (REP) of BI 765080, when measurable drug levels or PD effects are still likely to be present, is not known for this first-in-human trial. Conservatively, a minimum observation period of approximately 4-fold the estimated $t_{1/2}$ has been selected. Therefore, the individual subject's end of trial is on Day 84-87 following dosing with investigational drug at the earliest (see Flow Chart).

1.2.7 Drug product

BI 765080 is [redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 765080 is [redacted]

In this first-in-human trial, the effects of single rising doses of BI 765080 on safety, tolerability, pharmacokinetics, and pharmacodynamics will be assessed as the basis for further development in patients with CKD.

Within each dose group, all actively treated individuals will receive the same BI 765080 dose. The next higher dose will only be administered to the next group if the treatment in the preceding dose group was safe and well tolerated (see Section 3.1). The background for dose selection and escalation steps is described below.

1.3.1 Starting dose

The starting dose in healthy humans in this initial Phase I single-rising dose (SRD) trial is 1 mg (0.017 mg/kg).

[redacted]

1.3.2 Maximum dose and escalation

The following doses have been chosen for this trial: 1 mg, 10 mg, 25 mg, 50 mg, 100 mg and 200 mg. The selected doses are expected to cover the range of subtherapeutic, anticipated therapeutic, and supratherapeutic doses. The dose of 200 mg will allow for the collection of safety data in case higher doses are needed to assess efficacy in future clinical trials. Predictions based on preclinical testing may turn out to be too optimistic and higher doses/exposure may be required, i.e. 400 mg, maximal 600 mg. The dose higher than 200 mg will only occur if safety and tolerability of 200 mg support increasing the dose and 200 mg does not achieve the estimated exposure, which will be provided by substantial CTP amendment.

A dose of 200 mg is expected to be safe, since no adverse effects in rats or monkeys were associated with BI 765080 administration at dose levels up to 100 mg/kg (NOAEL; see Section 1.2). The planned maximum exposure in humans is predicted to be substantially lower than the exposures in the rat and monkey toxicity studies (Table 1.3.2: 1). The dose escalation up to and including the maximum dose will only occur if safety and tolerability of preceding dose levels support increasing the dose (see Section 3.1).

Table 1.3.2: 1 Planned maximum dose and estimated exposure multiples versus exposures in the rat and monkey

1.4 BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of a new therapy for CKD. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

1.4.1 Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising and, in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

The total volume of blood drawn per subject during the entire study 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.

1.4.2 Drug-related risks and safety measures

Factors of risk may derive from particular knowledge or the lack thereof, regarding (1) the mode of action, (2) the nature of the target, (3) the relevance of animal models and/or (4) findings in non-clinical safety studies.

Mode of action and nature of the target

The mode of action of BI 765080 and nature of the target are described in Section 1.1. [redacted]

Relevance of animal species and models

Rat and cynomolgus monkey are considered suitable species for the nonclinical safety profiling of BI 765080 [redacted]

Findings in non-clinical safety studies

The toxicity profile of BI 765080 has been assessed in repeat dose toxicity studies in rats and cynomolgus monkeys that included immunotoxicology and/or core safety pharmacology endpoints (cardiovascular, neurologic, and respiratory function), [redacted] No adverse findings were associated with BI 765080 administration at dose levels up to 100 mg/kg. The nonclinical safety package for BI 765080 supports clinical trials in humans with i.v. administration for up to 13 weeks. The potential for BI 765080 immunogenicity in humans is considered low.

Safety measures

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

- Careful dose selection, as described in Section 1.3, with large safety margins up to the maximum dose, based on a sound preclinical data package including repeat dose toxicity studies in rats (4 weeks) and monkeys (13 weeks)
- The i.v. administration as 30 min infusion allows immediate discontinuation and the ability to adapt further drug administration should any safety concerns arise (please refer to Section 4.1.1)
- For safety reasons, each dose group is divided into 3 cohorts: on the first study day of each dose level, only 2 subjects will be treated: one will receive active treatment, the other subject will receive placebo. If BI 765080 treatment is safe and tolerated in this first cohort, 2 subjects on active will be treated in the second cohort no sooner than on

the next day. The remaining 4 subjects (either active or placebo) are the third cohort and will be treated no sooner than after 2 days following the first cohort. This design ensures that there is a time interval of at least 1 day between the first and second active dose of each dose level, which covers the t_{max} of BI 765080 (end of infusion) and the period of highest risk / peak effect. If BI 765080 is safe and shows acceptable tolerability in the first two cohorts, the remaining third cohort of the respective dose level can be dosed as close as 10 minutes apart.

