Clinical Trial Protocol

	Document Number:	**c35408932-03**
EudraCT No.	2021-003281-13	
BI Trial No.	1450-0002	
BI Investigational Medicinal Product	BI 765080	
Title	Absolute bioavailability, safety, tolerability, and pharmacodynamics following subcutaneous (SC) injection of 100 mg BI 765080 relative to intravenous (IV) dose in healthy male subjects	
Lay Title	A study in healthy men to test how BI 765080 is taken up in the body when given as an injection under the skin compared with an infusion into the vein	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: [redacted] 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: 20 Oct 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	09 Aug 2021
Revision date	20 Oct 2021
BI trial number	1450-0002
Title of trial	Absolute bioavailability, safety, tolerability and pharmacodynamics following subcutaneous (SC) injection of 100 mg BI 765080 relative to intravenous (IV) dose in healthy male subjects
Principal Investigator:	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	To investigate the absolute bioavailability of BI 765080 following subcutaneous injection
Trial objectives	- To investigate the absolute bioavailability of 100 mg BI 765080 administered as subcutaneous (SC) injection versus intravenous (IV) infusion - To investigate safety, tolerability, pharmacokinetics [redacted] of 100 mg BI 765080 administered as subcutaneous injection and intravenous infusion
Trial design	Randomised, open-label, single-dose, matched parallel group design
Trial endpoints:	Primary endpoints: $AUC_{0-tz,}$ and C_{max} of BI 765080 Secondary endpoints: • $AUC_{0-\infty}$ of BI 765080 • Occurrence of drug-related adverse event
Number of subjects **total entered** **each treatment**	 28 14
Diagnosis	Not applicable

Main criteria for inclusion	Healthy male subjects, age of 18 to 55 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	100 mg
mode of admin.	Subcutaneous (SC) injection as bolus (Test, T) Intravenous (IV) as 30 min infusion (Reference, R)
Duration of treatment	Single dose
Statistical methods	Absolute bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary PK endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for treatment and the matched pair. CIs will be calculated based on the residual error from the ANOVA. Drug-related adverse event will be described with descriptive statistics. Descriptive statistics will be calculated for all endpoints.

FLOW CHART - IV GROUP

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK serum	[redacted]	12-lead ECG	[redacted]	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]	Query regarding local tolerability[8]
SCR	1	-21 to -3			Screening (SCR)[1]	x			x		x		
	2	-2	-48:00	8:00	Ambulatory visit	x[9,11]						x	
		-1	-14:00	18:00	Admission to trial site	x[5,9]						x	
		1	-3:00	06:00	Allocation to treatment[2]	x[2]	x[2]		x[2]		x[2]	x[2]	
			0:00	08:00	Drug administration start of infusion								
			0:30	08:30	end of infusion		x		x			x	x
			2:00	10:00	Light breakfast[3]		x		x		x		x
			4:00	12:00			x		x		x	x	
			8:00	16:00	Snack (voluntary)[3]		x		x		x		
			12:00	20:00			x		x		x	x	
		2	24:00	08:00	Breakfast[3]	x	x		x		x	x	
			34:00	18:00	Dinner[3]		x				x	x	
		3	48:00	08:00	Breakfast[3], discharge from trial site (confirmation of fitness[7])		x		x		x	x	
		4	72:00	08:00	Ambulatory visit		x					x	
		6	120:00	08:00	Ambulatory visit		x					x	
		8	168:00	08:00	Ambulatory visit	x	x		x		x	x	
		11	240:00	08:00	Ambulatory visit		x					x	
		14	312:00	08:00	Ambulatory visit	x	x		x		x	x	
		21	480:00	08:00	Ambulatory visit		x		x		x	x	
		28	648:00	08:00	Ambulatory visit	x	x		x		x	x	
		56	1320:00	08:00	Ambulatory visit	x	x		x		x	x	
FU	3	56 to 59			End of trial (EoTrial) examination[4]	x			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, inclusive body temperature if it is still needed based on the status of pandemic, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, 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. Confirmation of fitness includes physical examination.
8. Standardized assessment of local tolerability using the criteria swelling, induration, heat, redness, pain or other findings.
9. SARS-CoV-2 PCR test will be performed prior to admission on Day -1 or Day -2 if it is needed in the current status of pandemic.

[redacted]

11. 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.

