Clinical Trial Protocol

	Document Number:	**c31692550-05**
EudraCT No.	2020-001036-10	
BI Trial No.	1445-0001	
BI Investigational Medicinal Product	BI 1595043	
Title	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1595043 (single-blind, partially randomised, placebo-controlled, parallel (sequential) group design) in healthy male subjects	
Lay Title	A study in healthy men to test how different doses of BI 1595043 are tolerated	
Clinical Phase	I	
Clinical Trial Lead	[redacted] Phone: [redacted] Fax: [redacted]	
Principal Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 4))	
Version and Date	Version: 5.0	Date: 14 January 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	11 May 2020
Revision date	14 January 2021
BI trial number	1445-0001
Title of trial	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1595043 (single-blind, partially randomised, placebo-controlled, parallel (sequential) group design) in healthy male subjects
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	As a transition from non-clinical investigations to clinical development, in this first-in-man trial, safety, tolerability and pharmacokinetics of BI 1595043 will be assessed in healthy male volunteers using single rising oral doses in order to provide the basis for a clinical development in the indication of Crohn's disease.
Trial objectives	To investigate safety, tolerability and pharmacokinetics following single rising doses of BI 1595043
Trial endpoints	Primary endpoint: the percentage of subjects with drug-related adverse events after single doses of BI 1595043 Secondary endpoints: $AUC_{0-\infty}$ and C_{max} of BI 1595043 after single doses
Trial design	Single-blind, partially randomised within dose groups, placebo-controlled, parallel (sequential) group design
Number of subjects **total entered** **each treatment**	64* 8 per dose group (6 on BI 1595043 and 2 on placebo) * Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose is not exceeded. Thus, the actual number of subjects entered may exceed 64, but is not to exceed 72. The addition of further dose levels exceeding the already tested dose levels for the evaluation of safety findings will be subject to a substantial CTP amendment requiring approval from IRB/IEC and RA.
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Test product	BI 1595043 solution (2.5 mg/mL)
dose	1 mg, 3 mg, 6 mg, 12 mg, 25 mg, 50 mg, 90 mg, 160 mg q.d.
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h.
Comparator product	Matching placebo as solution (i.e. solvent)
dose	Not applicable
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h.
Duration of treatment	Single dose
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[15]	PK blood[10,11]	[redacted]	12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
1	-28 to -1			Screening (SCR)[1]	A			x		x	
2	-3 to -1	-72:00 to -24:00	08:00	Ambulatory visit[7]	B						x
	1	-1:30	06:30	Admission to trial site[16,17]	x[5]						
		-1:00	07:30	Allocation to treatment[2]		x[2]		x[2,13]		x[2]	x[2]
		0:00	**08:00**	**Drug administration**					▲		
		0:30	08:30			x		x[9]	|	x	x
		1:00	09:00			x		x[9]	|	x	x
		1:30	09:30			x		x[9]	|	x	x
		2:00	10:00	240 mL fluid intake		x[8]		x[9]	|	x	x
		2:30	10:30			x		x[9]	|	x	x
		3:00	11:00			x		x[9]	|	x	x
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x		x[9]	▼	x	x
		6:00	14:00			x		x[9]		x	x
		8:00	16:00	Snack (voluntary)[3]		x		x[9]		x	x
		10:00	18:00	Dinner[3]		x					
		12:00	20:00			x		x[9]		x	x
	2	24:00	08:00	Breakfast[3]	B	x		x[9]		x	x
		29:00	13:00	Lunch[3]							
		32:00	16:00	Snack (voluntary)[3]							
		34:00	18:00	Dinner[3]		x		x[9]		x	x
	3	48:00	08:00	Breakfast (voluntary)[3], discharge from trial site	B	x		x[9]		x	x
	4	72:00	08:00	Ambulatory visit		x				x	x
	5	96:00	08:00	Ambulatory visit	B	x		x		x	x
	6	120:00	08:00	Ambulatory visit		x				x	x
	7	144:00	08:00	Ambulatory visit		x		x		x	x
	8	168:00	08:00	Ambulatory visit		x				x	x
	9	192:00	08:00	Ambulatory visit		x				x	x
3	10 to 15			End of trial (EoTrial) examination[4]	C			x		x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, ophthalmological examination (exclusion of ocular disorders), check of vital signs, 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; procedures are to be performed and completed within the 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, ophthalmological examination (exclusion of ocular disorders), body weight, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at the time of admission to trial site (refer to Section 5.2.4).

6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this ambulatory visit can be omitted if the screening examination is performed on Days -3, -2 or -1.
8. Only in dose group 4 (12 mg of BI 1595043), one additional blood sample for stability testing will be taken at this time (refer to Section 5.3.2.4).
9. The ECG recording has to be performed in triplicate ECGs at this time.
10. Sampling times and periods may be adapted based on information obtained during the trial (e.g., due to preliminary PK data) including addition of samples and visits as long as the total blood volume removed does not exceed 500 mL per subject.
11. Only in dose group 4 (12 mg of BI 1595043), additional blood sampling will be performed for metabolite identification (refer to Section 5.3.2.2).
[redacted]
13. At baseline (i.e. Day 1, prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes (refer to Section 5.2.5).
14. [redacted]
15. For details of safety laboratory testing at Visit 1 (A), Visit 2 (B) and Visit 3 (C) refer to Section 5.2.4 and Table 5.2.4: 1.
16. Admission to the trial site is allowed in the evening of Day -1 (refer to Section 6.2.2).
17. SARS-CoV-2 PCR test will be performed shortly (within 72 hours) before admission to trial site.

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
[redacted]	[redacted]
ALT	Alanine transaminase
AST	Aspartate transaminase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BA	Bioavailability
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CD	Crohn's disease
CI	Confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTM	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
ECGPCS	ECG pharmacokinetic concentration set
eCRF	Electronic case report form

eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
[redacted]	[redacted]
GCP	Good Clinical Practice
GI	Gastro-intestinal
gMean	Geometric mean
HED	Human Equivalent Dose
[redacted]	
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
IEC	Independent Ethics Committee
IPV	Important protocol violation
IRB	Institutional Review Board
ISF	Investigator site file
IV	Intravenous
[redacted]	[redacted]
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
LOAEL	Lowest observed adverse effect level
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MIST	Metabolites in Safety Testing
MRD	Multiple-rising dose
MRSD	Maximum Recommended Starting Dose
[redacted]	[redacted]
NC	Not calculated
NOAEL	No observed adverse effect level
[redacted]	[redacted]
[redacted]	[redacted]
PE	Polyethylene
PfOS	Powder for reconstitution of an oral solution
PK	Pharmacokinetic(s)

PKS	Pharmacokinetic set
PO	Oral
PP	Polypropylene
PR	Pulse rate
RA	Regulatory authorities
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 product
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SNP	Single nucleotide polymorphism
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
T	Test product or treatment
[redacted]	[redacted]
[redacted]	[redacted]
TMDD	Target-mediated drug disposition
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
[redacted]	[redacted]
ULN	Upper limit of normal
[redacted]	[redacted]
[redacted]	[redacted]
XTC	Ecstasy

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Crohn's disease (CD) is characterized by transmural inflammation with ulcerative lesions affecting any site within the gastrointestinal tract, with most frequent involvement of terminal ileum, often combined with inflammation in colon. CD incidence and prevalence have been rising in all ethnic groups; the recent incidence and prevalence have been reported to range from 7.9 to 20.2 and from 161 to 319 per 100,000, respectively (R13-2231). CD typically follows a relapsing and remitting course, and causes substantial acute and long-term morbidity and increased mortality. Patients often develop local complications (e.g. fistulas, abscesses, strictures, or perforation), systemic complications (e.g. uveitis, arthritis), or side effects of treatment, and may require major surgery. Roughly a third of patients fall into each of the categories of mild, moderate, and severe disease.

Unmet need in CD is highest in patients with moderate to severe disease. Patients not responding to conventional therapy of orally administered aminosalicylates (e.g. 5-ASA), glucocorticoids and immunomodulator agents (azathioprine or 6-MP), are treated with biologic TNFα inhibitors (TNFi). Induction therapy with a TNFi results in clinical remission in fewer than 50% of patients, and only about 25% of patients achieve mucosal healing.

Another 30-40% of patients receiving TNFi have only a limited response, or lose their response over time (maintenance therapy). Additionally, there remain concerns over infection and lymphoma risks with these agents. Additional biologic options (vedolizumab, ustekinumab) offer alternative additional treatments options for patients who fail TNFi, but response rates to these agents do not exceed those associated with TNFi treatment. Medical treatment options for fistulizing and fibrotic disease remain limited. Thus, a substantial unmet need remains for agents with greater efficacy than current therapies, either as a standalone therapy or in combination with existing therapies.

In CD, vanin enzymes are dysregulated and are linked to development of epithelial barrier injury through their product cysteamine (R18-3167, R17-3322, R17-3323). As described in Section 5.2, by reducing cysteamine levels, a vanin inhibitor is expected to provide the epithelial barrier with a broad protective effect against diverse disease-driving stimuli, leading to direct epithelial barrier repair resulting in mucosal healing. In addition, a vanin inhibitor is expected to attenuate chronic inflammation underlying the disease. Oral medicines with a novel mode of action that includes repair of epithelial barrier (leading to mucosal healing) would be particularly attractive for the current unmet need in CD and will provide an additional benefit of convenience of oral vs. parenteral treatments. Therefore, Boehringer Ingelheim is starting a clinical development program for a vanin inhibitor candidate, BI 1595043.