- Dose escalation will be shallow. In addition, a time interval of at least 14 days will be maintained between first administration of study drug in the actual dose level and first administration in the next dose level, which is expected to cover the period of highest risk / peak effect. The decision to proceed to the next dose will be based upon the safety and tolerability of the preceding dose. The next dose will only be given if no safety concerns arise in the previous dose group (i.e. no dose-limiting events occur) and if none of the pre-specified trial-specific stopping criteria are met (see Section 3.3.4).
- Doses will only be escalated if previously approved 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 in a documented Safety Review (see Section 3.1)
- Extensive monitoring of ECG and vital signs is incorporated, with continuous ECG monitoring over 4 hours post dose to cover the anticipated period of highest drug exposure. As an additional measure, triplicate ECGs and repeated single 12-lead ECGs are scheduled in the further course of the study. The rationale for the intensified ECG monitoring is not an expected increased risk of BI 765080 mediated effects on cardiac repolarization. Rather, it has been implemented to collect thorough ECG data at an early point in clinical development to perform ECG interval assessment under drug. In general, for biologics, QT prolongation is not usually an issue (unless there are mechanistic effects with the antibody that can lead indirectly to ECG changes [R09-2768], which is not expected to be the case for BI 765080)
- Extensive safety laboratory testing will be performed
- At each dose level, the subjects will stay at the site for at least 48 hours following drug administration
- During in-house-confinement, the subjects will be under close medical observation and thoroughly monitored for both expected and unexpected adverse events

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety; see also Section 5.2.6.1.4, adverse events of special interest.

Conclusion

Although not tested in humans to date, BI 765080 has the potential to become an effective treatment for CKD, an indication with a large medical need.

Based on the mode of action, the pharmacological target, and the non-clinical toxicology data, BI 765080 is not considered a high-risk compound for adverse outcomes in clinical trials. Healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of this compound. Considering the medical need for an effective treatment for CKD, the benefit of this trial is considered to outweigh the potential minimal risks and justifies the exposure of healthy human volunteers.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate safety, tolerability, and pharmacokinetics of BI 765080 in healthy male subjects following i.v. administration of single rising doses.

2.1.2 Primary endpoint

The primary endpoint for assessment of safety and tolerability of BI 765080 is the percentage of subjects with drug-related adverse events.

2.1.3 Secondary endpoints

The following pharmacokinetic parameters of BI 765080 will be determined if feasible:

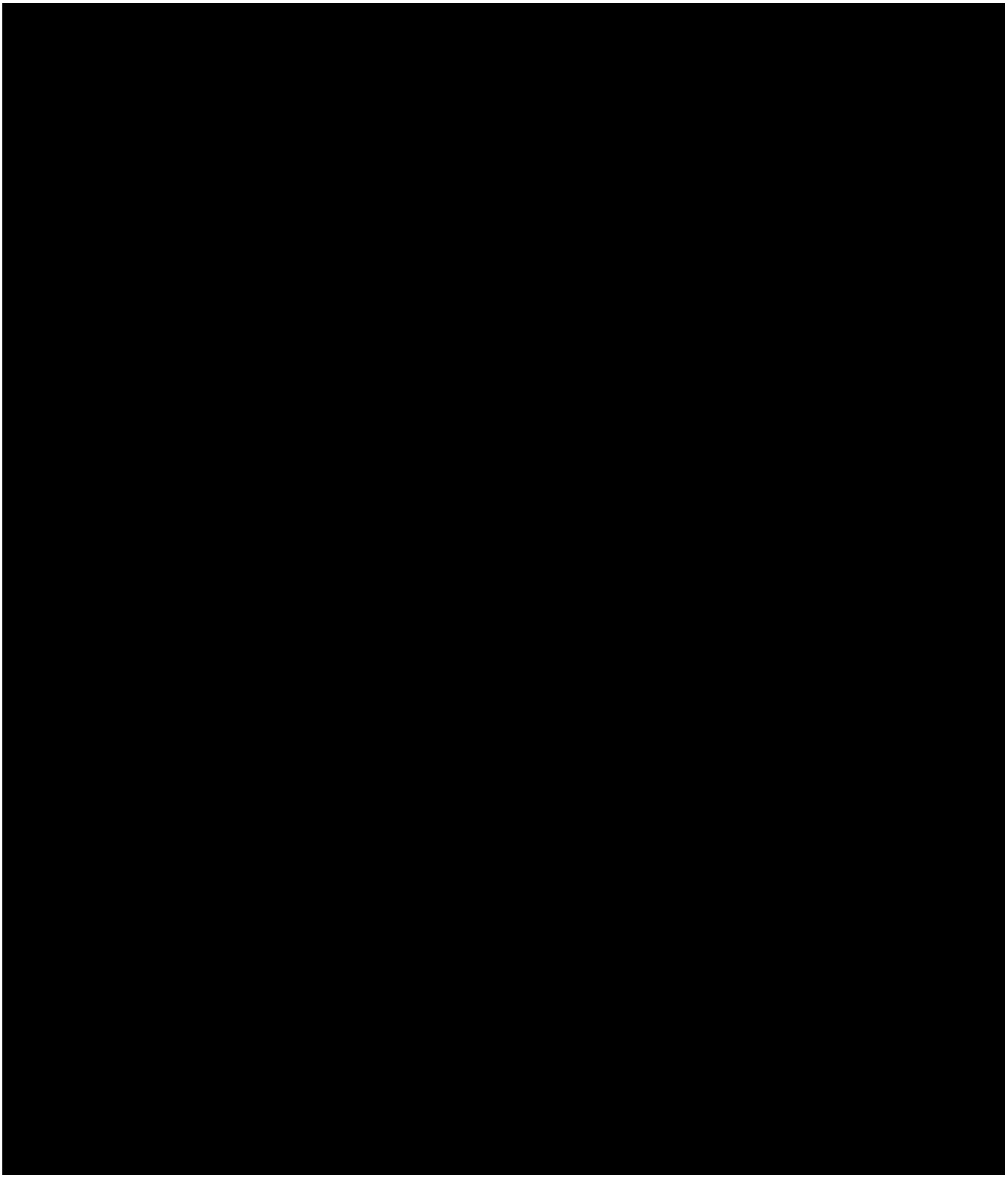
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in serum)

[redacted]

2.2.2.1 Safety and tolerability

Safety and tolerability of BI 765080 will be assessed based on:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring
- Vital signs (blood pressure, pulse rate), oral body temperature
- Local tolerability assessment



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single-rising dose trial is designed as single-blind, randomised within dose groups, and placebo-controlled within parallel dose groups.