FLOW CHART - SC GROUP

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{serum}	[redacted]	12-lead ECG	[redacted]	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]	Query regarding local tolerability[8]
SCR	1	-21 to -3			Screening (SCR)[1]	x			x		x		
	2	-2	-48:00	8:00	Ambulatory visit	x[9,11]						x	
		-1	-14:00	18:00	Admission to trial site	x[5,9]						x	
		1	-3:00	06:00	Allocation to treatment[2]	x[2]	x[2]		x[2]		x[2]	x[2]	
			0:00	08:00	Drug administration/injection								
			0:30	08:30								x	x
			1:00	09:00					x		x	x	
			1:30	09:30								x	
			2:00	10:00	Light breakfast[3]				x		x		x
			3:00	11:00								x	
			4:00	12:00			x		x		x	x	x
			8:00	16:00	Snack (voluntary)[3]				x		x		x
			12:00	20:00			x		x		x	x	
		2	24:00	08:00	Breakfast[3]	x	x		x		x	x	x
		3	48:00	08:00			x		x		x	x	x
		4	72:00	08:00	Breakfast[3], discharge from trial site (confirmation of fitness[7])		x		x		x	x	x
		5	96:00	08:00	Ambulatory visit		x					x	x
		6	120:00	08:00	Ambulatory visit		x					x	x
		7	144:00	08:00	Ambulatory visit	x	x		x		x	x	x
		8	168:00	08:00	Ambulatory visit		x					x	
		11	240:00	08:00	Ambulatory visit		x					x	
		14	312:00	08:00	Ambulatory visit	x	x		x		x	x	
		21	480:00	08:00	Ambulatory visit		x		x		x	x	
		28	648:00	08:00	Ambulatory visit	x	x		x		x	x	
		56	1320:00	08:00	Ambulatory visit	x	x		x		x	x	
FU	3	56 to 59			End of trial (EoTrial) examination[4]	x			x		x	x	x

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TABLE OF CONTENTS

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
ANGPT1	Angiopoietin 1
ANGPT2	Angiopoietin 2
ANOVA	Analysis of variance
ARB	Angiotensin-receptor blocker
AST	Aspartate amino transferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Clinical Monitor Local
COVID-19	Corona virus disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form

eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial/EOT	End of trial
ESRD	End-stage renal disease
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FDA	Food and Drug Administration
FIH	First-in-human
FLD	Fibrinogen-like domain
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
gMean	Geometric mean
HD	Hemodialysis
IB	Investigator's brochure
IEC	Independent Ethics Committee
INR	International Normalization Ratio
IPD	Important protocol deviation
IPV	Important protocol violation
IRB	Institutional Review Board
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV/i.v.	Intravenous
[redacted]	
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
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)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC/s.c.	subcutaneous
SCR	Screening
SGLT2	Sodium-glucose co-transporter-2
SNP	Single nucleotide polymorphism
SOP	Standard operating procedure
SRD	Single-rising dose
T	Test product or treatment
Tie2	Angiopoetin-1 receptor, TEK tyrosine kinase
TMDD	Target mediated drug disposition
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
[redacted]	
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
[redacted]	
WBC	White blood cells
WFI	Water for Injection
WHO	World Health Organisation
WOCBP	Women of child-bearing potential
XTC	Ecstasy

1. INTRODUCTION

BI 765080 is intended for the treatment of chronic kidney disease (CKD). The first trial in humans (SRD 1450-0001 [c31414158]) is ongoing. This is the second 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]. In developed countries, CKD is generally associated with diabetes, hypertension, old age, obesity, and cardiovascular disease.

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].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

The Tie2 antagonist angiopoietin 2 (ANGPT2) blocks ANGPT1-mediated Tie2 activation in glomerular endothelial cells. In patients with diabetic nephropathy, a SNP in ANGPT2 was associated with a 20% elevation in the circulating protein and increased disease severity [R20-1041]. Glomerular ANGPT2 mRNA expression is elevated in diabetic nephropathy [R20-1027]. However, glomerular expression of ANGPT1, the endogenous agonist of Tie2 [R20-1027], and circulating ANGPT1 protein [R20-1028, R20-1029] are unchanged in diabetic nephropathy thereby favouring ANGPT2-bound Tie2 in the context of renal disease progression.

Key clinical observations linking dysregulation of the ANGPT2-Tie2 pathway with CKD were born from trials where patients were stratified by disease severity (from stage 1 to end-stage renal disease (ESRD) / hemodialysis (HD)) and where circulating ANGPT2 was progressively elevated [R20-1029] and inversely correlated with a decline in inulin-measured glomerular filtration rate (GFR) [R20-1030].

BI 765080 is a high affinity neutralizing antibody to ANGPT2, expected to limit antagonistic binding of ANGPT2 to Tie2, restore podocyte to endothelial cell cross-talk, and enable ANGPT1-Tie2 signalling. Enhanced Tie2 signalling via ANGPT1 is expected to stabilize the glomerular capillary structure, reduce endothelial activation, and restore filtration barrier

integrity. In total, these effects are expected to decrease proteinuria and preserve renal function resulting in a slowed disease progression in patients with CKD.

1.2 DRUG PROFILE

1.2.1 Nonclinical pharmacology

BI 765080 binds the ANGPT2 fibrinogen-like domain (FLD) and blocks the physical interaction between the ANGPT2 FLD and the extracellular domain of the Tie2 receptor.

[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. No adverse findings were associated with BI 765080 administration at dose levels up to 100 mg/kg.