1.2 DRUG PROFILE

[redacted]

[redacted]

1.2.1 Nonclinical pharmacology

1.2.1.1 Primary pharmacodynamics

In vitro primary pharmacodynamics

[redacted]

In vivo primary pharmacodynamics

[redacted]

[redacted]

1.2.1.2 Safety pharmacology

General and safety pharmacology studies have been conducted with BI 1595043 to assess possible effects on cardiovascular, CNS, respiratory, renal and hepatic function.

Cardiovascular system

BI 1595043 was tested for blocking hERG-mediated potassium current in HEK293 cells (n00270147). [redacted]

Respiratory system

[redacted]

Central nervous system

[redacted]

Renal and hepatic system

[redacted]

Further considerations on safety pharmacology

[redacted]

[redacted]

1.2.1.3 Pharmacodynamic interactions

No pharmacodynamics interaction studies have been carried out to date.

[redacted]

For a more detailed description of the BI 1595043 profile, please refer to the current Investigator's Brochure (IB) (c31270124).

1.2.2 Toxicology

The nonclinical safety program investigating the in vivo toxicological profile of BI 1595043 comprised repeat-dose studies up to 13 weeks of once daily oral treatment in rats and dogs and a complete battery of in vitro and in vivo studies assessing the genotoxic and phototoxic potential of the compound. Rats and Beagle dogs were employed as suitable animal species for general toxicology investigations (see Section 1.4.3.2).

A comprehensive detailed description of the BI 1595043 profile is provided in the current IB (c31270124). Main findings are summarized in the following sections.

1.2.2.1 Single dose toxicity

Single-dose toxicity studies were not conducted but acute toxicity information was obtained from short-duration toxicity studies, in which high doses of BI 1595043 were administered. BI 1595043-related effects were observed i[redacted]

[redacted]

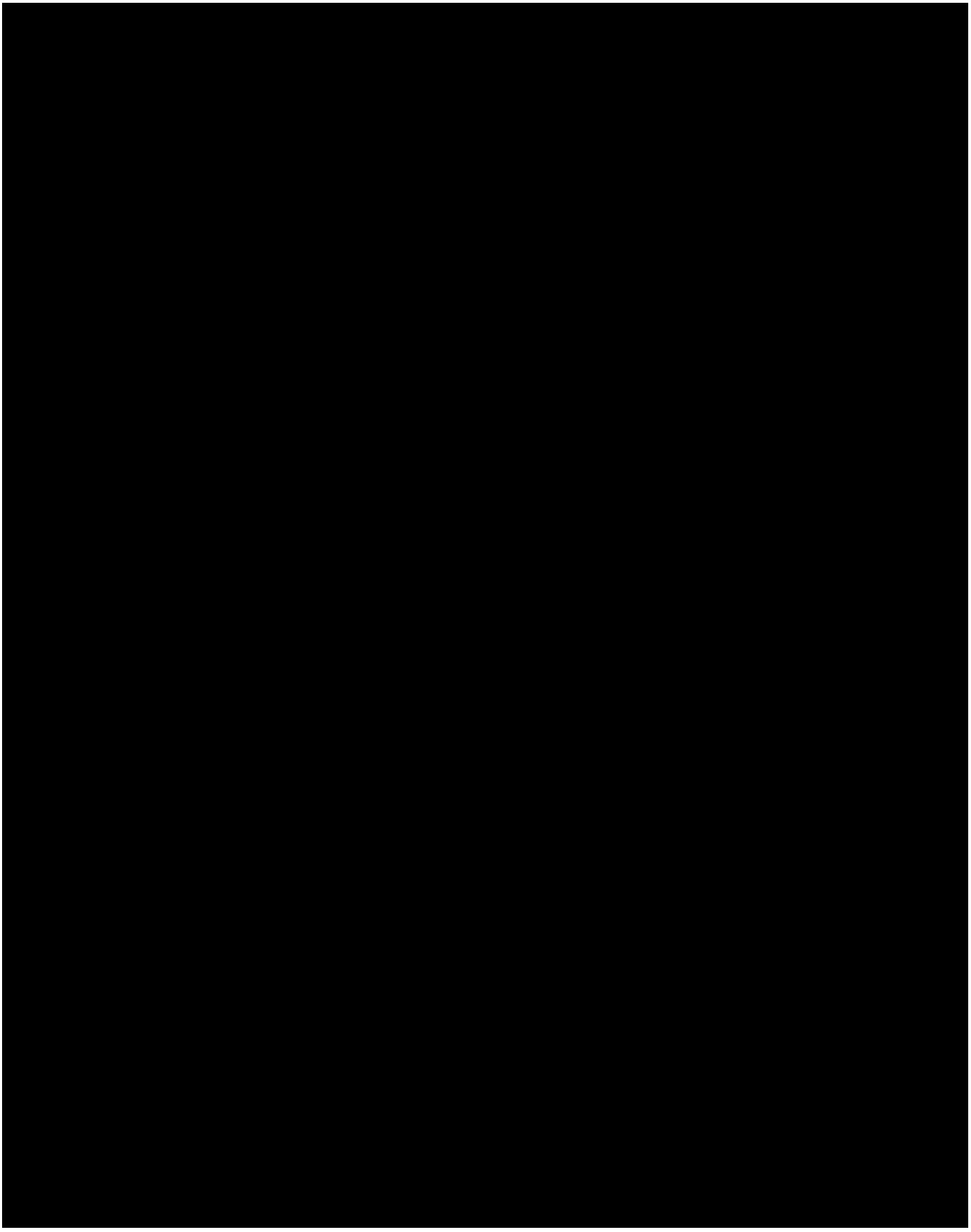
[redacted]

1.2.2.2 Repeated dose toxicity

[redacted]

Ophthalmology findings:

[redacted]



[redacted]

1.2.2.3 Genotoxicity

BI 1595043 was not mutagenic [redacted]).

1.2.2.4 Carcinogenicity

Carcinogenicity studies have not yet been conducted.

1.2.2.5 Reproductive and developmental toxicity

[redacted]

1.2.2.6 Local tolerance

No local tolerance studies have been conducted.

1.2.2.7 Other toxicity studies

[redacted]

Overall, it is considered that BI 1595043 is unlikely to cause phototoxicity at clinically relevant doses.

For a more detailed description of the BI 1595043 profile, please refer to the current IB (c31270124).

1.2.3 Nonclinical pharmacokinetics

1.2.3.1 Methods of analysis

To support GLP toxicity studies, GLP LC/MS/MS assay methods were validated for quantification of BI 1595043 [redacted].

1.2.3.2 Absorption

The pharmacokinetics (PK) of BI 1595043 following single intravenous (IV) or oral (PO) doses were investigated in male Wistar Han rats, male beagle dogs, and female minipigs (n00274794).

The PK parameters in animals (n00274794) are summarized in Table 1.2.3.2: 1. The disposition of BI 1595043 is characterized in rats, dogs and minipigs [redacted]

[redacted]

2. BA values are model based and incorporate non-linear binding to target.
3. Rat BA was calculated based on modeling of all available rat PK data.

1.2.3.3 Distribution

Plasma protein binding

[redacted]

Distribution in pigmented rat

Quantitative tissue distribution of total drug-related radioactivity was investigated in male pigmented (Long-Evans) rats administered a [redacted].

[redacted]

1.2.3.4 Metabolism

Data from hepatocyte incubations, conducted in both human and preclinical species (rat, dog, minipig), in addition to in vivo data from preclinical species, were used to predict human hepatic clearance. [redacted]

1.2.3.5 Excretion

[redacted]

1.2.3.6 Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies have been conducted.

1.2.3.7 Toxicokinetics

PK parameters were assessed in GLP-toxicological studies (n00268703, n00270419) and are displayed in Table 1.2.3.7: 1:

[redacted]

For a more detailed description of the BI 1595043 profile, please refer to the current IB (c31270124).

1.2.4 Prediction of human therapeutic dose

A two compartment population PK model with first-order oral absorption and a TMDD process was constructed using PK data from the completed dose groups from this clinical trial (see Table 1.2.5.2). [redacted].