It is planned to include a total of 48 healthy male subjects in the trial. The subjects will be assigned to 6 groups consisting of 8 subjects per group; the groups will be dosed sequentially (see Table 3.1: 1). The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose groups (e.g., add low and/or intermediate dose groups) based on experience gained during the study (for instance, based on preliminary PK data), provided the planned and approved highest dose is not exceeded. Thus, the actual number of subjects entered may be more than 48, but is not to exceed 80. Such changes may be implemented via non-substantial CTP amendments.

Within each dose group, 6 subjects will receive BI 765080 and 2 will receive placebo. Only one dose is tested within each dose group. For safety reasons, each dose group will consist of 3 cohorts. The trial medication will be administered in the following order:

- Cohort 1: 1 subject on active treatment followed by 1 subject on placebo (in total 2 subjects)
- Cohort 2: 2 subjects on active treatment (in total 2 subjects)
- Cohort 3: randomised to 3 subjects on active treatment and 1 subject on placebo (in total 4 subjects)

Between cohort 1 and cohort 2 there will be a time interval of at least 1 day, which is expected to be sufficient to detect relevant acute effects of BI 765080. Cohort 1 and cohort 3 will be separated by at least 2 days. This design ensures that between first and second active dose of each dose level, there is a time interval of at least 1 day, which covers the t_{max} of BI 765080 (end of infusion) and the period of highest risk / peak effect. If BI 765080 was safe and showed acceptable tolerability in the first two cohorts, the remaining third cohort of the respective dose level could be dosed as close as 10 minutes apart.

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
Dose (mg)	1	10	25	50	100	200
Number of subjects	8	8	8	8	8	8
Subjects receiving placebo	2	2	2	2	2	2
Subjects receiving BI 765080	6	6	6	6	6	6

The groups will be dosed consecutively in ascending order, and a time interval of at least 14 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 of all the preceding dose groups. Preliminary PK [redacted] assessments may be performed between dose groups (see Section 7.4). The next dose group will only be treated if, in the opinion of the investigator, no safety concerns have arisen in the preceding dose groups (i.e. no dose-limiting events occurred), and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.1).

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 study (for instance, due to the occurrence of any unforeseen adverse events). Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the clinical trial leader (or an authorised deputy). In addition, at least data from 6 evaluable subjects per dose level need to be available for escalation to higher dose.

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 3.3.4.1).

The minimum data up to at least 48 hours post dosing set for review consists of the following:

- AEs in the current and preceding dose groups, including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead ECG and continuous ECG monitoring in the current and preceding dose groups based on assessment of the study site.
- Vital signs in the current and preceding dose groups
- Clinical laboratory tests in the current and preceding dose groups

[redacted]

- 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 the 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 Clinical Trial Leader (or an authorised deputy), and will be filed in the ISF and TMF.

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

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

For single-rising dose trials, the rising dose design described in Section 3.1 is viewed favourably under the provision not to expose the subjects involved to undue risks.

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

It is standard in single or multiple rising dose trials involving healthy volunteers to include a placebo group to control for safety, tolerability, [redacted] effects of the trial medication. Each dose group consists of 8 subjects, with 6 on active treatment, and 2 on 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 pharmacokinetics.

The administration of the study drug as i.v. infusion is considered advantageous since the administration of BI 765080 can be immediately stopped in case safety concerns arise during the running infusion. A further advantage of the i.v. route is the possibility to investigate supratherapeutic exposure unbiased from individual variability in bioavailability.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 48 healthy male subjects will enter the study. The actual number of subjects entered may exceed the total of 48 if additional doses are tested (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

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

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation

3.3.3 Exclusion criteria

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

1. 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 45 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. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
7. History of relevant orthostatic hypotension, fainting spells, or blackouts
8. Chronic or relevant acute infections
9. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
10. Use of drugs with a long half-life (more than 24 h) within 30 days or less than 10 half-lives of the respective drugs prior to administration of trial medication.
11. Within 10 days prior to administration of trial medication, use of drugs that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. 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
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more 30 g per day)

16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. Male subjects with WOCBP partner who are unwilling to use a highly effective method of birth control from time point of administration of trial medication until 60 days thereafter. Highly effective methods of birth control are:
    - Male subject is sexually abstinent
    - Male subjects is vasectomised (vasectomy at least 1 year prior to enrolment), *plus* condom in male subject
    - Use of intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) by female partner
    - Use of progestogen-only hormonal contraception by female partner that inhibits ovulation (only injectables or implants), *plus* condom in male subject
    - Use of combined (estrogen and progestogen containing) hormonal contraception by female partner that prevents ovulation (oral, intravaginal or transdermal), *plus* condom in male subject
    - Female partner is surgically sterilised (including hysterectomy)
    - Female partner is postmenopausal, defined as no menses for 1 year without an alternative medical cause)

    Subjects are required to use condoms to prevent unintended exposure of the partner (both, male and female) to the study drug via seminal fluid. Male subjects should use a condom throughout the study and for 60 days after investigational medicinal product (IMP) administration.

    Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle.

    If a subject is usually not sexually active but becomes active, with their partner, they must comply with the contraceptive requirements detailed above.

Male subjects should not donate sperm for the duration of the study until at least 60 days after IMP administration. In addition, the following SARS-CoV-2-specific exclusion criteria apply:

24. A positive PCR test for SARS-CoV-2 and clinical symptoms suggestive for this disease on Day -2.

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

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

At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.6), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
3. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
4. 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
5. 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
6. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk assessment. Dose escalation will be terminated if 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 one drug-related serious adverse event is reported.
3. Violation of GCP, the CTP, or the contract with BI, impairing the appropriate conduct of the trial.
4. The sponsor decides to discontinue the further development of the investigational product
5. Dose escalation will be stopped if at least 2 subjects on active treatment at one dose level have relevant individual QT prolongations, i.e. a QTc increase of greater than 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording
6. Occurrence of severe non-serious adverse events considered as drug-related by the investigator in 2 subjects of the same dose group (8 subjects)

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

3.3.5 Replacement of subjects

If some subjects do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject [redacted] replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product BI 765080 was manufactured by BI Pharma GmbH & Co. KG.

[redacted]

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 765080
Pharmaceutical formulation:	Powder for solution for injection/infusion
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg/vial
Posology:	1-0-0
Route of administration:	i.v. infusion
Duration of use:	Single dose

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

Substance:	Matching placebo (0.9% saline for injection)
Pharmaceutical formulation:	Solution for infusion
Source:	Purchase by [redacted] (e.g. [redacted])
Unit strength:	Not applicable
Posology:	1-0-0
Route of administration:	i.v. infusion
Duration of use:	Single dose

At the time of use, the i.v. solution for dosing will be prepared as detailed in the instruction given in Appendix 10.1.

4.1.2 Selection of doses in the trial

The doses selected for this trial cover the range of subtherapeutic, anticipated therapeutic, and supratherapeutic doses and include a safety margin (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups (3 cohorts per dose group) according to their temporal availability. As soon as enough subjects are allocated to 1 of the 18 dose cohorts (3 cohorts per dose group), 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) prior to the first administration of trial medication. For this purpose, the randomisation list will be provided to the trial site in advance. Numbers of the randomisation list will be allocated to subjects by drawing lots. Subjects are then assigned to treatment according to the randomisation list.

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 3.1: 1 and Appendix 10.1, Table 10.1.3.3: 1. The dose volume for placebo corresponds to the dose volume of the corresponding dose level. Subjects receiving placebo are equally distributed across dose groups. Start- and end time of the infusion will be recorded.

Detailed instructions for the dilution of the trial product, the preparation of the infusion solution, the volume to be administered and the infusion time is provided in Appendix 10.1. In all subjects, the infusion solution will be intravenously administered over 30 minutes approximately between 8.00 h and 10.00 h of the respective study day.

In case of safety concerns, e.g. due to infusion reactions, it is in the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited slowing down the infusion rate, stopping of the infusion and provided no further safety concern exist restarting at a slower rate. Further based on [redacted] medical judgment he/she will provide medications such as steroids, etc. as needed.

For administration of the infusion, an intravenous indwelling catheter is placed into an arm vein of the subject and closed with a mandrin. A second indwelling catheter used for collection of blood samples will be placed on the contralateral arm.

The administration of the trial medication will be done under supervision of the investigating physician or a designee. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. For the purpose of drug accountability, the infusion set will be weighed before and after drug administration.

Water is allowed except for 1 hour before start of infusion and 1.5 h after end of infusion. On Day 1, from 2 hours post-dose, liquid intake is restricted at additional 3000 mL until the morning of Day 2. Standardised meals will be served as outlined in the Flow Chart. Subjects will be kept under close medical surveillance until 48 h following drug administration. On

Day 3, subjects will be discharged from the trial site and further assessments will be conducted in an ambulatory fashion. For restrictions with regard to diet, see also Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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

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

All trial data will be handled open label. This means that trial functions of the sponsor are unblinded (including clinical trial leader, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated personnel of the trial site).

Within the [redacted] the staff involved with interval measurements and assessments will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician.

Access to the randomisation schedule will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF.

4.1.5.2 Unblinding and breaking the code

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

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal product BI 765080 will be provided by BI. It will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice. The placebo solution will be provided by the trial site.

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 EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms. Examples of the labels will be available in the ISF.

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 local clinical monitor (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 from the sponsor when the following requirements are fulfilled:

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

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

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused trial medication will be disposed of locally by the trial site upon written authorisation of the trial clinical monitor. 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. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. On Day 1, no food is allowed for at least 10 h before and 1.5 h after administration of the study drug (= end of infusion).