1.2.2 Toxicology

Rat and cynomolgus monkey were chosen as the rodent and non-rodent toxicology species due to conserved biological function of ANGPT2 among these species and humans. 4-week (rat) and 13-week (monkey) GLP repeat dose toxicity studies were evaluated. BI 765080 administered up to 100 mg/kg/week was well tolerated in animals. Genetic toxicity studies are generally not applicable to therapeutic antibodies, as they are not expected to interact directly with DNA.

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

1.2.3 Clinical experience in humans

In Phase I, BI 765080 is evaluated in a first-in-human (FIH) SRD trial.

FIH-Study (Trial 1450-0001)

The FIH (first-in-human) trial [c31414158] is ongoing and explored safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenously administered BI 765080 in healthy male subjects. Subjects received single ascending IV doses of 1 mg up to 200 mg BI 765080 or placebo. Overall, the study included 48 male subjects with 36 subjects treated with BI 765080 and 12 subjects treated with placebo.

At preferred term level, all the reported treatment-emergent AEs are shown below:

headache (BI 765080: 3/38 subjects [8.3 %]; placebo: 1/12 subjects [8.3%]), upper respiratory tract infection (BI 765080: 2/36 subjects [5.6 %]; placebo: 0), post vaccine reactogenicity (BI 765080: 1/36 subjects [2.8 %]; placebo: 0), headache post vaccine Covid-19 (BI 765080: 1/36 subjects [2.8 %]; placebo: 0), vomiting (BI 765080: 1/36 subjects [2.8 %]; placebo: 0), vision blurred (BI 765080: 1/36 subjects [2.8 %]; placebo: 0), back pain (BI 765080: 1/36 subjects [2.8 %]; placebo: 0), bronchitis (BI 765080: 1/36 subjects [2.8 %]; placebo: 0), tooth abscess (BI 765080: 1/36 subjects [2.8 %]; placebo: 0), myalgia right upper leg (BI 765080: 1/36 subjects [2.8 %]; placebo: 0), throat irritation (BI 765080: 0; placebo: 1/12 subjects [8.3 %]), weight increased (BI 765080: 0; placebo: 1/12 subjects [8.3 %]), herpes zoster reactivation (BI 765080: 0; placebo: 1/12 subjects [8.3 %]),

All of treatment-emergent AEs were assessed as not drug-related. There were six AEs of moderate intensity (four AEs with BI 765080 and two AEs with placebo). Four moderate AEs with BI 765080 included tooth abscess, headache post vaccine Covid-19 and upper respiratory infection in two subjects. Two moderate AEs with placebo included headache and herpes zoster reactivation. All remaining AEs were of mild intensity.

There were no relevant changes compared to placebo for laboratory safety, including clinical chemistry, hematology, coagulation parameters, and urinalysis. Deaths, serious AEs, and protocol-specified AEs of special interest were not reported in this trial. No clinically relevant changes were observed in 12 lead ECGs, vital signs, and physical examinations. In addition, no adverse event related to local tolerability was reported.

Pharmacokinetics
The preliminary single-dose PK parameters of BI 765080 from dose groups 1 to 6 (1 to 200 mg) are summarized in Table 1.2.3: 1. The preliminary data show that after iv infusion, $AUC_{0-\infty}$ exposure increased with dose in a supraproportional fashion up to the 100 mg dose, consistent with target-mediated drug disposition (TMDD). Dose-adjusted $AUC_{0-\infty}$ was about the same for the 200 mg dose as the 100 mg dose, suggesting TMDD may have neared saturation at the 100 mg dose. C_{max} increased in a near dose-linear fashion at doses ≥ 10 mg. The elimination half-life increased with increasing dose ranging from 12 hours at the 1 mg dose to 267 h at the 200 mg dose.

Table 1.2.3: 1 gMean (gCV%) values of BI 765080 PK parameters after single iv infusion of BI 765080 – SRD Trial 1450-0001 [c31414158]

Parameter	Dose (mg)					
	1	10	25	50	100	200
AUC_{0-tz} (h·µgl/L)	4330 (50.4%)	241000 (24.9%)	868000 (31.3%)	2500000 (39.5%)	7100000 (25.4%)	13200000 (16.0%)
$AUC_{0-\infty}$ (h·µg/L/L)	4930 (48.4%)	258000 (20.7%)	870000 (31.3)	2520000 (39.9%)	7160000 (25.2%)	16300000 (27.3%)
C_{max} (nmol/L)	274 (21.4%)	3490 (11.0%)	7930 (16.2%)	16900 (29.0%)	35400 (13.7%)	64500 (11.6%)
t_{max} (h)*	1.0 (0.5-1.0)	1.0 (0.5-2.0)	1.0 (0.5-1.0)	2.5 (1.0-10)	2.0 (1.0-4.0)	2.5 (0.5-4.0)
t½ (h)	12.1 19.4%)	43.6 (20.0%)	68.6 (14.1%)	89.3 (26.4%)	137 (29.0%)	NC
CL (mL/min)	3.38 (48.4%)	0.645 (20.7%)	0.479 (31.3%)	0.330 (39.9%)	0.233 (25.2%)	NC

* median (min-max)
NC – Not Calculated, incomplete data in elimination phase

1.2.4 Residual Effect Period

The Residual Effect Period (REP) is the period after the last dose with measurable drug levels and/or PD effects still likely to be present.