1.2.5 Clinical experience in humans

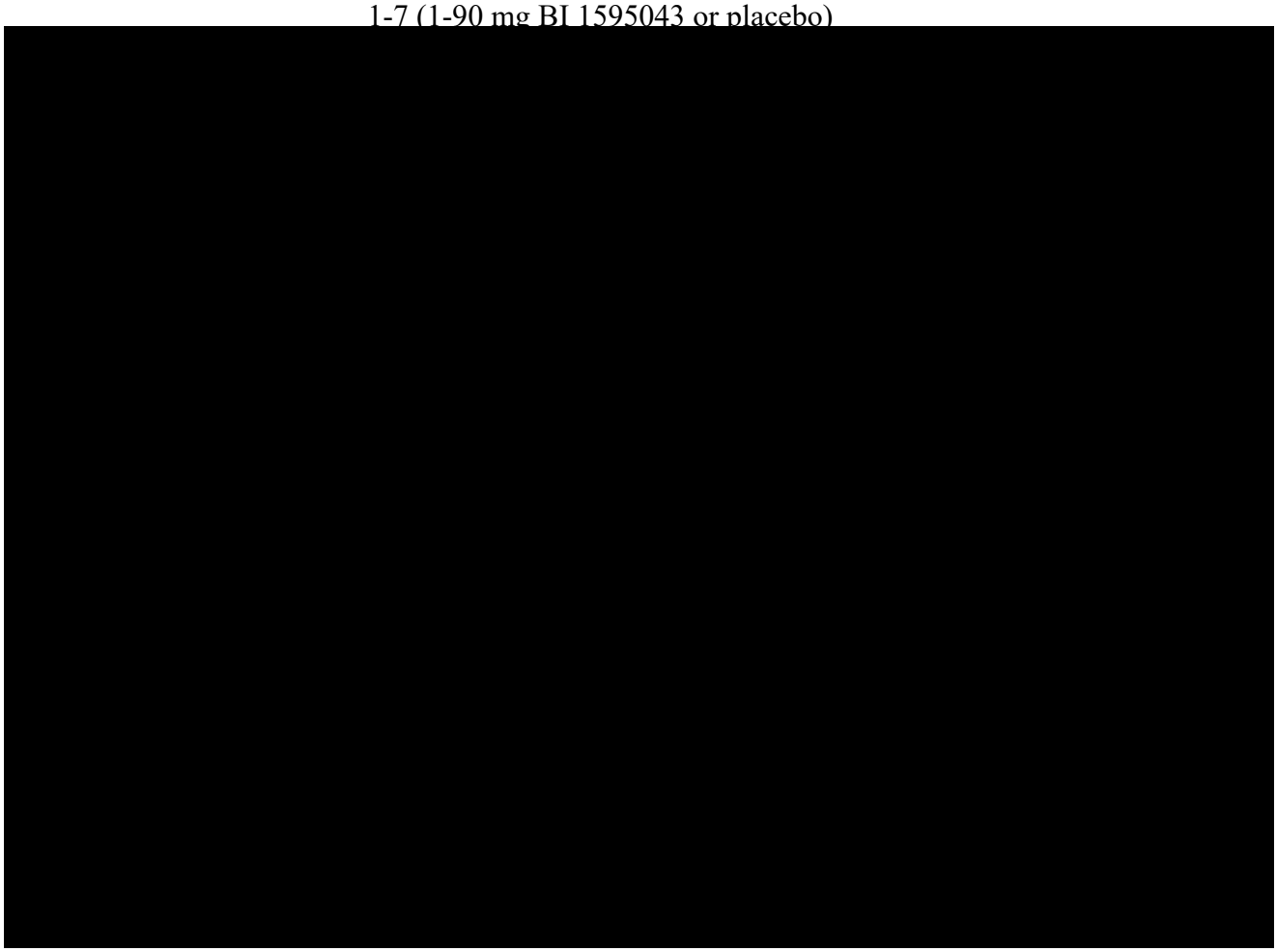
This is the first-in-human trial with the [redacted] BI 1595043 consisting of 7 original dose groups that have been completed. These include dose levels 1 mg, 3 mg, 6 mg, 12 mg, 25 mg, 50 mg, and 90 mg of BI 1595043, administered as oral solution, with 6 subjects in each dose group assigned to active treatment and 2 subjects assigned to placebo. To date, BI 1595043 was administered to 42 healthy male subjects within 7 dose groups, and additional 14 healthy male subjects received matching placebo.

The clinical trial protocol is being amended to add the new maximum dose level of 160 mg of BI 1595043 (see Section 1.3.2).

Safety

The safety evaluation in Trial 1445-0001 includes physical examination, ophthalmological examination, vital signs, 12-lead ECG, laboratory tests and adverse event (AE) assessment. In the completed dose groups, i.e. up to an oral single dose of 90 mg, BI 1595043 was well tolerated with a low frequency of AEs of mild intensity (see Table 1.2.5: 1). [redacted]

Table 1.2.5: 1 Frequency [N (%)] of patients with AEs by treatment, primary system organ class and preferred term – SRD Trial 1445-0001 – Dose Groups 1-7 (1-90 mg BI 1595043 or placebo)



Pharmacokinetics

A preliminary PK data analysis for BI 1595043 in Trial 1445-0001 has been performed using planned sampling times instead of actual sampling times. As actual sampling time should deviate from planned time only slightly, the principal PK conclusions are not expected to be subject of clinically relevant change.

The single-dose PK parameters of BI 1595043 from dose groups 1 to 7 (1 to 90 mg) are summarized in Table 1.2.5: 2. After a single oral solution dose, BI 1595043 was

Table 1.2.5: 2 gMean (gCV%) values of BI 1595043 PK parameters after single oral doses of BI 1595043 – SRD Trial 1445-0001 – Dose Groups 1-7

1.2.6 Residual Effect Period

The residual effect period (REP) for BI 1595043, when measurable drug levels or PD effects are still likely to be present after the last administration, is 6 days (estimated based on 5 times terminal $t_{1/2}$ of dose group 5 of up to 29.3 h). Conservatively, all AEs reported until the end of trial examination will be considered on treatment.

1.2.7 Drug product

Please refer to Section 4.1.

For a more detailed description of the BI 1595043 profile, please refer to the current IB (c31270124).

1.3 RATIONALE FOR PERFORMING THE TRIAL

As a transition from non-clinical investigations to clinical development, in this first-in-human trial, safety, tolerability, pharmacokinetics and pharmacodynamics of BI 1595043 will be assessed in healthy male volunteers, using single rising oral doses in order to provide the basis for the clinical development of BI 1595043, a [redacted], in the indication of CD.

Young, healthy male subjects will be recruited for this study. They (1) provide a relatively stable physiological, biochemical and hormonal basis for studying drug effects, (2) show no disease-related variation and (3) are not taking regular concomitant medications.

Within each dose group, all actively treated individuals will receive the same BI 1595043 dose. The next higher dose will only be administered to the next group, if the treatment in the preceding dose group was safe and showed acceptable tolerability.

[redacted]

1.3.1 Starting dose

Maximum Recommended Starting Dose (MRSD) was estimated on the basis of the US FDA Guidance for Industry “Estimating the Maximum Recommended Safe Starting Dose in Initial Clinical Trials for Therapeutics in Healthy Volunteers” (R06-1037).

[redacted]

[redacted]

1.3.2 Maximum dose and dose escalation

Based on the cross-species comparison of [redacted] (Section 1.4.3.2), and the results of 13-week general toxicology studies (Sections 1.2.2.2 and 1.3.1), dog was chosen as the most relevant toxicological species to humans and providing more conservative safety margins compared to rat.

[redacted]

[redacted]

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 to for the development of BI 1595043, which represents a novel approach for the treatment of patients with Crohn's disease. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

1.4.1 Expected benefit for the target indication

[redacted]

1.4.2 Procedure-related risks

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

The total volume of blood withdrawn per subject during the entire study will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

1.4.3 Drug-related risks and safety measures

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

1.4.3.1 Mode of action and nature of the target

[redacted]

1.4.3.2 Relevance of animal models

In conclusion, rat and dog were considered suitable species for nonclinical safety profiling of BI 1595043, with dog as the most sensitive species. Confidence in the suitability of rat and dog as toxicology species was increased by favorable oral pharmacokinetics characteristics (see Section 1.2.3), demonstration of pharmacological activity of BI 1595043 in the rat and dog dose range finding studies (n00266340, n00266444), and similar metabolite profiles in human and rat/dog.

1.4.3.3 Findings in non-clinical safety studies

Toxicology data of BI 1595043 support clinical studies in men with daily oral administration for up to 91 days.

[redacted]

consideration of large safety margin across the planned dose range in the study.

1.4.3.4 Clinical findings

To date, BI 1595043 was administered to 42 healthy male subjects as single doses up to 90 mg in this FIH study. Overall, BI 1595043 was well tolerated with a low frequency of AEs of mild intensity. There were no AEs considered to be dose limiting and no SAEs (see Section 1.2.5).

1.4.3.5 Drug induced liver injury

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 5.2.7.1.4, adverse events of special interest.

1.4.3.6 Risk minimization (safety precautions and stopping rules)

The following risk minimization measures, including safety precautions and stopping rules, **will be implemented in this study:**

- Careful selection of starting dose, as described in Section 1.3.1.
- Decreasing escalation factors with increasing doses, as described in Section 1.3.2. Dose escalations will only be allowed after documented interim safety reviews (see Section 3.1).
- Preliminary measurement of BI 1595043 pharmacokinetics (C_{max}, AUC_{0-24}; see Section 7.3.2). The expected exposure in the next higher dose group will be estimated based on preliminary PK data of preceding dose groups. The next higher dose level will only be administered, if estimated mean values of C_{max} and AUC_{0-24} do not exceed the maximum acceptable human exposure (see Section 1.3.2).
- For safety reasons, division of each dose group of 8 subjects (6 on active treatment, 2 on placebo) into 3 staggered cohorts. On the first study day of each dose level, 2 subjects (Cohort 1) will be treated (one with active treatment, the other with placebo). On the second study day, the next 2 subjects (Cohort 2) will be treated (two with active treatment). On the third study day of each dose level, the remaining 4 subjects (Cohort 3) will be treated (three with active treatment, one with placebo). If BI 1595043 was safe and well tolerated in Cohort 1, the study will continue with Cohort 2. If it was safe and well tolerated in the preceding cohorts, the study will continue with Cohort 3. Between the first application of BI 1595043 in each cohort, there will be a time interval of at least 24 h which is expected to cover the peak exposure of the compound. In Cohort 2 and Cohort 3, subjects will be dosed at least 10 min apart.