On Day 1, no fluid intake is allowed starting 1 hour before drug administration until 1.5 h after the end of infusion. From breakfast until 24 hours post-dose water intake will be within 1000 to 3000 mL. Total fluid intake on all in-house days is recommended to be at least 1.5 L and should not exceed 3.5 L.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed on in-house days. On the ambulatory days, it is restricted to a maximum of 200 mL (coffee, tea, cola, red bull, energy drinks) or 50 g (chocolate and chocolate products).

Smoking is not allowed during in-house confinement while admitted to the trial site.

Alcoholic beverages are not permitted starting 7 days before the first administration of trial medication until Day 14.

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

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma/ serum concentrations 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 documentation of demographics, height and body weight, smoking and alcohol history, !"#$%&'&#()%**+,(-#)(.%)/".0")%*+)%1, ,.),*,0 '.)%234 %*)%1, *,5%*),06relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR) and body temperature, 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of weight.

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 in healthy volunteers) will be measured by a blood pressure monitor (Dinamap Pro 100, [redacted]) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required. The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

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
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; 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
	Prothrombin time – INR (International Normalization Ratio)	X	X
	Fibrinogen	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
	Creatine Kinase [CK]	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X
	Lactic Dehydrogenase	X	X
	Lipase	X	X
	Amylase	X	X
	Serum tryptase	X	--
Hormones	Thyroid Stimulating Hormone	X	--
	Free T3 - Triiodothyronine	X	--
	Free T4 – Thyroxine	X	--
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	C-Reactive Protein (Quant)	X	X
	Uric Acid	X	X
	Cholesterol, total	X	X
	Triglyceride	X	X
Electrolytes	Sodium	X	X
	Potassium	X	X
	Chloride	X	X
	Calcium	X	X
	Phosphate (as Phosphorus, Inorganic)	X	X

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 and Visit 3 (for time points refer to Flow Chart)

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	BI test name [comment/abbreviation]	A	B
Urinalysis (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leucocytes (qual)	X	X
	Urine pH	X	X
Urine sediment and microscopic examination	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 Visit 1 (screening examination)
B: parameters to be determined at Visit 2 and Visit 3 (for time points refer to Flow Chart)

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. It is planned to perform these tests at screening only, except for drug screening and the SARS-CoV-2 PCR test, which will be performed on Day -1 and Day -2 respectively.

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/XTC
	Opiates
	Phencyclidine
	Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative)
	Hepatitis B core antibody (qualitative)
	Hepatitis C antibodies (qualitative)
	HIV-1 and HIV-2 antibody (qualitative)
	SARS-CoV-2 PCR test

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 6510 and Alcotest® 5510, [redacted]) will be performed prior to treatment and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

In case of a potential systemic allergic reaction blood samples for the determination of serum tryptase will be collected 0.5 h, 2 h, 6 h, and 24 h after onset of the event.

[redacted]

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted], with the exception of drug screening tests. These tests will be performed at the trial site using Alere Triage TOX Drug Screen or a comparable test system. [redacted] will be performed at [redacted]

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

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 (Motara Device, [redacted]) at the time points given in the Flow Chart. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

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 study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart.

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

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

Storing

All ECGs will be stored electronically at the site.

Data transfer

For time points specified in the Flow Chart as triplicate ECGs, ECGs will be transferred electronically to the [redacted] for evaluation and/or storage except for ECG from screening and EoTrial which will not be transferred.

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

Data transfer from the [redacted] to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation

a) [redacted]

[redacted]evaluation will be performed (during the study and/or after the study) for the first of three replicate ECGs per time point in the Flow Chart. For baseline, where 3 triplicate ECGs are recorded, only the first triplicate ECG (i.e. 3 single ECGs) will be evaluated. The remaining second and third replicate ECGs will be stored for additional analyses 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.

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 automatic interval measurements, no lead will be provided. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

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

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

b) Trial site

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

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB 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 [redacted] In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening) 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

Cardiac rhythm (including heart rate) will be monitored by means of continuous 2-lead ECG recording using the Dräger Telemetry monitoring system, Infinity M300 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

5.2.5.1 Local tolerability

Local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings.

5.2.5.2 Oral body temperature

Oral body temperature will be measured at the times indicated in the Flow Chart using a standard device.

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 or not considered related to the medicinal product.

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

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

5.2.6.1.3 AEs considered ‘Always Serious’

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

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

The latest list of ‘Always Serious AEs’ can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

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

Hepatic injury is considered an AESI in this trial. A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, 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 the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced

- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced)

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 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 subsequently noted.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end time, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to 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:
    - 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 or trial database 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 related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF

5.2.6.2.2 AE reporting to the sponsor and timelines

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

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information.

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

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

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B). The ISF will contain the Pregnancy Monitoring Form for

Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Date and clock times of drug administration and pharmacokinetic sampling will be recorded in the eCRFs.

Exact times of blood sampling will be derived from the electronic data capturing system ClinSpark and documented in the eCRFs by the medical personnel or sent as electronic files to the trial data manager. 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. as a result of preliminary PK data), including addition of samples and visits, as long as the total blood volume taken per subject does not exceed 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 765080 concentrations in serum, approximately 3.0 mL of blood will be drawn from an antecubital or forearm vein into a serum collection tube (SST II Advance tube or equivalent) at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

The sample tubes will be inverted six times without shaking and left upright for at least 30 minutes to allow the sample to thoroughly clot. Serum is prepared by centrifugation for approximately 10 -15 minutes at approximately 1500 g to 2000 g at room temperature. Immediately transfer 0.5 mL serum from the collection tube into each of the labelled cryotubes.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time, aliquot #1 or #2, serum, and PK.