For BI 765080, a REP has not yet been determined. Conservatively, an observation period of 8 weeks has been selected, which is about 9-fold of the estimated $t_{1/2}$ at 100 mg (approx. 6 days). Therefore, the individual subject's end of trial is on Day 56 to *59* following administration of investigational drug at the earliest (see Flow Chart).

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 765080 is in development for the treatment of CKD, currently in Phase I development.

In FIH BI 765080 was administered as intravenous infusion. However, the subcutaneous injection route is considered for the further clinical studies. For this reason absolute bioavailability is investigated and local tolerability is examined following subcutaneous injection.

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 a new therapy for CKD. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

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 sensitivity, 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 drawing of this volume of blood.

Drug-related risks and safety measures

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), as well as in vitro cytokine release assay and for tissue cross reactivity. 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 clinical safety and tolerability profile of BI 765080 was comparable to placebo in male subjects following intravenous doses of up to 200 mg administered as single dose. There were no deaths or other serious adverse events. There were no drug-related adverse events. There were no dose or exposure related abnormalities in safety laboratory parameters and no safety or tolerability concerns that would preclude further clinical development of BI 765080.

Based on SRD study (1450-0001 [c31414158]) in healthy subjects, no specific drug-related risks are anticipated. Nevertheless, the following safety measures will be applied in this study in order to minimize the risk for the healthy subjects:

- At any time during the ongoing study, further dosing will be stopped in case of safety and tolerability concerns based on the criteria defined in Section 3.1.
- Monitoring of ECG, vital signs, and extensive safety laboratory testing (Table 5.2.3:1) is conducted throughout the study.
- After dosing, the subjects with IV will stay at the site for at least 48 hours and the subjects with SC will stay at the site for at least 72 hours.
- BI 765080 will be administered in a hospital setting and subjects will be under close medical observation during their hospitalisation (see Section 6.2), as well as after their

discharge and until the end of observation period. Safety will be closely monitored during site visits 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.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the absolute bioavailability of 100 mg of BI 765080 administered in healthy male subjects as subcutaneous (SC) injection versus intravenous (IV) infusion.

2.1.2 Primary endpoints

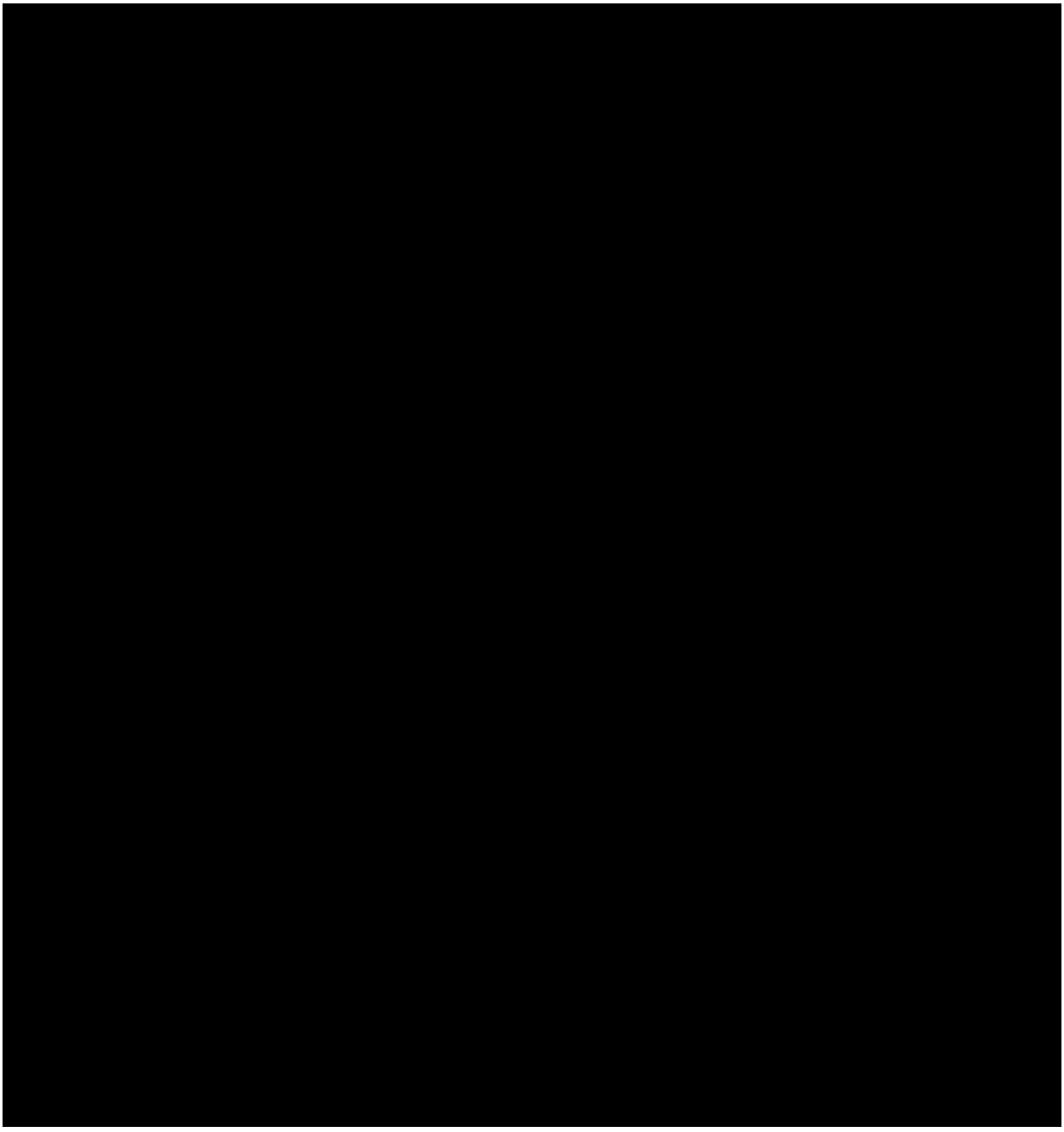
The following pharmacokinetic parameters will be determined for BI 765080:

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoints

- AUC0-∞ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- To assess safety and tolerability of BI 765080: Occurrence of drug-related adverse event

[redacted]



2.2.2.2 Safety and tolerability

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

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open-label, matched parallel group trial in healthy male subjects in order to compare subcutaneous injection administration (T) to intravenous infusion (R). The treatments will be one single 100 mg BI 765080. For details, refer to Section 4.1.

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule 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

This study will explore the absolute bioavailability, safety, tolerability and pharmacodynamics following intravenous (IV) infusion or subcutaneous (SC) injection of BI 765080 in matched pairs of healthy male subjects (matching is done based on age and body weight, see Section 3.3). By dosing test and reference treatment to a matched pair on the same day the influence of confounding factors can be reduced to a minimum.

The trial will be conducted open-label. Blinding is not possible because the treatments are distinguishable. The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analyte, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 28 healthy male subjects (14 subjects with IV and 14 subjects with SC) will enter the study to have at least 12 evaluable subjects available in each group. They will be recruited from the volunteers' pool of the trial site.

Participants in SC and IV groups will be matched for age (18-36 or 37-55 years at screening) and body weight (±10% inclusive). That means, that the 2 subjects of one matched pair are either 18-36 years (inclusive) or 37-55 years old (inclusive) and that the difference of their body weight does not exceed 10% (e.g. 80 kg and 88 kg).

Only Caucasian male subjects will be included in the study.

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

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy Caucasian male subjects according to the assessment of the investigator, as based on a complete medical history, a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 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 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. Use of drugs within 10 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. 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 than 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 in males) 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 90 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 90 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 90 days after IMP administration.

In addition, the following SARS-CoV-2-specific exclusion criteria apply:

24. A positive PCR test for SARS-CoV-2 or clinical symptoms suggestive for this disease prior to the admission.

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

3.3.4.1 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 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.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. 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. 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

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reasons 4 and/or 5 are met, the trial should be discontinued immediately):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational product
3. Deviation from GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial.
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment.
5. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported
6. Further dosing will be stopped if at least 2 subjects at one group (14 subjects) 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
7. Occurrence of severe non-serious adverse events considered as drug-related by the investigator in 2 subjects of one group (14 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

In case more than two subjects per treatment group 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 he replaces. Matching conditions (body weight, age) have to be considered for replacement subjects. Subjects may not be replaced if they drop out for safety reasons, e.g. increase in liver transaminases.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product BI 765080 has been manufactured by BI Pharma GmbH & Co. KG. [redacted]

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the reference (R) 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:	2-0-0
Route of administration:	IV infusion
Duration of use:	Single dose

The characteristics of the test (T) 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:	2-0-0
Route of administration:	SC administration
Duration of use:	Single dose

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

4.1.2 Selection of dose in the trial

The dose of 100 mg of BI 765080 selected for this trial has been selected to correspond to the

potential dose for maintenance treatment in clinical trials in patients.

4.1.3 Method of assigning subjects to treatment groups

Prior to the start of the study, subjects willing to participate in this study will be recruited to treatment groups according to their temporal availability (this includes the ability to participate as well in the IV-arm as in the SC-arm). From the eligible subjects matched pairs (based on age and body weight, see Section 3.3) are formed by the investigator.

The randomisation list will be provided to the trial site in advance. Subjects are then assigned to treatment according to the randomization list with a block size of 2. The allocation of these two random numbers to one matched pair of subjects will be done by drawing lots in the morning of Day 1.

Once a random number has been assigned to a subject, it cannot be reassigned to any other subject.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. Each subject will receive one single dose of trial medication. Detailed instructions for the dilution of the trial product, the preparation of the IV infusion and SC injection solutions, the volume to be administered and the infusion/injection time is provided in Appendix 10.1. In the subjects with IV, the infusion solution will be intravenously administered over 30 minutes.

Table 4.1.4: 1 Dosage and treatment schedule

Dose Group	Route of administration	Application volume	Total dose
1	IV	50 mL	100 mg
2	SC	2 mL	100 mg

Subcutaneous injection

Following an overnight fast of at least 10 hours, the medication will be administered. Trial drug will be injected subcutaneously within 60 seconds in the abdominal region. Detailed handling instruction see Appendix 10.1. Subjects will be kept under close medical surveillance until 72 hours following drug administration. On Day 4, subjects will be discharged from the trial site and further assessments will be conducted in an ambulatory fashion For restrictions with regards to diet, see Section 4.2.2.2.

Intravenous infusion

Following an overnight fast of at least 10 hours, the medication will be administered. The infusion solution will be administered intravenously over 30 minutes. Start and time of the

infusion will be recorded. Detailed handling instruction for the infusion see Appendix 10.1. Subjects will be kept under close medical surveillance until 48 h following drug administration. Day 3, subjects will be discharged from the trial site and further assessments will be conducted in an ambulatory fashion. For restrictions regarding diet, see also Section 4.2.2.2.

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.

4.1.5 Blinding and procedures for unblinding

No blinding will be performed. This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias is low and does not outweigh practical considerations.

Emergency envelopes will not be provided, because the trial medication is known to investigators and subjects.

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

4.1.6 Packaging, labelling, and re-supply

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

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

The 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.

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 delivered from the sponsor 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 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/injection).

On Day 1, no fluid intake is allowed starting 1 hour before drug administration until 1.5 h after the end of injection/ 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.

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

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.

Excessive physical activity (such as competitive sport) should be avoided from 7 days before the first 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 of trial medication will provide additional confirmation of compliance.

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 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.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap Pro 100, [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.

Oral body temperature will be measured using a standard device if it is still needed in the current status of pandemic.

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 (Subjects are advised to come fasted overnight when visiting in the morning, 4h when visiting in the afternoon for the screening) . 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 t examination 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]
Haematology	Haematocrit Haemoglobin Red Blood Cell Count/Erythrocytes White Blood Cells/Leucocytes Platelet Count/Thrombocytes (quant)
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.
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 Prothrombin time – INR (International Normalization Ratio) Fibrinogen
Enzymes	AST [Aspartate transaminase] /GOT, SGOT ALT [Alanine transaminase] /GPT, SGPT Alkaline Phosphatase Gamma-Glutamyl Transferase Creatine Kinase [CK] Creatine Kinase Isoenzyme MB Lactic Dehydrogenase Lipase Amylase
Hormones	Thyroid Stimulating Hormone (only at SCR) Free T3 - Triiodothyronine (only at SCR) Free T4 – Thyroxine(only at SCR)
Substrates	Glucose (Plasma) Creatinine Bilirubin, Total Bilirubin, Direct Protein, Total C-Reactive Protein (Quant) Uric Acid Cholesterol, total Triglyceride

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]
Electrolytes	Sodium Potassium Chloride Calcium Phosphate (as Phosphorus, Inorganic)
Urinalysis (Stix)	Urine Nitrite (qual) Urine Protein (qual) Urine Glucose (qual) Urine Ketone (qual) Urobilinogen (qual) Urine Bilirubin (qual) Urine RBC/Erythrocytes (qual) Urine WBC/Leucocytes (qual) Urine pH
Urine sediment	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

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 during screening only, except for drug screening and the SARS-CoV-2 PCR test, which will be performed prior to admission, if it is needed in the current status of pandemic .

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 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.

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 Triage TOX Drug Screen or a comparable test system.

SARS-CoV-2 PCR test will be performed by [redacted]

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph ([redacted]) at the times provided in the Flow Chart.

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 approximately10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be recorded, interpreted and stored electronically at the site. 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).

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

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.

5.2.6 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 CRF and BI SAE form (if applicable):

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

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

5.2.6.1.2 Serious adverse event

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

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

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. A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described Section 5.2.6.2.

Cancers of new histology 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 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines**'.

5.2.6.1.4 Adverse events of special interest

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

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

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

No other AESIs have been defined for this trial.

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
- There is an alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned
- Disappearance of the event even though the trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

Subjects will be required to report spontaneously any AEs 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 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 sufficiently 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

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 765080 concentrations in serum, 3mL 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 at least 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 parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, ECG parameters, and local tolerability 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 IV and SC 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.

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).

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

- ± 30 min up to and including 48 h
- ± 120 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] 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 scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the 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) at Visit 2.

Trial medication will be administered as IV infusion or SC injection 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 (IV group) or 72 h (SC group) 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.

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

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's 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 objective of this trial is to investigate the absolute bioavailability of (SC) injection of100 mg BI 765080 (Test, T) compared with IV dose of 100 mg BI 765080 (Reference, R) following administration on the basis of the primary and secondary safety and pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. The trial is designed to allow inter-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints and descriptive analysis for AEs.

[redacted]

The assessment of safety and tolerability as well as local tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.2 and 2.2.2.3.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The absolute bioavailability of SC injection compared with IV dose will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 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 allocated and treated with at least one dose of study drug. 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 defined as primary or secondary and 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 to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol violation (IPV) categories will be specified in the IPD specification file prior to trial initiation, IPVs will be identified no later than in the Report Planning Meeting, and the IPV categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug BI 765080 will be calculated according to the relevant SOP of the Sponsor (current version).

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol violation 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 violations may be

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

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

- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve.

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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 provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

7.3.1 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following source of variation: treatment and matching pair. The effect of treatment will be considered as fixed. For each matched pair in the study a pair number will be assigned for analysis purpose. The resulting variable 'matched pair' will be considered as random effect. The model is described by the following equation:

$y_{km} = \mu + \tau_k + s_m + e_{km}$, where

y_{km} = logarithm of response measured on subject m receiving treatment k,

μ = the overall mean,

τ_k = the k^{th} treatment effect, k = 1, 2,

s_m = the effect associated with the m^{th} matching pair, m = 1, 2,…, 14,

e_{km} = the random error associated with the m^{th} subject who received treatment k.

where $s_m \sim N(0,\sigma_B^2)$ i.i.d., $e_{km} \sim N(0, \sigma_w^2)$ i.i.d., σ_W^2 and s_m, e_{km} are independent random variables.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

[redacted]

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

7.3.2 Secondary endpoint analyses

The secondary PK endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics’ and will be assessed statistically using the same methods as described for the primary endpoints.

Drug-related adverse event will be presented descriptively by treatment group.

[redacted]

7.3.3.2 Safety and tolerability analyses

Further safety and tolerability endpoints will analysed descriptively.

7.3.4 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2 and 2.2.2.3. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

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

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of trial examination (including the anticipated REP (see Section 1.2.3)) 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 final 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 values defined as possibly clinically significant 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.

Relevant ECG findings will be reported as AEs.

[redacted]

7.4 INTERIM ANALYSES

No formal interim analysis is planned. A preliminary analysis of PK parameters and safety may be performed, if requested by the Clinical Trial Leader, the investigator, or Trial Clinical Pharmacokinetics.

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 (current version).

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

7.6 RANDOMISATION

This is a randomized trial. Consecutive subject numbers will be assigned via the eDC system. Subjects will be randomized within each matched pair in a 1:1 ratio (IV to SC).

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 28 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed geometric coefficient of variation (gCV) for BI 765080 in the 1450-0001 trial [c31414158] was roughly 14% for C_{max} and 25% for AUC.

For various assumptions around the gCV of 25%, Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a matched pair parallel trial *(N=28)*

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
22.5	1.13	25	22.10	28.28
22.5	1.13	60	53.04	67.87
22.5	1.13	90	79.56	101.81
25.0	1.15	25	21.81	28.66
25.0	1.15	60	52.34	68.78
25.0	1.15	90	78.51	103.18
27.5	1.16	25	21.52	29.04
27.5	1.16	60	51.65	69.70
27.5	1.16	90	77.48	104.55

*Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230] using R Version 4.0.1.

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.

Term and conditions can be provided to the investigator or subject upon request ,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 respective 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 sitemust retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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, biobanking and future use of biological samples and clinical data, in particular

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

Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first subject in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last subject in the whole trial ('Last Subject Completed').
Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The EC/competent authority will be notified about the trial milestones according to the laws of the EU member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial, 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.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [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 (BI 765080) will be provided by the [redacted].

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], [redacted].

[redacted], [redacted].

[redacted] but may be not analyzed.

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 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.

9. REFERENCES

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9.2 UNPUBLISHED REFERENCES

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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 [redacted]). 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.

In case of a significant temperature excursion, the Sponsor must be notified as described in the ISF using the "**Product/Device Complaints Form**".

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 of 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/injection, the vials should be checked for any changes (e.g. color) and for the absence of particles. After reconstitution the solution should be colorless 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/injection 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 10.1.4.2: 1 for I.V. 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

Type	**Qualitative composition**
Syringe 50 mL intended for use with syringe pumps (Graduation: 1 mL)	Polypropylene
Syringe 3 mL; Graduation: 0.1 mL	Polypropylene
Syringe 1 mL (Graduation: 0.01 mL)	Polycarbonate/ Polypropylene
Syringe closure	Polyethylene
20G 1½ needle	Stainless steel / Polypropylene
18G x 1 ½" blunt filter needle	Stainless steel
Syringe adapter or Discofix 3-way stopcock	Polyethylene or Polyamid

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 – IV Dose

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.
3. Discard needle and syringe and swirl the vial gently until the lyophilizate is dissolved and homogenized. Do not shake. Avoid the generation of foam. The full reconstitution should be finished within 10 minutes. The resulting concentration is 50 mg/mL.
4. In case 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 – 100 mg IV dose

1. Withdraw 48 mL 0.9% Saline in a 50 mL syringe (compatible with syringe pump).

2. Pool 2 mL of reconstituted drug product in a 3 mL syringe.
3. Combine both syringes with a syringe adapter / discofix connector and mix the content of the syringes by gently transferring back and forth times. The resulting concentration is 2 mg/mL.
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.

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.

10.1.3.4 Preparation of the study medication –SC Dose

10.1.3.4.1 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. Discard needle and syringe and swirl the vial gently until the lyophilizate is dissolved and homogenized. Do not shake. Avoid the generation of foam. The full reconstitution should be finished within 10 minutes. The resulting concentration is 50 mg/mL.
3. In case foam generation during reconstitution wait with further processing until foam has settled. This should take not more than 60 min.

10.1.3.4.2 Dose preparation (100 mg dose)

1. Attach an 18G filter needle to a 3 mL syringe and pool slightly more than the target injection volume of 2 mL of the reconstituted drug product.
2. Replace the filter needle by a syringe closure if the medication will not be injected immediately.

10.1.3.5 In-Use stability statement

10.1.3.5.1 Ready to administer drug product (IV administration)

Chemical and physical in-use stability of BI 765080 has been demonstrated for a concentration range from 0.1 mg/mL to 8mg/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.

10.1.3.5.2 Ready to administer drug product (SC administration)

Chemical and physical in-use stability of BI 765080 has been demonstrated for a concentration range from 5 mg/mL to 50 mg/mL diluted with 0.9% saline solution or undiluted for 4 h at ambient conditions in the syringe intended for administration.
Do not freeze.

From a microbiological point of view, the solution for injection should be used immediately. The solution for injection 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 Administration Instructions

10.1.4.1 General Remarks

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

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. The SC injection will be given as one bolus.
In case of complications during infusion, please refer to the protocol.

10.1.4.2 Administration (IV Dose)

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**
Tubing intended for syringe pump use, ≤300cm	Polyethylene
0.2 µm Filter	Polyethersulfone (uncharged), e.g. Sterifix 4099303
Discofix C	Polyamide, Polycarbonate, Polypropylene
Catheter 24G	Polyurethane

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

10.1.4.3 Administration (SC Dose)

1. Replace the syringe closure by a 27G x ½" needle and adjust the volume to 2 mL.
2. For administration of s.c. injection, trial drug will be injected subcutaneously within 60 seconds in the abdominal region.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		16 Sep 2021
EudraCT number **EU number**		2021-003281-13
BI Trial number		1450-0002
BI Investigational Medicinal Product(s)		BI 765080
Title of protocol		Absolute bioavailability, safety, tolerability, and pharmacodynamics following subcutaneous (SC) injection of 100 mg BI 765080 relative to intravenous (IV) dose in healthy male subjects
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		1.2.3 Clinical experience in humans 3.3.3 Exclusion criteria
Description of change		1.2.3: added local tolerability assessment “no adverse event related to local tolerability was reported”; 3.3.3: changed contraception measures application from 60 days to 90 days. Sperm donation is not allowed until at least 90 days after IMP administration
Rationale for change		Changes based on the recommend by EC Local tolerability assessment updating

11.2 GLOBAL AMENDMENT 2

Date of amendment		20 Oct 2021
EudraCT number **EU number**		2021-003281-13
BI Trial number		1450-0002
BI Investigational Medicinal Product(s)		BI 765080
Title of protocol		Absolute bioavailability, safety, tolerability, and pharmacodynamics following subcutaneous (SC) injection of 100 mg BI 765080 relative to intravenous (IV) dose in healthy male subjects
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		6.1 Visit schedule 10.1 Reconstitution instructions
Description of change		6.1: PD added to have it consistence with PK 10.1: Inserted the priming of the needles for sc injection to take the void volume into account.
Rationale for change		Minor editorial changes. Clarification and correction.

APPROVAL / SIGNATURE PAGE

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

Title: Absolute bioavailability, safety, tolerability, and pharmacodynamics following subcutaneous (SC) injection of 100 mg BI 765080 relative to intravenous (IV) dose in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	20 Oct 2021 15:01 CEST
Author-Trial Statistician		20 Oct 2021 17:18 CEST
Approval-Team Member Medicine		21 Oct 2021 01:55 CEST
Verification-Paper Signature Completion		21 Oct 2021 09:20 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**