- A monitoring of safety laboratory with specific focus on plasma glucose levels and liver enzymes (see Flow Chart).

- An ECG monitoring including continuous ECG measurement over 4 hours post dose to cover the anticipated period of highest drug exposure and additional repeated triplicate 12-lead ECGs up to 48 hours following drug administration. Dose escalation would be stopped as soon as at least 2 subjects at one dose level showed relevant QT prolongation (see Section 3.3.4.3).

- Safety monitoring (including e.g. vital signs and adverse events) with a special focus on blood pressure and heart rate measurements.

- Ophthalmological examination at Screening and EoTrial Visit (see Section 5.2.3).

- Hospitalization of subjects at the trial site for at least 48 hours after study drug administration at each dose level. Based on the longest gMean terminal $t_{1/2}$ in dose group 5 of up to [redacted] (based on preliminary PK data) for BI 1595043 in this study, this is expected to cover the period of highest risk/ peak effect. During in house-confinement, subjects will be under medical observation and thoroughly monitored for both expected and unexpected adverse events.

- Application of the next higher dose, only if the respective dose of BI 1595043 is safe, shows acceptable tolerability, and no stopping criterion is met (see Section 3.3.4.3). At least 7 days will be maintained between the first drug administration to subjects in the previous dose group and the first drug administration to subjects in the subsequent dose group.

- Exclusion of acetaminophen (paracetamol) as concomitant medication.

- Due to observed teratogenicity in rat, women will not be enrolled in this study.

1.4.4 Overall assessment

BI 1595043, a [redacted], has been thus far administered to 42 healthy subjects within this study. Despite the novelty of the target, non-clinical safety data in relevant animal species, the inhibitory mode of action as well as the risk assessment suggest that BI 1595043 is not a high-risk compound and support the application of single doses of BI 1595043 in this first-in-man trial.

Based on the risk mitigation strategy, comprising of safety precautions and stopping rules, healthy subjects should not be exposed to undue risks by the intake of BI 1595043. Healthy volunteers are not expected to have any direct benefit from participation in this trial, as is usually the case in Phase I studies. Considering the high medical need for novel, effective and safe treatment for Crohn's disease, it is believed that the benefit of this trial outweighs the potential risks and justifies exposure of healthy volunteers to BI 1595043.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate safety, tolerability and pharmacokinetics (PK) of BI 1595043 in healthy male subjects following oral administration of single rising doses.

2.1.2 Primary endpoint

The primary endpoint for assessment of safety and tolerability of BI 1595043 is the percentage of subjects with drug-related adverse events.

2.1.3 Secondary endpoint

The following pharmacokinetic parameters will be determined for BI 1595043 if feasible:

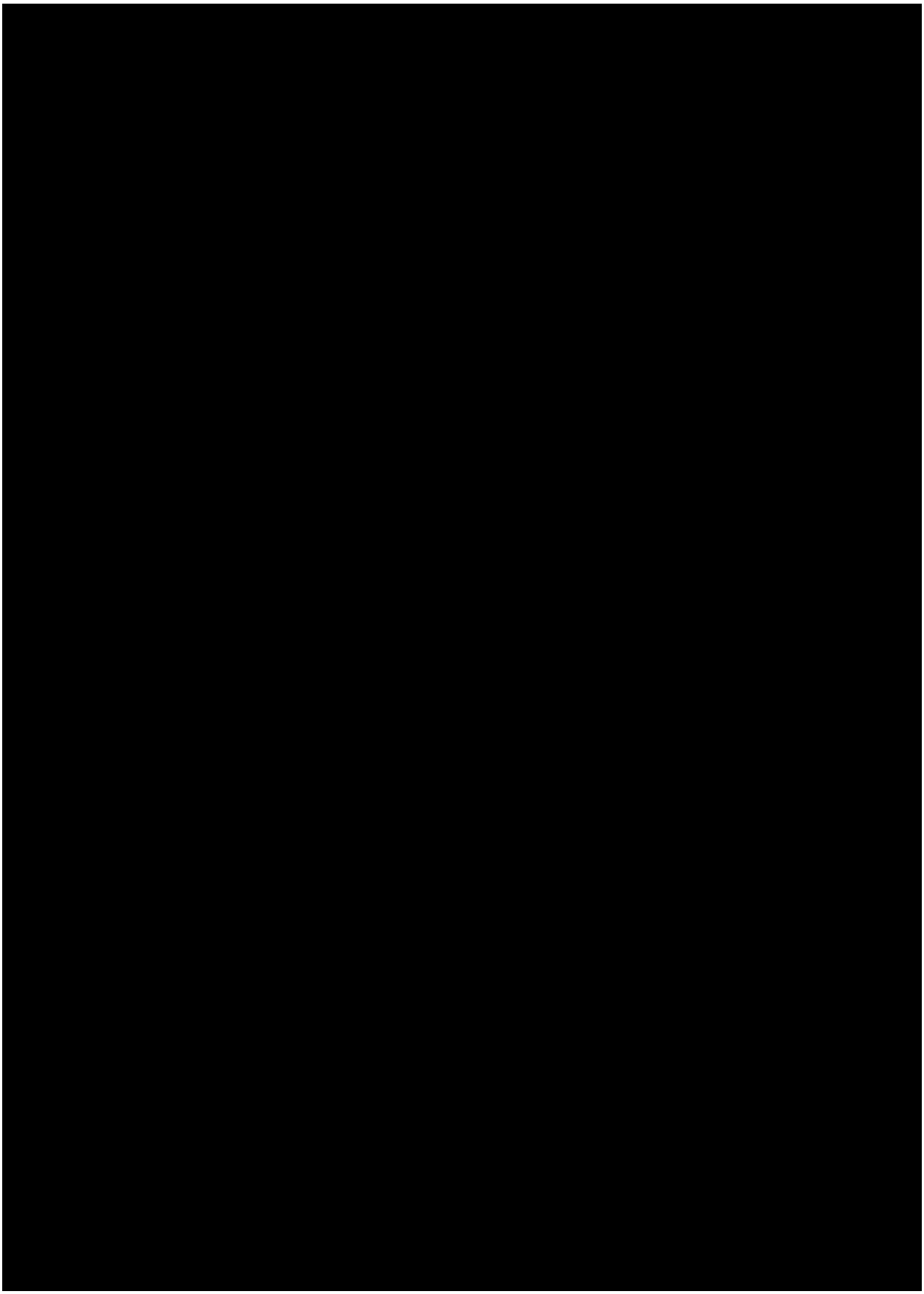
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

[redacted]

2.2.2.1 Safety and tolerability

Safety and tolerability of BI 1595043 will be assessed based on:

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



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

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

It is planned to include a total of 64 healthy male subjects in the trial. The subjects will be assigned to 8 groups consisting of 8 subjects per group; the groups will be dosed sequentially (see Table 3.1: 1). The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose groups (e.g., add low and/or intermediate dose groups) on the basis of experience gained during the study (for instance, based on preliminary PK data), provided the planned and approved highest dose is not exceeded. Thus, the actual number of subjects entered may be more than 64, but is not to exceed 72. Such changes, which are based on preliminary PK data, may be implemented via non-substantial CTP amendments. Changes, based on safety findings, will be implemented only via substantial CTP amendments.

Within each dose group, 6 subjects will receive BI 1595043 and 2 will receive placebo. Only one dose is tested within each dose group. For safety reasons, each dose group will consist of 3 cohorts. The trial medication will be administered in the following order:

- Cohort 1 (fixed order): the 1st subject on active treatment and the 2nd subject on placebo (in total 2 subjects)
- Cohort 2 (fixed order): 2 subjects on active treatment (in total 2 subjects)
- Cohort 3 (randomized): 3 subjects on active treatment and 1 subject on placebo (in total 4 subjects)

Between first drug administrations in Cohort 1, Cohort 2 and Cohort 3 there will be a time interval of at least 24 hours, and Cohort 1 and Cohort 3 will be separated by at least 2 days, which based on an anticipated half-life of BI 1595043 of approximately 11.6 hours and expected to cover the peak exposure and be sufficient to detect relevant acute effects. If BI 1595043 was safe and well tolerated in Cohort 1, the study will continue with Cohort 2. The 2 subjects of Cohort 2 will be dosed at least 10 min apart. If BI 1595043 was still safe and well tolerated in all subjects of Cohort 1 and Cohort 2, the study will proceed with the 4 subjects of Cohort 3, who will be dosed at least 10 min apart. At each dose level Cohort 3 may be started only after at least 2 subjects have been treated with BI 1595043 in the preceding Cohort 1 and Cohort 2.

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

Table 3.1: 1 Dose groups

Dose Group	1	2	3	4	5	6	7	8
Dose (mg)	1	3	6	12	25	50	90	160
Number of subjects	8	8	8	8	8	8	8	8
Subjects receiving placebo	2	2	2	2	2	2	2	2
Subjects receiving BI 1595043	6	6	6	6	6	6	6	6

The groups will be dosed consecutively in ascending order, and a time interval of at least 7 days will be maintained between the last drug administration to subjects in the previous dose group and the first drug administration to subjects in the subsequent dose group. The decision to treat the next dose group will be based upon safety, tolerability and pharmacokinetic data of all the preceding dose groups. The next dose group will only be treated if, in the opinion of the investigator, no safety concerns have arisen in the preceding dose groups (i.e. no dose-limiting events occurred), and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.1).

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

Although no formal Safety Review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.1).

At minimum, data from 4 subjects on active drug need to be available for escalation to a higher dose. For the minimum dataset with regards to preliminary PK data, see Section 7.4. The minimum data set for review consists of the following:

- AEs in the current and preceding dose groups up to at least 48 h post dosing, including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead ECG and continuous ECG monitoring in the current and preceding dose groups up to at least 48 h post dosing
- Vital signs in the current and preceding dose groups up to at least 48 h post dosing
- Clinical laboratory tests in the current and preceding dose groups up to at least 48 h post dosing
- Preliminary PK data for the selected time as per Section 7.4. For escalation from dose group 1 to dose group 2, preliminary PK data are not required.
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the Clinical Trial Lead (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs, and out-of-range laboratory results (if considered clinically significant). In addition and depending on the results and findings, suitable experts from the sponsor or external institutions may be consulted on as needed basis. In these cases expert recommendations will be documented in the minutes of the Safety Review and considered for the decision making. Dose escalation will only be permitted if no safety concerns exist neither in the opinion of the Principal Investigator (or an authorised deputy) nor the Clinical Trial Lead (or an authorised deputy).

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

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

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

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

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

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that 64 healthy male will enter the study. The actual number of subjects entered may exceed the total of 64, if additional intermediate doses are tested (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

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

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation
5. Male subjects who meet any of the following criteria from at least 30 days before the first administration of trial medication until 30 days after trial completion:
   - Use of adequate contraception, e.g. use of condom (male subjects) plus any of the following methods (female partners): intrauterine device, hormonal contraception (e.g. implants, injectables, combined oral or vaginal contraceptives) that started at least 2 months prior to first drug administration to the male subject, or barrier method (e.g. diaphragm with spermicide), or surgically sterilised (including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy), or postmenopausal, defined as at least 1 year of spontaneous amenorrhea
   - Sexually abstinent
   - Vasectomised (vasectomy at least 1 year prior to enrolment) in combination with a barrier method (e.g. condom)

   Unprotected sexual intercourse with a pregnant female partner and sperm donation is not allowed throughout the study and until 30 days after trial completion.

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance

4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more 30 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms 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

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

23. History of acute pancreatitis
24. History of relevant ophthalmological disorders (with exception of myopia and hyperopia) or detection of ocular disorders in slit lamp examination at screening.

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 first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR.

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

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject 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. An AE or clinically significant laboratory change or abnormality occurs that the investigator assesses as warranting discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg), clinically relevant changes in ECG requiring intervention, or unexplained hepatic enzyme elevations at any time during the trial
6. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk assessment. Dose escalation will be terminated if more than 50% of the subjects at one dose level show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.
3. Violation of GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial.
4. The sponsor decides to discontinue the further development of the investigational product
5. Dose escalation will be stopped if at least 2 subjects on active treatment at one dose level have relevant individual QT prolongations, i.e. a QTc increase of greater than 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording
6. Dose escalation will be stopped, if the C_{max} or AUC_{0-24} of at least 1 subject of one dose group increases above the following exposure thresholds or if the estimated gMean exposure is expected to exceed a C_{max} of [redacted] or an AUC_{0-24} of [redacted]. Estimation will be done based on preliminary PK results of preceding dose groups (see Section 7.4)
7. Occurrence of severe non-serious adverse events considered as drug-related by the investigator in 2 subjects of the same dose group (8 subjects).

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

3.3.5 Replacement of subjects

If some subjects do not complete the trial, the Clinical Trial Lead 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.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product has been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 1595043
Pharmaceutical formulation:	Powder for oral solution
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	2.5 mg/mL
Posology:	1-0-0 (0.4 mL = 1 mg, 1.2 mL = 3 mg, 2.4 mL = 6 mg, 4.8 mL = 12 mg, 10 mL = 25 mg, 20 mL = 50 mg, 36 mL = 90 mg, 64 mL = 160 mg)
Route of administration:	oral
Duration of use:	Single dose

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

Substance:	Not applicable, solvent only (Tartaric acid 5 mg/mL)
Pharmaceutical formulation:	Solvent only
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	Not applicable
Posology:	1-0-0 (0.4 mL, 1.2 mL, 2.4 mL, 4.8 mL, 10 mL, 20 mL, 36 mL, 64 mL)
Route of administration:	oral
Duration of use:	Single dose

4.1.2 Selection of doses in the trial

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

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups (3 cohorts per dose group) according to their temporal availability. As soon as enough

subjects are allocated to 1 of the 21 dose cohorts, the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. Because the trial includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. In Cohorts 3 of each dose group, subjects will be randomly assigned to treatments, while treatments in Cohort 1 and Cohort 2 will be assigned in a fixed order for safety reasons, as described in Section 3.1.

For the purpose of random assignment, the randomisation list will be provided to the trial site in advance. Numbers of the randomization list will be allocated to subjects by the method 'first come - first served' at the time of registration. Subjects are then assigned to treatment according to the randomisation list. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

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

Table 4.1.4: 1 BI 1595043 and placebo treatments, oral administration

Dose group	Substance	Pharmaceutical form	Unit strength	Dose volume per administration	Total daily dose
1	BI 1595043	oral solution	2.5 mg/mL	0.4 mL q.d.	1 mg
2	BI 1595043	oral solution	2.5 mg/mL	1.2 mL q.d.	3 mg
3	BI 1595043	oral solution	2.5 mg/mL	2.4 mL q.d.	6 mg
4	BI 1595043	oral solution	2.5 mg/mL	4.8 mL q.d.	12 mg
5	BI 1595043	oral solution	2.5 mg/mL	10 mL q.d.	25 mg
6	BI 1595043	oral solution	2.5 mg/mL	20 mL q.d.	50 mg
7	BI 1595043	oral solution	2.5 mg/mL	36 mL q.d.	90 mg
8	BI 1595043	oral solution	2.5 mg/mL	64 mL q.d.	160 mg
1-8	Placebo*	oral solution (solvent only)	--	identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups

The oral solutions for dosing (active treatment and placebo) will be prepared by pharmacists or qualified pharmacy staff members or qualified medical study personnel at the trial site under the responsibility of the investigator according to the instructions provided in Appendix 10.1.

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

authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a sitting or standing position. 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 preparation of trial medication and its administration to subjects.

Subjects will be kept under close medical surveillance until 48 h after drug administration. During the first 2 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination) or to sleep.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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

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

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

Within the central ECG lab, the staff involved with interval measurements will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician. No more than two different blinded readers will evaluate the ECGs of the study.

If a preliminary analysis of ECG data is required during the trial, a part of the staff of the central ECG lab (different from the ECG evaluation team) may be unblinded. This part of the staff will receive the necessary information, which will be stored with no access to the ECG evaluation team.

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

4.1.5.2 Unblinding and breaking the code

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

4.1.6 Packaging, labelling, and re-supply

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

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

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

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

All unused trial medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Lead. 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.

Acetaminophen (paracetamol) is prohibited as concomitant mediation in this study. If necessary, short-term use of ibuprofen or acetylsalicylic acid is acceptable.

Drugs with a known hepatotoxicity profile should be avoided during the entire study.

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. No food is allowed for at least 4 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served on Day 1 at 2 h and 4 h post-dose (mandatory for all subjects).

[redacted]

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 10 h before the administration of trial medication until the end of the in-house period at the trial site. 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 the end of trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

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

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (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, ophthalmological examination, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, ophthalmological examination, and a physical examination including determination of weight.

5.2.2 Vital signs

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

5.2.3 Ophthalmological examination

A slit lamp examination (e.g. [redacted] RSL 110) will be conducted by an ophthalmologist at Screening and EoTrial examination to exclude findings suspicious for signs of cataract and/or other ocular disorders.

Data from ophthalmological examination will not be transferred to the CRF/database, only abnormal findings will be recorded as AEs if judged clinically relevant by the Investigator.

5.2.4 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required. The parameters that will be determined are listed in Tables 5.2.4: 1 and 5.2.4: 2. Reference ranges will be provided in the ISF, Section 10.

Manual differential white blood cell count will be performed if there is an abnormality detected with the automatic blood cell count. Urine microscopic examinations will be performed in addition to urinalysis (Stix) in order to correctly evaluate possible abnormalities detected at the urinalysis (Stix).

Table 5.2.4: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count (Erythrocytes), absol.	X	X	X
	Reticulocytes, absol.	X	X	X
	White Blood Cells (Leucocytes), absol.	X	X	X
	Platelet Count (Thrombocytes), absol.	X	X	X
Automatic WBC differential, relative	Neutrophils/ Leukocytes; Eosinophils/ Leukocytes; Basophils/ Leukocytes; Monocytes/ Leukocytes; Lymphocytes/ Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/ Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/ Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X	X
	Fibrinogen	X	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X
	Lactic Dehydrogenase	X	X	X
	Lipase	X	X	X
	Amylase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
	Free T3 - Triiodothyronine	X	--	--
	Free T4 – Thyroxine	X	--	--
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	Albumin	X	X	X
	Albumin (Protein Electrophoresis)	X	--	--
	Alpha-1-Globulin (Protein Electrophoresis)	X	--	--
	Alpha-2-Globulin (Protein Electrophoresis)	X	--	--
	Beta-Globulin (Protein Electrophoresis)	X	--	--
	Gamma-Globulin (Protein Electrophoresis)	X	--	--
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	X	X
	Cholesterol, total	X	X	X
	Triglyceride	X	X	X

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Days -3 to -1, 2, 3 and 5 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (end of trial examination)

Table 5.2.4: 1 Routine laboratory tests (cont).

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Calcium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X
	Urine Protein (qual)	X	X	X
	Urine Glucose (qual)	X	X	X
	Urine Ketone (qual)	X	X	X
	Urobilinogen (qual)	X	X	X
	Urine Bilirubin (qual)	X	X	X
	Urine RBC/Erythrocytes (qual)	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Days -3 to -1, 2, 3 and 5 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (end of trial examination)

The tests listed in Table 5.2.4: 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. Drug screening will be performed at screening and after admission to the trial site. Infectious serology will be performed at screening only.

Table 5.2.4: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA
	Barbiturates
	Benzodiazepine
	Cannabis
	Cocaine
	Methadone
	Methamphetamines/MDMA/XTC
	Opiates
	Phencyclidine
	Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative)
	Hepatitis B core antibody (qualitative)
	Hepatitis C antibodies (qualitative)
	HIV-1 and HIV-2 antibody (qualitative)
COVID-19[1]	SARS CoV-2 PCR test

[1] evaluation will be performed shortly (within 72 hours) before admission to trial site as per Flow Chart

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 6510 and Alcotest® 5510, [redacted]) will be performed at admission to the trial site, 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 5.2.4: 1 and 5.2.4: 2 will be performed at [redacted], with the exception of drug screening. These tests will be performed at the trial site using e.g.Triage® TOX Drug Screen, [redacted] or Combur9 Test®, or comparable test systems. SARS-CoV-2 virus PCR test will be performed either by [redacted] or the trial site.

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

5.2.5 Electrocardiogram

5.2.5.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (e.g. [redacted] device, [redacted] at the time points given in the Flow Chart. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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

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

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart. For baseline, 3 triplicate-ECGs will be recorded, the recordings should be separated by at least 15 minutes.

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

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

Storing

All ECGs will be stored electronically at the site.

Data transfer

For time points of triplicate ECGs specified in the Flow Chart, ECGs will be transferred electronically to the central ECG lab ([redacted]) for evaluation.

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

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

Evaluation

a) Central ECG lab (only triplicate ECGs)

Central ECG lab evaluation will be performed only for the first of three replicate ECGs per time point specified in the Flow Chart. The remaining second and third replicate ECGs will be stored for additional analyses if required, e.g. by authorities at a later time point.

This will include the determination of cardiac QRS-axis as assessed by the ECG machine´s algorithm, as well as the intervals RR, PR, QRS and QT measured semi-automatically.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g.QTcF and QTcB) will be determined by the Sponsor (see TSAP for details).

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

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

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

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

b) Trial site

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

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

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.5.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 5-lead ECG recording using the monitor (e.g. [redacted]) for at least 15 min before drug administration (for baseline assessment) and for 4 h following drug administration). This continuous ECG monitoring supports the early detection of adverse events such as clinically relevant bradycardia, tachycardia, or arrhythmia at the trial site. Beyond this clinical evaluation at the trial site, no further data collection or analyses are performed based on continuous ECG monitoring.

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

5.2.6 Other safety parameters

Not applicable.

5.2.7 Assessment of adverse events

5.2.7.1 Definitions of adverse events

5.2.7.1.1 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.

5.2.7.1.2 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

5.2.7.1.3 AEs considered ‘Always Serious’

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in 5.2.7.2, subsections ‘AE Collection’ and ‘**AE reporting to sponsor and timelines’**.

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

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

5.2.7.1.4 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 5.2.7.2.2.

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - o An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - o Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

5.2.7.1.5 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

5.2.7.1.6 Causal relationship of AEs

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

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

5.2.7.2 Adverse event collection and reporting

5.2.7.2.1 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 new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF

5.2.7.2.2 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.

5.2.7.2.3 Information required

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Plasma samples will be collected for the purpose of pharmacokinetic analysis. Only in dose group 4 (12 mg of BI 1595043), additional blood samples will be collected for stability testing and metabolism analysis [redacted]. The time points of the samples collection are 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 used for determination of pharmacokinetic parameters.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK data), including addition of samples and visits, as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1595043 concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube 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 EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma, the second aliquot will contain the remaining plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min, with interim storage of blood samples and aliquots in ice water or on ice. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

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

After completion of the trial, the plasma samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites). However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) 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.

5.3.2.2 Blood sampling for metabolism analysis

Additional K_2-EDTA plasma samples for the identification of drug metabolites will be investigated in dose group 4 (12 mg of BI 1595043). Based on the knowledge gained during the trial conduct, e.g. from preliminary PK results, the dose group may be modified to a different one. The change will be implemented via a non-substantial CTP amendment.

The blood samples will be drawn at the same time points as PK samples (see Flow Chart). At each of these times, 2.7 mL blood will be needed for metabolite analysis. The blood samples will be processed in the same way as the PK samples (see Section 5.3.2.1).

Two plasma aliquots will be obtained and stored in polypropylene (PP) tubes. The first aliquot (labelled as MIST-1 samples), should contain at least 0.5 mL plasma. The remaining

plasma will be the second aliquot (labelled as MIST-2 samples). The process from blood collection to the transfer of plasma aliquots into the freezer should be completed within 90 min, with interim storage of blood samples on crushed ice between blood collection and centrifugation. Until transfer on dry ice to the metabolism laboratory, the aliquots will be stored at the trial site. Samples will be positioned upright and will be frozen at approximately -70°C. The second aliquot will be shipped to the metabolism laboratory after the metabolism scientist has acknowledged safe arrival of the first aliquot. At the metabolism laboratory, the plasma samples will be stored at approximately -70°C until analysis.

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, day, planned sampling time and 'MIST-1' or 'MIST-2'. Further information such a matrix and analyte may also be provided.
Plasma samples dedicated to metabolism investigation are transferred to:

[redacted]

Phone: [redacted]

Only data related to the parent compound and its metabolites will be acquired. Evaluation of drug metabolism will be reported separately and will not be included in the CTR. The study samples will be discarded after completion of the experiments but not later than 5 years after the CTR has been archived.

[redacted]

[redacted]

5.3.2.4 Additional blood sample for stability-testing

In order to assess the stability of the analyte in whole blood, one additional blood sample will be obtained from all subjects of dose group 4 (12 mg of BI 1595043). Based on the knowledge gained during the trial conduct, e.g. from preliminary PK results, the chosen timing or dose group may be changed to a different one. The change will be implemented via a non-substantial CTP amendment.

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

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

- One aliquot ('stability ***reference***') will be centrifuged within 10 min after collection. Centrifugation will last for approximately 10 min (at approximately 2000 g to 4000 g and 4 to 8 °C), plasma will be separated and transferred into a freezer
- The second aliquot ('stability ***test***') will be stored for about 4 h at room temperature and ambient light conditions (storage time must be documented) and will then be centrifuged and stored as for the first aliquot.

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

Until transfer to the analytical laboratory, both aliquots will be stored at approximately -20 °C or below at the trial site. Both aliquots will be provided to the responsible bioanalyst together with the information about sample handling (i.e., storage time of stability test sample at room temperature). After receipt, the aliquots will be stored at the bioanalytical laboratory at approximately -20°C or below until analysis.

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

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

An analysis of the relationship between pharmacokinetic and pharmacodynamic parameters may be investigated in an exploratory manner, see Section 7.3.5.

[redacted]

[redacted]

[redacted]

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Pharmacogenomic evaluations are not considered necessary for assessment of response to BI 1595043 and will not be conducted.

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, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. [redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration and ± 30 min thereafter. Starting from 48 h post-dose a deviation from the scheduled time for vital signs, ECG and laboratory tests of ±120 min is acceptable.

If several activities are scheduled at the same time point in the Flow Chart, blood sampling, vital signs, and 12-lead ECG should be the first and meal the last activity. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration sampling times [redacted], as well as PD 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 Section 5.2.

6.2.2 Treatment period

Each subject will receive one dose of trial medication (BI 1595043 or placebo) at Visit 2.

Trial medication will be taken orally by each subject under direct supervision of the investigator 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 in the morning of Day 1 (or in the evening of Day -1) and kept under close medical surveillance for at least 48 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee. On all other study days, subjects will be treated in an ambulatory fashion.

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

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

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.2 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

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

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

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

- ECG pharmacokinetic concentration set (ECGPCS):This subject set includes all subjects from the TS who provide at least one pair of a valid drug plasma concentration and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analyses. For placebo subjects, the plasma concentration is set to zero and hence always considered as valid. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the Report Planning Meeting before data base lock. The ECGPCS will be used for the exposure-response analyses.

[redacted]

Adherence to the protocol will be assessed by the trial team. Important protocol violation (IPV) categories will be specified in the TSAP, 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 2.1.3 and Section 2.2.2.2 for drug BI 1595043 will be calculated by means of non-compartmental analysis. Non-compartmental PK parameters will be calculated based on actual sampling times using a validated pharmacokinetic software ([redacted] Descriptive statistics will be used to evaluate plasma concentration data and PK parameters. The derivation of PK parameters will be according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

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

Plasma [redacted] 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.

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

If a pre-dose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a pre-dose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.
- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

[redacted]

7.3.1 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. The analysis will be based on the treated set (TS) and will be descriptive in nature. See Section 7.3.4 for further details.

7.3.2 Secondary endpoint analyses

Primary analyses

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

Further exploratory analyses

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

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

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

where

y_{km}	logarithm of response (PK parameter) measured on subject m receiving dose k,
x_{km}	response (PK parameter) measured on subject m receiving dose k,
μ	the overall mean,
β	slope parameter of linear regression line,
D_k	level of dose k, k=1,…,8,
e_{km}	the random error associated with the m^{th} subject who was administered dose k ($e_{km} \sim N(0, \sigma^2)$ iid).

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

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

[redacted]

7.3.4 Safety analyses

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

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

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

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the 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 intake of trial medication will be assigned to the screening period, those between the trial medication intake and end of REP (see Section 1.2.6) will be assigned to the treatment period. Events occurring after the REP but prior to trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.7.1) and other significant AEs (according to ICH E3) will be listed separately.

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

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

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

The ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints. These endpoints and their analyses will be described in the TSAP.

[redacted]

7.4 INTERIM ANALYSES

No interim analysis is planned.

A preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 1595043) provided as individual values and geometric means of all available data from at least 4 subjects on active treatment per current dose level, supported by all the available data from subjects of preceding dose levels, will be performed before proceeding to the next higher dose level. For escalation from dose group 1 to dose group 2, and after the last dose group, preliminary PK data are not required, see Section 3.

In contrast to the final PK calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results. The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without subject identification information. The preliminary results will be distributed to the investigator and the trial team.

Depending on the results of available preliminary PK analyses and the tolerability and safety of the compound, changes to the dosing schedule (e.g., additional intermediate doses),) and additional PK/PD preliminary analysis may be performed if requested by the Clinical Trial Lead, the investigator, or Trial Clinical Pharmacokineticist. Preliminary PK results will not be reported in the CTR. No formal preliminary PK report will be written.

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

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Each dose group will be divided into three cohorts. The subjects of the first 2 cohorts (2 subjects per cohort) will not be randomized to maintain a treatment sequence of active-placebo (Cohort 1) and active-active (Cohort 2) due to safety reasons. In the third cohort of each dose level (4 subjects) the subjects will be assigned to active or placebo treatment using a 3:1 allocation ratio (test treatment to placebo).

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 64 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics.

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 64, but will not exceed 72 subjects entered.

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

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

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. As treatment assignments will be known to investigators, rules about emergency code breaks are not applicable (see Section 4.1.5.2). For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

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

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

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

- 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 [redacted] 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 [redacted] data

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted 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 Lead, 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 clinical trial manager (CTM), Clinical Research Associates, and investigators of participating trial sites

The trial medication will be provided by the [redacted]

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

Analyses of BI 1595043 concentrations in plasma [redacted] will be performed at [redacted].

Analyses of BI 1595043 metabolites concentrations in plasma will be performed at the Department of [redacted]

[redacted] will be performed at the Department of [redacted]

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

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

Data management and statistical evaluation will be done 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

9.1 PUBLISHED REFERENCES

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

10.1 RECONSTITUTION INSTRUCTIONS

10.1.1 Drug supplies overview

a) BI 1595043 Powder for Oral Solution 200 mg (target solution concentration BI 1595043: 2.5 mg/mL), provided in 100 mL amber glass bottles with plastic screw cap

b) Solvent for Oral Solution 80 mL (Tartaric acid 5mg/ml) provided in 100 mL amber glass bottle with plastic screw cap

10.1.2 Required equipment and dosing aids - overview

a) Mechanical (orbital) shaker for bottles (e.g. [redacted] Typ KL2)

b) Dosing dispensers/syringes and bottle adapters

For the withdrawal of respective volume aliquots from the final Oral Solution to be administered, amber [redacted] ExactaMed Syringes should be used in a size as close as possible to the required dose volume. For this purpose, a range of syringe sizes from 1 mL up to 60 mL should be stocked in the trial site.
In order to ease the withdrawal of the oral solution from the glass bottles with the amber [redacted] ExactaMed syringes, [redacted] bottle adapters and dispenser tip caps should be used and stocked in the trial site, preferably [redacted] Adapta Cap Bottle Adapters (E-28 mm) or [redacted] Press-In Bottle Adapters (PIBA™)

Possible [redacted] Med Oral amber dispensers

- [redacted] ExactaMed amber oral dispenser 1 mL
- ExactaMed amber oral dispenser 3 mL
- ExactaMed amber oral dispenser 5 mL
- ExactaMed amber oral dispenser 10 mL
- ExactaMed amber oral dispenser 20 mL
- ExactaMed amber oral dispenser 50 mL

Only CE certified syringes are to be used!

10.1.3 Reconstitution procedure

2 bottle concept, see also Appendix 10.1.4.

10.1.3.1 Reconstitution procedure for the preparation of the active BI 1595043 oral solution 2.5mg/ml

Necessary materials

a) BI 1595043 Powder for Oral Solution 200 mg (target solution concentration BI 1595043: 2.5 mg/mL), provided in 100 mL amber glass bottles with plastic screw cap.

b) Solvent for Oral Solution 80 mL (Tartaric acid 5 mg/ml) provided in 100 mL amber glass bottles with plastic screw cap.

Reconstitution procedure

Step 1: Open the bottle containing the Solvent for Oral Solution 80 mL (Tartaric acid 5 mg/ml)

Step 2: Transfer the content of the Solvent for Oral Solution 80 mL (Tartaric acid 5 mg/ml) completely and carefully into the bottle containing the BI 1595043 Powder for Oral Solution 200 mg

Step 3: Close the bottle with the plastic screw cap and shake the bottle manually until the BI 1595043 powder is wetted. Mount the bottle in a horizontal recumbent position on a mechanical shaker (e.g. [redacted] Typ KL2)

Step 4: Let the bottle shake orbitally for 30 min. at 350 rpm in its horizontal recumbent position.

Step 5: Visually control that the powder is completely dissolved (clear to almost clear solution).

The final BI 1595043 Oral Solution concentration is 2.5 mg/mL.

The allowable dose range is from 0.5 mg - 175 mg

10.1.3.2 Solvent for oral solution for use as placebo solution

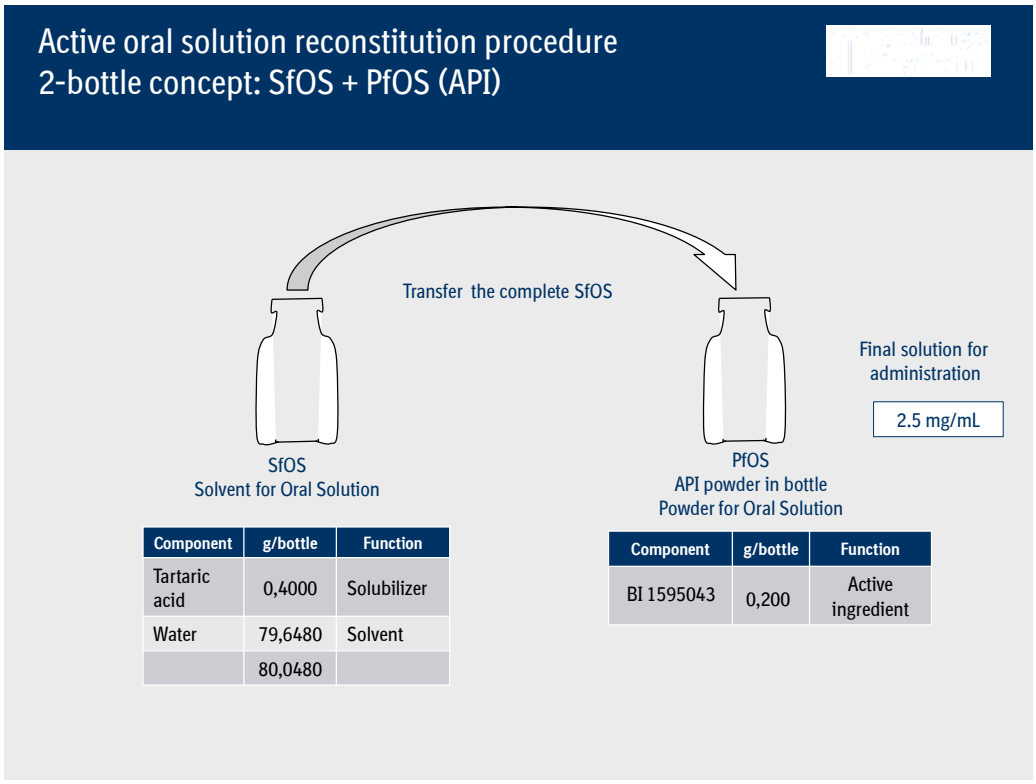
Necessary materials

a) Solvent for Oral Solution 80 mL (Tartaric acid 5mg/ml) provided in 100 mL amber glass bottles with plastic screw cap.

The Placebo Solution is the Solvent for Oral solution 80 ml (Tartaric acid 5 mg/ml).

10.1.4 Illustration of reconstitution procedure

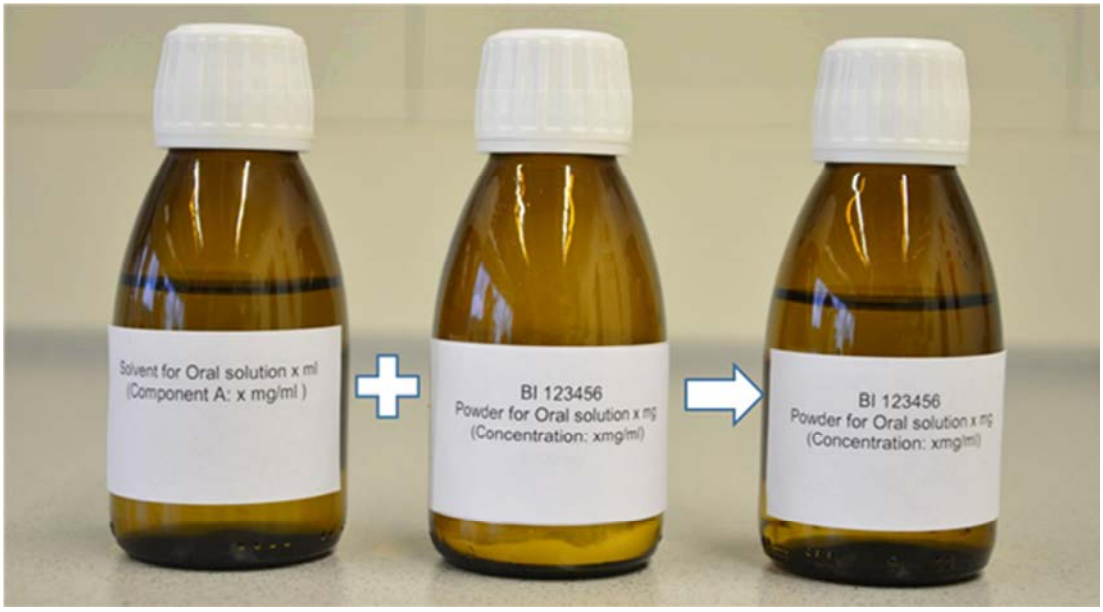
The following scheme on the principle followed for the present PfOS formulation, 2-bottle concept, should serve as an additional illustration to clarify, how the reconstitution procedure for the preparation of the active oral solution has to be performed.



Component	g/bottle	Function
Tartaric acid	0,4000	Solubilizer
Water	79,6480	Solvent
	80,0480	

Component	g/bottle	Function
BI 1595043	0,200	Active ingredient

The following picture shows the bottles needed to prepare the active PfOS formulation to clarify the procedure in additional.



10.1.5 In-use stability

The in-use stability of both placebo and the reconstituted solution is 24 h after its preparation, incl. storage in [redacted] dispensers until administration.

10.1.6 Mode of application

Withdraw the required volume aliquot to obtain the required doses. In case the complete content of a bottle is used, content is administered directly out of the bottle.
Use amber [redacted] ExactaMed syringes for dose withdrawal/administration, and subsequently if necessary amber glass bottles for administration of aliquots.
Use [redacted] ExactaMed syringes at a volume size as close as possible to the volume to be withdrawn.

Please note that it is the responsibility of the CTL to assure that appropriate supplies are used for administration of a dose, based on guidance in the clinical trial protocol, and dosing is limited to the allowed dosing range for a specific dose formulation as stated in this Reconstitution Instruction.

10.1.7 General remarks - important!

Because of lacking analytical coverage beyond the instructed preparation procedure of the different dose formulations no further (external) dilutions of the reconstituted solutions are allowed!

The present reconstitution instruction does not contain any advice how to withdraw a specific dose from the reconstituted solutions. The specific dose volumes to be withdrawn from the described dose formulations in order to obtain a required dose will be calculated and documented by [redacted] in the Clinical Trial Protocol (CTP) and subsequent documents (e.g. work sheets)!

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		12 June 2020
EudraCT number **EU number**		2020-001036-10
BI Trial number		1445-0001
BI Investigational Medicinal Product(s)		BI 1595043
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1595043 (single-blind, partially randomised, placebo-controlled, parallel (sequential) group design) 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. Flow Chart (pages 4 - 5) 2. Table 5.2.3: 1 Routine laboratory tests 3. Table 5.2.3: 2 Exclusionary laboratory tests 4. Section 5.2.3 5. Section 5.2.4.1
Description of change		1. A) Footnote 17 has been added to the Flow Chart, B) Clarification to footnote 5 has been made, C) Discrepancy between footnote 12 and the Flow chart has been corrected; 2. Glutamate Dehydrogenase (GLDH) was removed from the routine laboratory tests; 3. SARS-CoV-2 virus PCR test has been added to the exclusionary laboratory tests, and footnote 1 explaining the time points; 4. A) Clarification to a breath alcohol test at admission has been added, B) Details of SARS-CoV-2 virus PCR test have been provided; 5. Clarification to storing and evaluation of ECGs at the central ECG lab has been added.

Rationale for change		1, 3, 4. Due to the recent COVID-19 outbreak, and given infected individuals may be clinically asymptomatic, SARS-CoV-2 virus PCR tests are being implemented shortly before admission to the research site. Implementation of these tests should safeguard the subject's safety, and exclude infected volunteers from study participation. 2. Due to a feasibility feedback from the local safety laboratory at [redacted] Glutamate Dehydrogenase is removed from the list of required routine tests. 5. Due to a clarification received from the central ECG lab, the details of storing and evaluation of ECGs are updated.

11.2 GLOBAL AMENDMENT 2

Date of amendment		16 July 2020
EudraCT number **EU number**		2020-001036-10
BI Trial number		1445-0001
BI Investigational Medicinal Product(s)		BI 1595043
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1595043 (single-blind, partially randomised, placebo-controlled, parallel (sequential) group design) 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. Flow Chart (page 4) 2. Section 1.2.2.2 3. Section 1.4.3.3 4. Section 1.4.3.5 5. Section 2.2.2.1 6. Section 3.3.3 7. Section 5.2.1 8. Section 5.2.3 9. Section 5.2.5.1
Description of change		1. Clarification to footnotes 1 and 4 has been made: ophthalmological examination has been added to Screening and EoTrial Visit; 2. Ophthalmology findings in the 13-w toxicology study in rats have been described in details; 3. Clinical relevance of the ophthalmology findings in rats have been described; 4. Ophthalmological monitoring has been implemented as a risk minimization measure; 5. Clarification to further safety and tolerability endpoints has been made: clinically relevant findings from the ophthalmological examination will be reported as AEs; 6. Exclusion criterion 24 has been added: subjects with ocular disorders will be excluded;

		7. List of medical examinations at Screening and EoTrial Visit has been updated with the ophthalmological examination; 8. Details of the ophthalmological examination have been described; 9. Clarification to storing and evaluation of ECGs at the central ECG lab has been added.
Rationale for change		1. – 8. Changes are based on the regulatory feedback of FAMHP / EC after review of the study protocol as part of the approval procedure; 9. Further clarification to storing and evaluation of ECGs received from the central ECG lab.

11.3 GLOBAL AMENDMENT 3

Date of amendment		06 November 2020
EudraCT number **EU number**		2020-001036-10
BI Trial number		1445-0001
BI Investigational Medicinal Product(s)		BI 1595043
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1595043 (single-blind, partially randomised, placebo-controlled, parallel (sequential) group design) 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		Section 4.1.5.1
Description of change		Clarification to evaluation of ECG by the central ECG lab has been added, in case a preliminary analysis of ECG data is required during the trial.
Rationale for change		Changes are based on the clarification of the blinding procedures at the central ECG lab.

11.4 GLOBAL AMENDMENT 4

Date of amendment		14 January 2021
EudraCT number **EU number**		2020-001036-10
BI Trial number		1445-0001
BI Investigational Medicinal Product(s)		BI 1595043
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1595043 (single-blind, partially randomised, placebo-controlled, parallel (sequential) group design) 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. CTP Synopsis and other sections as applicable 2. Section 1.2.2.5 3. Section 1.2.4 4. Section 1.2.5 5. Section 1.2.6 6. Section 1.3.2 7. Section 1.4.3
Description of change		1. Dose group 8 (160 mg of BI 1595043) has been added, and the number of study subjects has been updated from 56 to 64 throughout the CTP text. 2. Details of pre-clinical embryo-fetal development toxicity studies have been added. 3. Prediction of human therapeutic dose has been updated. 4. Clinical experience with BI 1595043 has been described. 5. Evaluation of REP has been provided. 6. The maximum dose level to be tested in the study has been updated. 7. New pre-clinical and clinical data have been included into considerations on drug related risks and safety measures.

Rationale for change		The clinical trial protocol is being amended to add the new maximum dose level of 160 mg of BI 1595043 based on the available clinical data (Section 1.2.5) and the updated prediction of the human therapeutic dose (Section 1.2.4). Also, embryo-fetal development toxicity studies have been completed as described in Section 1.2.2.5.

APPROVAL / SIGNATURE PAGE

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

Title: Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1595043 (single-blind, partially randomised, placebo-controlled, parallel (sequential) group design) in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	14 Jan 2021 13:48 CET
Approval-Clinical Pharmacokinetics		14 Jan 2021 15:11 CET
Approval-Team Member Medicine		14 Jan 2021 15:19 CET
Author-Clinical Trial Leader		15 Jan 2021 19:02 CET
Verification-Paper Signature Completion		18 Jan 2021 08:23 CET
Approval-[redacted] Medicine		18 Jan 2021 18:45 CET

(Continued) Signatures (obtained electronically)

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