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/-94ºF 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 serum samples will be stored at approximately -70°C/-94ºF or below until analysis.

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

[redacted]

[redacted]

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

The acceptable deviation from the scheduled time for vital signs and ECG will be:

- ±20 min up to and including 12 h
- ±30 min from 12h up to and including 48 h
- ±60 min from 48 h up to Day 8
- ±4h from Day 8 onwards up to the last measurements

The tolerance for blood sampling for PK, [redacted] and laboratory parameters will be:

- ±1 min up to and including 30 min
- ±5 min from 30 min up to and including 12 h
- ±15 min from 12 h up to and including 48 h
- ±60 min from 48 h up to Day 8
- ±4h from Day 8 onwards up to the last measurements

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

For planned individual blood concentration sampling times, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the study. For information

regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

6.2.2 Treatment period

Each subject will receive one dose of trial medication (BI 765080 or placebo) at Visit 2.

Trial medication will be administered as i.v. infusion by the investigating physician or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

Study participants will be admitted to the trial site on Day -1 and kept under close medical surveillance for at least 48 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] designee. On all other study days, subjects will be treated in an ambulatory fashion.

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

The safety measurements performed during the treatment period are specified in Section 5.3 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

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 Sections 5.2.2 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objectives of this trial will be assessed by calculating descriptive statistics for safety as well as for PK [redacted] parameters, which will be compared between the treatment groups. Further analyses of these endpoints comprise the power model for assessment of dose proportionality.

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

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

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study 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 violation 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.

Descriptions of possible additional analysis sets will be provided in the TSAP, to be finalised prior to database lock.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be specified in the iPD specification file prior to trial initiation; iPDs will be identified no later than in the Report Planning Meeting and the iPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Sections 2.1 and 2.2 for BI 765080 will be calculated according to the relevant SOP of the Sponsor [001-MCS-36-472].

Serum concentration data and parameters of a subject will be included in the 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.

Relevant protocol deviations may be

- Randomized study drug not administered or wrong trial drug administered
- Incorrect dose of trial medication taken
- Missed/missing PK samples at important phases of PK disposition curve

A PK concentration or parameter will be considered as non-evaluable, if for example the subject did not receive the complete assigned infusion volume.

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

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of 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).

7.3.1 Primary endpoint analyses

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

7.3.2 Secondary endpoint analyses

Primary analyses

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

[redacted]

[redacted]

7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Sections 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 planned time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs). Therefore, measurements planned or AEs recorded prior to the intake of trial medication will be assigned to the screening period; those between the trial medication intake and the end of

trial examination (including the anticipated REP) will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

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

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

[redacted]

7.4 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.

A preliminary analysis of PK parameters [redacted] C_{max} of BI 765080) and [redacted] provided as individual values and geometric means, may be performed.

The PK parameters will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472]. The non-compartmental analysis will be performed using a validated software program such as Phoenix WinNonlin™ software (version 8.1 or higher, [redacted]) or SAS® Version 9.4 (or later version). A quality check of the preliminary data will be performed.

In contrast to the final PK[redacted] calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results.

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

The preliminary results will be distributed to the investigator and the trial team.

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

No inferential statistical interim analysis is planned. However, after completion of each 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.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Subjects will be randomised within cohort 3 of each dose group in a 3:1 ratio (active drug 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).

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 48 subjects in this 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. Thus, the actual number of subjects entered may exceed 48, but will not exceed 80 subjects entered.

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

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

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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

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

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

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

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

The EC/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 patient (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 [redacted] of [redacted] under the supervision of the Principal Investigator Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

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

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

The trial medication will be provided by the [redacted] (BI 765080) and Placebo NaCl will be obtained by clinical trial site from public pharmacy (NaCl 0,9%).

Safety laboratory tests will be performed by the local laboratory of the trial site ([redacted]

Analyses of BI 765080 concentrations in serum will be performed at [redacted]

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

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

Data management and statistical evaluation will be done by BI or CRO appointed by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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[redacted]

10. APPENDICES

10.1 RECONSTITUTION INSTRUCTIONS

10.1.1 Description of trial medication

Vials containing 50 mg BI 765080 powder for solution for injection / infusion (50mg/vial). presented in a 2 mL vial, will be provided by the Sponsor Boehringer Ingelheim. These vials will be labelled according to regulatory requirements

10.1.2 Temperature deviation during storage

The study drug product will be stored in the original packaging in a limited access area at the temperature specified on the drug label. For temperature monitoring all medication kits have an attached Mini-tag®. In case of a storage temperature excursion the Mini-tag® have to be read out and the results have to be documented in the form Mini-tag® Alarm Sequences which is available in the Investigator Site File (ISF). In case of at least one red Mini-Tag® submit a Product/Device Complaint Form (available in the ISF) the form Mini-tag® Alarm Sequences to the CTSU Complaint Team (CTSU_Complaints.bibatboehringer-ingelheim.com). The medication should be put in quarantine until the Complaint team has communicated the decision to release the concerned vials or to consider them as unusable.

10.1.3 Instructions for preparation the study medication

10.1.3.1 General Remarks

The pharmacist, his/her deputy or other appropriately licensed and authorized drug-preparation personnel will prepare the trial medication as requested by the investigator. Handling and preparation of the medicinal product should be performed according to routine site procedures using aseptic techniques. Prior to the preparation and the infusion, the vials should be checked for any changes (e.g. colour) and for the absence of particles. After reconstitution the should be colourless to slightly brownish yellow. If you have any questions or concerns regarding appearance of the solution, please do not use the solution. Please retain the solution and contact your CRA or the Clinical trial manager who may require you to complete a Complaints Form.

The final solution for infusion should be delivered to the unit or ward where the medication will be administered as soon as possible after preparation. Labelling of medication containers will be done according to institute standards.

10.1.3.2 Consumables

Materials tested to be compatible the study medication are listed in Table 10.1.3.2: 1 for preparation and in Table 10.1.3.2: 2 for administration.

Table 10.1.3.2: 1 Overview of materials used for preparation of BI 765080 Powder for solution for injection/infusion 50 mg/vial (50 mg/mL)

Type	**Qualitative composition**
Syringe 50 mL intended for use with syringe pumps (Graduation: 1 mL)	Polypropylene
Syringe 10 mL (Graduation: 0.2 mL)	Polypropylene
Syringe 5 mL (Graduation: 0.2 mL)	Polypropylene
Syringe 3 mL; Graduation: 0.1 mL	Polypropylene; Plunger: PE
Syringe 1 mL (Graduation: 0.01 mL)	Polypropylene
Syringe closure	Polyethylene
20G 1½ needle	Stainless steel / Polypropylene
25G needle	Stainless steel / Polypropylene
Discofix-	PA

Table 10.1.3.2: 2 Reconstitution Medium and Dilution medium

Description	**Purpose**
Water for Injection	Reconstitution of lyophilized powder
0.9% Saline Solution	Diluting the reconstituted drug product prior administration

10.1.3.3 Preparation of the study medication

In order to achieve the target doses after reconstitution with water for injection the drug product must be further diluted using isotonic saline to the concentrations assigned for each dose level. The target doses will be achieved by volume aliquotation. Further information on the concentrations to be administered per dose level and the resulting volume aliquot to be administered are provided in Table 10.1.3.3: 1.

Please note: In order to prepare dilutions with a concentration of 0.1 mg/mL 2 dilution steps are required.

Table 10.1.3.3: 1 Dilution Scheme

Dose level	Target Dose [mg]	Target Concentration [mg/mL]	$V_{BI\ 765080}$ [mL]	$V_{0.9\%\ Saline}$ [mL]	Administration Volume [mL]
1	1	0.1	1	49	--
			5	45	10
2	10	1	1	49	10
3	25				25
4	50				50
5	100	2	2	48	50
6	200	4	4	46	50

The site may prepare syringes containing an overfill as per site standard policies. The overfill is required in order to accommodate the dead volume of the infusion set.

Administration of the ready to use syringes will be done according to Section 4.

10.1.3.3.1 Reconstitution of the lyophilized powder

1. Attach a 3 mL syringe to the bottle containing water for injection (WFI) and withdraw 1.2 mL WFI.
2. Attach a 20G needle to the syringe and adjust the volume to 1.1 mL and gently inject the complete content of the syringe through the stopper, to the wall of the vial containing BI 765080 powder for solution for injection / infusion (50mg/vial).
3. Discard needle and syringe, and then gently swirl the vial until the lyophilizate is dissolved and homogenized. Do not shake. Avoid the generation of foam. The full reconstitution should be finished within 10 minutes.
4. In case of foam generation during reconstitution, wait with further processing until foam has settled. This should take not more than 60 min.

10.1.3.3.2 Dilution Procedure (DL 1)

1. Withdraw the volume aliquot of 0.9% saline defined in Table 10.1.3.2: 2 in a 50 mL syringe (compatible with syringe pump).
2. Withdraw the drug product volume defined in Table 10.1.3.2: 2 from the vial containing reconstituted BI 765080 50 mg / mL using an appropriate syringe.
3. Combine both syringes with a syringe adapter and mix the content of the syringes by gently transferring back and forth gently transferring back and forth 10 times. The resulting concentration is 1 mg/ mL.
4. Transfer 5 mL of the diluted drug product in a 5 mL syringe and discard the 50 mL syringe.
5. Withdraw 45 mL isotonic saline in a 50 mL syringe (compatible with syringe pump), combine both syringes via syringe adapter / discofix connector and mix the content of both syringes by gently transferring back and forth 10 times. The resulting concentration is 0.1 mg/ mL.
6. Collect the complete volume in the 50 mL syringe. Make sure that the complete volume has been transferred to the 50 mL syringe prior disconnecting the smaller syringe and the adapter. Lock the syringe using a syringe closure.

10.1.3.3.3 Dilution Procedure (DL 2-6)

1. Withdraw the volume aliquot of 0.9% Saline defined in Table 10.1.3.2: 2 in a 50 mL syringe (compatible with syringe pump).
2. Pool the drug product volume defined in Table 10.1.3.2: 2 from the vials containing reconstituted BI 765080 50 mg/mL using an appropriate syringe.
3. Combine both syringes with a syringe adapter / discofix connector and mix the content of the syringes by gently transferring back and forth gently transferring back and forth 10 times
4. Collect the complete volume in the 50 mL syringe. Make sure that the complete volume has been transferred to the 50 mL syringe prior disconnecting the smaller syringe and the adapter. Lock the syringe using a syringe closure.

10.1.3.3.4 Preparation of Placebo

Note: Commercially available 0.9% Saline for injection will be used as Placebo.

1. Withdraw the amount 0.9% Saline for Injection matching the administration volume of active drug product defined in Table 10.1.3.2: 2 in a 50 mL syringe (compatible with syringe pump).

10.1.3.4 In-Use stability statement

Chemical and physical in-use stability of BI 765080 has been demonstrated for a concentration range from 0.1 mg/mL to 8 mg/mL diluted with 0.9% saline solution for 24 hours at 2-8°C (36-46°F) followed by 6 h (4 h storage and 2 h infusion time) at 30°C (86°F) in clinical sets as described. Do not freeze.

From a microbiological point of view, the solution for infusion should be used immediately. The solution for infusion is not intended to be stored unless dilution has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

10.1.4 Infusion Instructions

10.1.4.1 General Remarks

In order to avoid an infusion reaction caused by the administration of low temperature solution the infusion container must be brought to room temperature before infusion.

Connect the infusion set (= infusion container connected with administration set and 0.2 µm in-line filter) with the catheter and administer the complete content of the infusion container over 30 min to the subject.

In case of technical issues or complications during infusion, please refer to the protocol.

10.1.4.2 Administration

Information on administration consumables:
The following medical consumables were tested within the in-use stability study.

Table 10.1.4.2: 1 Overview of materials for administration of BI 765080 Solution for Infusion

Type	**Material**
0.2 µm Filter	PES, e.g. Sterifix 4099303
Catheter 24G	PUR
Stopcock Discofix C	PA, PC, PP
Original Perfusor tubing 200 cm	PE
Compact plus syringe pump	[redacted] perfusor compact plus
Plastipak syringe 50 mL	PE

Syringe pump compatible with the 50 mL syringe used for preparation.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		08 December 2020
EudraCT number **EU number**		2020-004262-19
BI Trial number		1450-0001
BI Investigational Medicinal Product		BI 765080
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising intravenous doses of BI 765080 in healthy male subjects (single-blind, randomised, placebo-controlled, parallel-group design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Synopsis: Secondary endpoints; Test product Flow chart 1.3.2: Maximum dose and escalation Table 1.3.2:1: Planned maximum dose and estimated exposure multiples versus exposure in the rat and monkey 1.4.2: Drug-related risks and safety measures 2.1.3: Secondary endpoints [redacted] 3.1: Overall trial design and plan Table 3.1:1: Dose groups 3.3.3: Exclusion criteria Table 5.2.3:1: Routine laboratory tests 5.3.2.1: Blood sampling for pharmacokinetic analysis [redacted] 10.1: Reconstitution instruction
Description of change		Synopsis: changed the format of secondary endpoints; [redacted]

		deleted 400 mg and 600 mg in the part of Text product; Flow chart: time-points for local tolerability was added; 1:3:2: Maximal dose was changed to 200 mg; Added "If the doses up 200 mg are needed, the substantial CTP will be provided"; Table 1.3.2:1: maximal 600 mg was replaced by 200 mg; [redacted]"; 3.1: deleted "If 200 mg does not achieve the expected exposure, additional dose groups may be added up to a maximum of 600 mg."; Table 3.1:1: deleted wording of 400 mg and 600 mg groups; 3.3.3: exclusion criteria No. 23: changed contraception measures application from 30 days to 60 days. Sperm donation is allowed until at least 60 days after IMP administration; Table: 5.2.3:1: deleted glutamate dehydrogenase (GLDH) test; 5.3.2.1: updated blood sampling handling for PK analysis; [redacted]"; 10.1: deleted information of 400 mg and 600 mg
Rationale for change		Changes based on the request by BE FAMHP Minor editorial changes

11.2 GLOBAL AMENDMENT 2

Date of amendment		10 May 2021
EudraCT number **EU number**		2020-004262-19
BI Trial number		1450-0001
BI Investigational Medicinal Product		BI 765080
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising intravenous doses of BI 765080 in healthy male subjects (single-blind, randomised, placebo-controlled, parallel-group design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		3.1: Overall trial design and plan Table 10.1.4.2: 1: Overview of materials for administration of BI 765080 Solution for Infusion
Description of change		[redacted] Table 10.1.4.2:1: updated materials for infusion
Rationale for change		Infusion material updating Minor editorial changes

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-03

Title: Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising intravenous doses of BI 765080 in healthy male subjects (single-blind, randomised, placebo-controlled, parallel-group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	10 May 2021 14:34 CEST
Author-Trial Statistician		10 May 2021 14:49 CEST
Approval-Team Member Medicine		10 May 2021 20:11 CEST
Verification-Paper Signature Completion		11 May 2021 13:40 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed