Boehringer Ingelheim

Clinical Trial Protocol

Document Number:	c34388550-04
EudraCT No.	2020-004924-40
BI Trial No.	1445-0011
BI Investigational Medicinal Product	BI 1595043
Title	A randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 1595043 as tablets with and without food in healthy male subjects
Lay Title	A study in healthy men to test how BI 1595043 is taken up in the body when given with or without food
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 3))
Version and Date	Version: 4.0 — Date: 30 June 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	16 February 2021
Revision date	30 June 2021
BI trial number	1445-0011
Title of trial	A randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 1595043 as tablets with and without food in healthy male subjects
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	The trial is conducted to gain information about the effect of food on the relative bioavailability of the BI 1595043 tablet formulation to support upcoming clinical studies in terms of improved trial designs and optimized formulations.
Trial objective	To investigate the influence of food on the relative bioavailability of the tablet formulation of BI 1595043
Trial design	Open-label, randomised, two-way cross-over design
Trial endpoints	Primary endpoints: AUC_{0-tz} and C_{max} of BI 1595043 Secondary endpoint: $AUC_{0-\infty}$ of BI 1595043
Number of subjects	
total entered	14
each treatment	14
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 (T)	BI 1595043 as tablets (25 mg and 5 mg)
dose	30 mg
mode of admin.	Oral with 240 mL of water after a high fat/high calorie breakfast
Reference product (R)	BI 1595043 as tablets (25 mg and 5 mg)
dose	30 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h

Duration of treatment	One day (single dose) for each treatment, separated by a washout period of at least 8 days
Statistical methods	Relative bioavailability will be estimated by the ratios of the geometric means (test / reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for sequence, subjects nested within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [7]	PK blood [9,14]	12-lead ECG [10]	Vital signs (BP, PR) [13]	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening[1]	A		x	x[11]	
1/2 (two identical periods separated by a washout of at least 8 days between drug administrations)	2/3	-3 to -1[8]	-72:00	08:00	Ambulatory visit[8]	B			x[11]	x
		-1	-14:00	18:00	Admission to trial site[12]	x[5]				
		1	-02:00	06:00	Allocation to treatment (visit 2 only)[2]		x[2]	x[2]	x[2,11]	x[2]
			-00:30	07:30	High fat, high calorie breakfast (only in treatment T2)					
			00:00	08:00	**Drug administration**					
			00:15	08:15			x			
			00:30	08:30			x			
			00:45	08:45			x			
			01:00	09:00			x	x	x	x
			01:15	09:15			x			
			01:30	09:30			x			
			02:00	10:00	240 mL fluid intake[3]		x		x	x
			02:30	10:30			x			
			03:00	11:00			x			
			04:00	12:00	240 mL fluid intake, thereafter lunch[3]		x		x	x
			06:00	14:00			x			
			08:00	16:00	Snack (voluntary)[3]		x		x	x
			10:00	18:00	Dinner[3]					
			12:00	20:00			x		x	x
		2	24:00	08:00	Breakfast[3]	B	x	x	x[11]	x
			29:00	13:00	Lunch					
			32:00	16:00	Snack (voluntary)					
			34:00	18:00	Dinner[3]		x			x
		3	48:00	08:00	Confirmation of fitness and discharge from trial site, breakfast[3]		x		x[11]	x
		4	72:00	08:00	Ambulatory visit		x		x[11]	x
		5	96:00	08:00	Ambulatory visit	B	x		x[11]	x
		6	120:00	08:00	Ambulatory visit		x		x[11]	x
		7	144:00	08:00	Ambulatory visit		x		x[11]	x
		8	168:00	08:00	Ambulatory visit		x		x[11]	x
EoT	4	9 - 14			End of trial (EoTrial) examination[4]	C		x	x[11]	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, assessment of body temperature, ECG, safety laboratory (including drug screening and infectious serology), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration. 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, assessment of body temperature, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. 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.
8. Only for Visit 2: Safety laboratory to be taken and to be medically evaluated within 3 days prior to first single dose administration of study drug; this ambulatory visit can be omitted if the screening examination is performed on Days -3, -2 or -1.
9. Sampling times and periods may be adapted based on information obtained during the trial (e.g., due to preliminary PK data) including addition of samples and visits as long as the total blood volume removed does not exceed 500 mL per subject.
10. For details of 12-lead ECG, refer to Section 5.2.5.
11. Including assessment of body temperature.
12. PCR test for SARS-COV-2/ COVID-19 will be performed shortly (within 72 hours) before admission to trial site in each treatment period.
13. For details of vital signs evaluation, refer to Section 5.2.2.
14. For details of PK blood sampling for BI 1595043, refer to Section 5.3.2.

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
[redacted]	
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial
EudraCT	European Clinical Trials DataBAse
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
IB	Investigator's brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file

LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
[redacted]	
TS	Treated set
[redacted]	
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
[redacted]	
XTC	Ecstasy

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

[redacted]

1.2 DRUG PROFILE

Vanin-1 and -2 (Vascular Non-Inflammatory molecules 1 and 2) are extracellular enzymes expressed on epithelial cells, macrophages, monocytes, T-cells and neutrophils, shed in significant amounts into the extracellular milieu, and found in most extracellular compartments across tissues.

Inflammatory mediators and bacterial endotoxins drive expression of vanin-1 and 2 enzymes, whose common function is to convert pantetheine into pantothenic acid and cysteamine. It is through production of cysteamine that vanin enzymes directly impact extracellular metabolic homeostasis of tissues by depleting cystine in tissues through reducing it to cysteine. Cystine depletion is understood to alter the intracellular redox balance of tissues, resulting in increased oxidative stress, endoplasmic reticular stress, and disruption and eventual destruction of tissue. In addition, cystine depletion is postulated to result in increased extracellular cysteine levels, enhancing adaptive immune response, increasing CD4+ T-cell production of pro-inflammatory cytokines IFNγ, IL-4, IL-5 and IL-13.

Therefore, it is expected that inhibition of vanin enzyme function will directly restore tissue metabolite homeostasis and redox balance leading to tissue repair, while curbing chronic inflammation, which could prove beneficial in diseases characterized by tissue lesions and ulceration as well as the presence of chronic inflammation.

For consistency of nomenclature, vanin-1 and vanin-2 isoforms, unless referenced otherwise, will be referred to as vanin.

1.2.1 Nonclinical pharmacology

1.2.1.1 Primary pharmacodynamics

In vitro primary pharmacodynamics

In a human recombinant vanin-1 enzyme activity assay (n00273892), measuring pantothenic acid product formation, formed in a 1:1 ratio with cysteamine through cleavage of pantethine, BI 1595043 inhibited vanin-1 with an IC_{50} of 0.17 nM. In human whole blood, containing both vanin-1 and vanin-2 (n00273893), BI 1595043 inhibited vanin activity with a mean IC_{50} value of 1.9 nM. In a human ex vivo colon tissue assay, using non-inflammatory bowel disease human colon explants (n00273895), BI 1595043 inhibited vanin activity and lowered release of cytokeratin-18 (CK-18). CK-18 is a marker of epithelial injury, elevation of which is a hallmark of diseases of the epithelial barrier (R18-2868). Reduction of CK-18 was interpreted as a signal of epithelial healing. The effect of BI 1595043 on T-lymphocyte activity, measured by cytokine production (IFN gamma, IL-4 IL-13, IL-5) , was tested in human CD3/CD28 stimulated T-cells (n00273897). Cytokine production was significantly reduced in a majority of donors, which was interpreted as a sign of decreased inflammation.

In vivo primary pharmacodynamics

In a model of dextran sodium sulfate (DSS) mediated intestinal injury in C57Bl/6 mice (n00273898), BI 1595043 demonstrated target engagement, as measured by decreased levels of the vanin product, pantothenic acid, in both central plasma compartments and target colon tissue, as well as increased levels of the vanin substrate, pantetheine, in the plasma. Mice treated with BI 1595043 showed reduced epithelial damage assessed by histology score, but formation of inflammatory infiltrate was not significantly altered with BI 1595043.
BI 1595043 did not reduce intestinal permeability (assessed by detection of sucralose uptake through the colon). While other vanin inhibitors similar to BI 1595043, tested in separate

studies (n00259753), showed reduction of inflammation and improved barrier integrity, in BI 1595043's case a trend was observed that fell short of statistical significance.

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). BI 1595043 inhibited the current with the IC_{50} of 157.88 µM or 233-times the estimated human therapeutic C_{max}. Effect of BI 1595043 on cardiovascular function was assessed in conscious male telemetry-instrumented Beagle dogs at oral doses of 3, 10 or 200 mg/kg (n00271655). At doses of 3 and 10 mg/kg, no BI 1595043-related abnormalities were observed. At 200 mg/kg of BI 1595043, decrease in blood pressure with accompanying increase in heart rate were observed.

Respiratory system

BI 1595043 effects on the respiratory function was assessed at single oral doses of 10, 50 or 300 mg/kg in rat (n00270318). At doses of 10 and 50 mg/kg, BI 1595043 had no effect on the respiratory system. Rats administered 300 mg/kg had mildly lower tidal volume from 1 through 3 h post-dose and slightly lower minute volume from 1 through 2 h post-dose.

Central nervous system

BI 1595043 effects on neurological function were assessed in rat at single oral doses of 10, 50 or 300 mg/kg (n00270317). With the exception of transiently lower body temperature at 300 mg/kg, no effects of BI 1595043 were observed up to 24 hours post-dose.

Renal and hepatic system

The effect of BI 1595043 on urine- and serum-derived parameters was evaluated in rat after a single oral dose of 1, 3 or 10 mg/kg (n00275784). BI 1595043 had no relevant effect on urinary excretion or serum-based parameters following the oral doses of 1 and 3 mg/kg for most parameters assessed. Following the 10 mg/kg dose, BI 1595043 caused only slight effects on renal function or renal injury markers during 4 h post-dose.

Further considerations on safety pharmacology

In a vanin-1 knock-out/NOD diabetic mouse model, vanin deficiency aggravated islet cell death and diabetes, whereas treatment with super-physiological levels of cysteamine reduced pancreatic islet cell death and thus might play a role in islet cell protection (R17-3327). Other findings suggest that elevated expression of vanin-1 in pancreatic ductal adenocarcinoma cells aggravated loss of pancreatic islet function and was associated with the onset of pancreatic cancer-associated new-onset diabetes (R18-2866). However, further studies, assessing the metabolic impact of vanin-1 deficiency, absence of vanin-1 either in knock-out mice or by pharmacological inhibition, did not impact glycemic control (R18-2867). Pharmacological inhibition of vanin-1 in diabetic rats for 8 days using RR6, a small molecule vanin-1 inhibitor, was well tolerated and showed no significant effects on hepatic steatosis in diabetic rats (R18-2867). These diverse data suggest that BI 1595043 might impact islet cell survival and glycemic control although the findings of different studies are contradictory. Thus far conducted safety pharmacology, genetic toxicology and general toxicology studies did not indicate any toxicity of BI 1595043 related to glycemic control.

A human missense single nucleotide polymorphism (SNP) (rs2272996) in the gene encoding vanin-1 is associated with decreased blood pressure, with the SNP causing faster degradation of vanin-1 and significant reduction of vanin-1 plasma levels (R18-2692).

1.2.1.3 Pharmacodynamic interactions

No pharmacodynamics interaction studies have been carried out to date.

Conflicting literature exists regarding effect of vanin inhibition on acetaminophen (paracetamol) toxicity. An earlier study (R18-2954) suggested that vanin-1 deficiency (in knock-out mice) might protect mice against acetaminophen-induced liver toxicity. In another (R17-3326), acetaminophen-induced liver toxicity was exacerbated in vanin-1 knock-out mice compared to wild type littermates.

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 in rats at ≥300 mg/kg and in dogs at 200 mg/kg after single dose administration.

In an in vivo genotoxicity assay in rats (n00271724), clinical signs of piloerection, crusty eye and hunched posture were observed after administration of 500 mg/kg/day (250 mg/kg BID, 2 h apart). Decreased motor activity, slight labored breathing, piloerection, and hunched posture were noted after administration of 1000 mg/kg/day (500 mg/kg BID, 2 h apart) for one day. At 2000 mg/kg/day (1000 mg/kg BID, 2 h apart) in addition to the clinical signs observed at the lower doses, squinty eyes were noted. BI 1595043 induced a reduction in body weight gain at 1000 mg/kg/day. Three of six animals administered 2000 mg/kg/day were found dead on day 2 (n00271724).

Details of BI 1595043-related effects observed following single doses in a rat CNS study (transiently lower body temperature at 300 mg/kg) (n00270317), a rat respiratory study (transiently lower tidal and minute volumes at 300 mg/kg) (n00270318) and a dog cardiovascular function study (decrease in blood pressure with increase in heart rate) (n00271655) are detailed in Section 1.2.1.2. In the dog cardiovascular function study (n00271655), at 200 mg/kg, post-dose vomitus was observed in 5 out of 10 animals.

1.2.2.2 Repeated dose toxicity

In a 13-week GLP study in Wistar Han rats, BI 1595043 was administered for 13 weeks at oral doses of 10, 50 and 300 mg/kg/day, followed by a 10-week recovery period (n00268703). No mortality was observed. No BI 1595043-related effects on clinical signs or urinalysis were observed at any dose level.

At doses of ***≥10 mg/kg/day***, *non-adverse* body weight gain increase was observed in males and females.

At doses of ***≥50 mg/kg/day***, *non-adverse effects* were observed: increased thyroid gland weight in male and female without microscopic correlate; decreased AST in male and female.

At doses of ***300 mg/kg/day***, *non-adverse effects* were observed: body weight gain reduced in males and females; increased kidney weight in males and females without microscopic correlate; increased liver weight in males and females correlating to hepatocellular hypertrophy (diminished but not absent at the end of recovery); increased mean white blood cell counts and absolute lymphocytes counts in males and females (of lower magnitude at the end of recovery, suggesting reversibility of the effect); increased total T cell, T helper cell, T cytotoxic cell and B cell numbers in males (generally within range of control males at the end of recovery, suggesting reversibility of the effect); increased ALT in males and females, likely correlated with the incidence of hepatocellular hypertrophy and increase in hepatocellular microsomal enzyme activity.

Also, at doses of ***300 mg/kg/day***, *adverse* testicular changes (abnormal spermatogenesis, minimal spermatid retention) and *adverse* minimal-to-mild debris within duct lumen of the epididymides were observed in males, not present at the end of the recovery phase. The findings were considered adverse because they may indicate disruption of the normal spermatogenic cycle that could result in effects on fertility (R18-2864).

<u>Ophthalmology findings:</u>

During pretest-evaluation, no abnormalities were identified by indirect ophthalmoscopy. At the end of BI 1595043 dosing, unilateral or bilateral visualization of cataract was noted, a descriptive term used synonymous with a change in lens opacity, in rats in the ***50 mg/kg/day*** group (1/20 rats with unilateral cataract) and ***300 mg/kg/day*** group (8/20 male [7 bilateral and 1 unilateral] and 7/20 female rats [all bilateral]). No abnormalities were observed in control animals. At the end of recovery, this finding was observed in a total of 0/10 male and 4/10 female rats from the ***control group*** and 9/10 males (all bilateral) and 8/10 females (all bilateral) from ***300 mg/kg/day*** group. However, upon thorough histologic examination, there was no microscopic evidence of cataract formation correlating to any of these ophthalmoscopic observations in any rats. Due to a lack of histologic correlate, this finding is considered *non-adverse*.

Under the conditions of this study the NOAEL at steady state was considered to be 50 mg/kg/day, which corresponded to a C_{max} of 39,900 nM and AUC_{0-24} of 188,000 nM•h in males and C_{max} of 50,500 nM and AUC_{0-24} of 240,000 nM•h in females. As compared to the estimated human exposure at the predicted therapeutic dose, exposures at the NOAEL are about 58- and 75- fold higher for C_{max} in male and female respectively; and 54- and 69-fold higher for AUC in male and female respectively.

In a 13-week GLP study in Beagle dogs with a 10-week recovery period (n00270419), BI 1595043 was administered for at least 13 weeks in low- and mid-dose groups at oral doses of 3 and 10 mg/kg/day. High dose group dogs were given 200 mg/kg/day on days 1 and 2, which was reduced to 100 mg/kg/day on day 3 due to adverse vomitus/emesis. The female high dose dogs received 100 mg/kg/day from day 3 to the end of the dosing phase. Due to poor tolerability, male dogs in the high dose group receiving 100 mg/kg/day were not dosed between days 21 and 34; dosing resumed on day 35 at 30 mg/kg/day for the remainder of the dosing phase.

BI 1595043-related *moribundity* occurred in one male dog at the ***100 mg/kg/day*** dose level and resulted in humane euthanasia on day 16. Decrease in body weight corresponded to decreased food consumption, instances of liquid feces, vomitus, salivation, shivering or trembling and dehydration were observed. On day 16, results of blood tests showed increased absolute lymphocytes, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, and gamma-glutamyl transferase. At necropsy, the macroscopic observation of depressed foci in the liver corresponded microscopically to moderate panlobular hepatocellular degeneration with slight bile duct hyperplasia and moderate mononuclear parenchymal infiltrate. The macroscopic observation of abnormal coloration of the lung correlated microscopically to severe acute alveolar inflammation; and laryngeal ulcer. Decreased cellularity in the axillary lymph node and moderate decreased cellularity in the thymus.

There were no BI 1595043-related effects on ophthalmology, physical examinations, urinalysis or immunophenotyping observed at any dose level.

At doses of ***3 mg/kg/day*** and ***10 mg/kg/day***, no abnormalities were observed.

At doses of ***30 mg/kg/day***, reversible *adverse effects* on the liver was seen in males consisted of hepatocellular degeneration and loss of parenchyma (not evident in recovery animals).

At doses of ***≥100 mg/kg/day***, reversible *non-adverse effects* were observed: increases in mean heart rate in females; changes in hematology parameters (increased in red blood cell parameters (mean corpuscular volume, mean corpuscular hemoglobin, red cell distribution width), increased absolute neutrophils, decreased mean platelet volume) in females; increases in partial thromboplastin time and activated partial thromboplastin time in a single male dog; increase in mean triglycerides in males and females; increased creatinine in females.

Also, at doses of ***≥100 mg/kg/day***, administration of BI 1595043 resulted in *adverse reactions:* vomitus/emesis at 200 mg/kg/day which required dose reduction (to 100 mg/kg/day in females and 30 mg/kg/day in males); shivering or trembling in males at 200 mg/kg/day (decreased in frequency with a reduction in dose to 100 mg/kg/day); decreases in body weight and food consumption in males and females (comparable to control at the end of recovery); reversible increases in ALT, AST and alkaline phosphatase in males and females; increases in total bilirubin, direct bilirubin and gamma-glutamyl transferase in a single male correlated microscopically to slight periportal hepatocellular degeneration.

Under the conditions of this study the NOAEL at steady state was considered to be 10 mg/kg/day, which corresponded to a C_{max} of 8,550 nM and AUC_{0-24} of 81,700 nM•h in males and C_{max} of 10,700 nM and AUC_{0-24} of 81,400 nM•h in females. As compared to the estimated human exposure at the predicted therapeutic dose, exposures at the NOAEL are about 13- and 16- fold higher for C_{max} in male and female respectively, and about 23- fold higher for AUC in both sexes.

1.2.2.3 Genotoxicity

BI 1595043 was not mutagenic in the bacterial reverse gene mutation (Ames) test (n00271737) up to the dose limit of 5000 µg/ plate, and in the in vitro micronucleus assay (n00271739) up to the dose limit of 1 mM. In the in vivo rat bone marrow micronucleus assay (n00271724), BI 1595043 was concluded to be negative up to dose levels of 1000 mg/kg/day. Evaluation at the highest dose level of 2000 mg/kg/day was not conducted due to the overt clinical signs and mortality (see Section 1.2.2.1).

1.2.2.4 Carcinogenicity

Carcinogenicity studies have not yet been conducted.

1.2.2.5 Reproductive and developmental toxicity

Definitive embryo-fetal development toxicity studies have been completed in rat and rabbit (n00278622, n00278281). Maternal and embryo-fetal toxicity were not observed in these studies (rat NOAEL AUC 125,000 nM•h and C_{max} 25,500 nM, rabbit NOAEL AUC 323,000 nM•h and C_{max} 97,400 nM). Teratogenicity (digit malformations) was observed in rat (LOAEL AUC 6,900 nM•h and C_{max} 2,270 nM) (n00278622). Teratogenicity was not observed in rabbit (NOAEL AUC 323,000 nM•h and C_{max} 97,400 nM) (n00278281).

In the 13-week rat study (n00268703), there were adverse microscopic effects on the testis and epididymis at 300 mg/kg/day of BI 1595043 in males (see Section 1.2.2.2). No adverse effects on the reproductive tract were seen at 50 mg/kg/day in males, and at doses up to 300 mg/kg/day in female rats. No effects on the reproductive tract were seen in the 13-week dog study (n00270419).

1.2.2.6 Local tolerance

No local tolerance studies have been conducted.

1.2.2.7 Other toxicity studies

BI 1595043 exhibits an absorption band in the spectral region of 290-700 nm with absorbance peaks at 290 and 310 nm (molar extinction coefficient of 12505 L mol^{-1} cm^{-1} in PBS) (n00267953). In an in vitro assay using BALB/c 3T3 mouse fibroblasts (n00272671), BI 1595043 did not demonstrate phototoxic potential up to concentrations of 100 µg/mL.

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 in rat plasma (lower limit of quantitation (LLOQ): 5.00 nM) (n00270399), dog plasma (LLOQ: 15.0 nM) (n00270319), and rabbit plasma (LLOQ: 5.00 nM) (n00275663).

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 by low-to-moderate clearance (CL) and a moderate volume of distribution (V_{ss}). The half-life ($t_{1/2}$) was short in rats, short-to moderate in dogs, and moderate-to-long in minipigs. The bioavailability (BA) in rats and dogs was high, while the BA in minipigs was moderate.

Table 1.2.3.2: 1 Mean PK parameters in rats, dogs and minipigs for BI 1595043

PK Parameter	Male Han Wistar Rat (n=3 mean ± SD)		Male Beagle Dog (n=3, mean ±SD)		Female Minipig (n=3, mean ± SD)	
Route of Administration	IV	PO	IV	PO	IV	PO
Dose (mg/kg)	1[1]	12	0.4	4	0.4	4
CL (mL/min/kg)	18.6 ± 4.6	--	6.6 ± 0.4	--	10.8 ± 4.2	--
V_{ss} (L/kg)	2.32 ± 0.49	--	1.70 ± 0.14	--	2.43 ± 0.12	--
$t_{1/2}$ (h)	3.0 ± 0.66	3.11 ± 0.75	4.30 ± 0.72	8.68 ± 1.60	12.1 ± 0.83	8.63 ± 1.30
t_{max} (h) median (range)	--	2 (2-2)	--	0.83 (0.5-1)	--	3 (2-4)
C_{max} (nM)	--	7,850 ± 2,920	--	5,097 ± 365	--	293 ± 119
AUC_{0-inf} (nM•h)	2,370 ±670	22,100 ± 7,290	2,550 ± 140	27,570 ± 4,110	1,750 ± 770	4,740 ± 1,380
A_e renal (% dose)	±	17.7 ± 5.2	19.6 ± 4.1	11.8 ± 1.0	6.7 ± 2.1	1.0 ± 0.49
Renal CL (mL/min/kg)	±	3.5	1.3 ± 0.27	0.73 ± 0.15	0.77 ± 0.45	0.35 ± 0.06
BA (%) [2]	--	72.5 [3]	--	119	--	21.9

1. Three IV dose levels (0.01, 0.1, 1 mg/kg) were tested in the rat. The results of the highest dose tested are represented in this table.

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

The binding of [^{14}C]-BI 1595043 to plasma proteins was assessed in rat, dog and human plasma in vitro by equilibrium dialysis (n00275691). Binding in rat and human plasma is concentration-dependent due to saturable binding to target in plasma, ranging from 60.5-45.8% bound in rat plasma at concentrations from 0.001 to 100 µM, and 78.5% - 49.5% bound in human plasma at concentrations from 0.001 to 1 µM. Concentration-dependent binding was not observed in dog plasma (46.2% - 43.4% bound at all concentrations tested).

Distribution in pigmented rat

Quantitative tissue distribution of total drug-related radioactivity was investigated in male pigmented (Long-Evans) rats administered a single 10 mg/kg oral dose of [^{14}C]-BI 1595043 (n00273365).

As measured by autoradiography, tissue:plasma ratios were variable, ranging from 0.045 to 15 at 1 h post dose. At 24 h post dose, tissue:plasma ratios ranged from not detectable to 650, with the highest levels of radioactivity found in the liver, renal cortex, skin, cutis, eyeball, and melanin-containing tissues (MCT) of the ocular bulb. At 168 h post dose radioactivity was not measurable in any tissue. Radioactivity was detectable in the CNS only at 1 h post dose at levels of up to 8.1% in relation to the levels in whole blood. These results suggest low penetration of [^{14}C]-BI 1595043 into the CNS.

The approximate half-lives (β-phase) of radioactivity in total eyeball and MCT of the ocular bulb, based on limited data (2 data points) from 24 to 168 h, were 42 and 45 h, respectively.

The approximate half-life of radioactivity in plasma was determined to be 3.3 h. These data indicate high affinity and long-term (yet reversible) exposure of radioactivity to ocular tissues. In the skin and cutis, approximate half-lives calculated from 1 to 24 h were 12 and 15 h, respectively. These data indicate moderate affinity and medium-term exposure of radioactivity to the integumentary system.

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. From this in vitro - in vivo correlation, hepatic clearance in human was estimated to be 1.7 mL/min/kg. Based on this estimate, hepatic clearance is considered to be the major route of elimination in humans. Additionally, renal clearance was estimated to be 0.4 mL/min/kg based on data scaled from non-rodent species (n00274794).

1.2.3.5 Excretion

In Wistar Han rats, excretion of radioactivity was assessed after a PO dose (10 mg/kg) or an IV dose (2 mg/kg) of [^{14}C]-BI 1595043 (n00275520). Little to no difference in excretion patterns were noted between PO and IV dosing, indicating good absorption.

Following the PO dose and collection of urine up to 96 h, 30.8% and 51.1% of the administered radioactivity was recovered from male and female rats, respectively, while the recovery of total radioactivity in feces was 62.8% and 43.7% in male and female rats, respectively. These data indicate slight differences in excretion patterns between male and female rats, with female rats showing slightly more urinary excretion than male rats, and male rats showing slightly more fecal excretion than female rats.

The excretion of radioactivity after IV and PO dosing was rapid, with >90% of dosed radioactivity recovered within 24 h for both male and female rats.

In bile duct cannulated rats administered an IV dose of [^{14}C]-BI 1595043 the biliary excretion within 6 h was 28.0%. This time course in bile suggests that biliary excretion is not completed within this time interval.

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:

Table 1.2.3.7: 1 PK parameters in GLP toxicological studies following oral administration of BI 1595043

Study Type (Study or Report No.)	Dose (mg/kg /day)	C_{max} (nM)[1]		AUC_{0-24}[1] (nM•hr)		C_{max} Multiple[2]		AUC Multiple[2]	
		M	F	M	F	M	F	M	F
13 Week Rat (n00268703)	10	7,050	11,700	15,600	28,500	10	17	4	8
	50	**39,900**	**50,500**	**188,000**	**240,000**	**59**	**74**	**54**	**69**
	300	167,000	188,000	1,910,000	2,080,000	246	277	547	595
13 Week Dog (n00270419)	3	2,570	2,190	25,600	18,800	4	3	7	5
	10	**8,550**	**10,700**	**81,700**	**81,400**	**13**	**16**	**23**	**23**
	30	35,700	NA	352,000	NA	53	NA	101	NA
	100	NA	127,000	NA	1,580,000	NA	187	NA	452
Human	30 mg/day	678		3,494					

1. Data shown are end of study exposures
2. Multiples calculated based on estimated human therapeutic exposure

Exposures corresponding to NOAEL dose are listed in **bold**.

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 of the first in human single rising dose (SRD) study 1445-0001 (see Section 1.2.5.2). This model was linked to the original PK/PD model to derive the human therapeutic dose that is expected to lead to a 75% reduction in cysteamine exposure over a 24 h period ($AUC_{24,\ cysteamine}$). The linked PK/PD model was developed using *in vitro* and *in vivo* data from preclinical species, human *in vitro* data regarding the binding properties of BI 1595043 to vanin, and a correlation between target engagement in mouse and *ex vivo* analysis using human intestinal tissue (n00274794). From the linked PK/PD model, it is expected that clinical efficacy will be maintained at a BI 1595043 dose of 30 mg q.d. At this dose, $C_{max,ss}$ and $AUC_{24,ss}$ are predicted to be 678 nM and 3,494 nM•h, respectively.

1.2.5 Clinical experience in humans

The first in human study SRD study 1445-0001 is ongoing at the time of current 1445-0011 clinical trial protocol preparation. The SRD study consists of 7 original dose groups of 8 subjects each 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. The SRD clinical trial protocol is being amended to add one additional dose level of 160 mg of BI 1595043 at the time of preparation of 1445-0011 clinical trial protocol.

At this point in the clinical trial, BI 1595043 has been administered to 42 healthy male subjects as oral single doses of oral solution within 7 dose groups. Additionally, 14 healthy male subjects have received matching placebo.

1.2.5.1 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: 1). The most frequent AE was headache reported in 17.1% (n=3) subjects on BI 1595043 and 14.3% (n=2) subjects on placebo. During planned ophthalmological examination, a mild retinal haemorrhage was observed at the End-of-Trial visit in one subject who received 12 mg of BI 1595043 without any symptoms. At the follow up ophthalmological investigation, the AE was resolved without consequences, and the AE was considered as not drug related. There were no AEs considered to be dose limiting, in particular no AEs of severe intensity and no SAEs. Vital signs evaluation and safety laboratory testing did not reveal relevant findings [c34604736]. Thorough descriptive ECG analyses did not reveal a marked prolongation of the QT/QTc interval. There were no QTc increases to >500 ms or changes from baseline of >60 ms [c34816263].

Table 1.2.5.1: 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)

System organ class/ Preferred term	**Placebo N (%)**	**1 mg N (%)**	**3 mg N (%)**	**6 mg N (%)**	**12 mg N (%)**	**25 mg N (%)**	**50 mg N (%)**	**90 mg N (%)**	**BI Total N (%)**	**Total N (%)**
Number of subjects	14 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	42 (100)	56 (100)
Total with adverse events	6 (42.9)	0 (0)	1 (16.7)	1 (16.7)	2 (33.3)	3 (50)	4 (66.7)	0 (0)	11 (26.2)	17 (30.4)
Nervous system disorders	3 (21.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	3 (50)	0 (0)	4 (9.5)	7 (12.5)
Headache	2 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (50)	0 (0)	3 (7.1)	5 (8.9)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	1 (2.4)	1 (1.8)
Somnolence	1 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	1 (2.4)	2 (3.6)
Eye disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	1 (2.4)	1 (1.8)
Retinal haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	1 (2.4)	1 (1.8)
Gastrointestinal disorders	2 (14.3)	0 (0)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0)	0 (0)	0 (0)	3 (7.1)	5 (8.9)
Diarrhoea	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)	1 (1.8)
Flatulence	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	1 (2.4)	1 (1.8)
Nausea	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)	1 (1.8)
Angular cheilitis	1 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)
Dyspepsia	1 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)
Gastrointestinal pain	1 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)
General disorders and administration site conditions	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (16.7)	0 (0)	2 (4.8)	2 (3.6)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (16.7)	0 (0)	2 (4.8)	2 (3.6)
Infections and infestations	1 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	1 (2.4)	2 (3.6)
Conjunctivitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	1 (2.4)	1 (1.8)
Rhinitis	1 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)

1.2.5.2 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: 2. After a single oral solution dose, BI 1595043 was rapidly absorbed with median t_{max} values of 0.75-1 h. C_{max} increased in a close to dose proportional manner. AUC_{0-24} increased in a less than dose-linear manner between 1 and 6 mg, and at doses above 6 mg, AUC_{0-24} increased approximately dose proportionally. Geometric mean terminal $t_{1/2}$ ranged from 16 to 29 h.

In Trial 1445-0001, 160 mg has been selected as maximum dose, predicted to result in a C_{max} of 3,550 nM and AUC_{0-24} of 17,620 nM•h in humans based on the interim population PK model.

Table 1.2.5.2: 2 gMean (gCV%) values of BI 1595043 PK parameters after single oral doses of BI 1595043 – SRD Trial 1445-0001 – Dose Groups 1-7

Parameter	Dose (mg)						
	1	3	6	12	25	50	90†
AUC_{0-24} (h·nmol/L)	207 (16.6)	453 (7.20)	747 (11.2)	1450 (16.4)	2810 (16.8)	5150 (19.5)	11400 (8.76)
AUC_{0-tz} (h·nmol/L)	258 (27.8)	537(14.3)	921 (18.8)	1790 (19.2)	3140 (20.1)	5460 (20.2)	NC
C_{max} (nmol/L)	23.6 (16.6)	78.4 (10.9)	119 (21.2)	286 (20.5)	516 (26.2)	1100 (27.1)	2500 (20.0)
t_{max} (h)*	1.0 (0.5-1.0)	1.0 (0.5-1.0)	1.0 (0.5-1.5)	0.75 (0.5-1.0)	1.0 (1.0-1.0)	0.75 (0.5-1.0)	0.75 (0.5-1.0)
t½ (h)	16.8 (28.2)	15.6 (35.2)	21.3 (59.6)	26.8 (33.9)	29.3 (25.9)	20.6 (43.6)	NC
CL/F (mL/min)	143 (27.0)	220 (15.0)	263 (19.7)	274 (19.2)	327 (19.5)	382 (20.3)	NC
V_z/F (L)	209 (9.61)	298 (20.6)	486 (40.8)	637 (29.9)	830 (34.2)	683 (26.3)	NC

* median (min-max)
† 90 mg dose, concentration data are available only to 24 h post-dose. All quantifiable concentrations at all time points are available for all other doses.
NC – Not Calculated, too few data points available

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 about 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

The trial is conducted to gain information about the effect of food on the relative bioavailability of the BI 1595043 tablet formulation. The data obtained in this study will support the optimization of trial design in upcoming clinical studies, and may be crucial information for formulation development.

Dose selection of 30 mg of BI 1595043 is based on the assumption to include a potential therapeutic dose (see Section 1.2.4).

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

BI 1595043, a first-in-class vanin inhibitor, will be developed in CD. There is a substantial unmet medical need for agents with greater efficacy than current therapies, like aminosalicylates (e.g. 5-ASA), glucocorticoids, immunomodulator agents (azathioprine or 6-MP), biologic TNFα inhibitors (TNFi), or other biologic options (vedolizumab, ustekinumab). Concerns over infection- and lymphoma risks attached to some of these treatments remain. Treatment options for fistulizing and fibrotic disease are limited.

In CD, direct barrier injury is believed to be (at least partially) channeled through vanin enzymes and their product, cysteamine. By reducing cysteamine levels, a vanin inhibitor is expected to lead to direct epithelial barrier repair, resulting in mucosal healing, and to attenuate the chronic inflammation that is underlying the disease. Oral medicines with a novel mode of action that includes repair of epithelial barrier would address the unmet medical need in CD.

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

Vanin-1 and -2 are extracellular enzymes expressed in humans on epithelial (lung, kidney, and intestinal tract), liver-, and immunological cells. It is shed in significant amounts into the extracellular milieu, and is found in most tissues. It's function is to convert pantetheine into pantothenic acid and cysteamine. Through the production of cysteamine, vanin is directly impacting extracellular metabolic homeostasis of different tissues by chemically reducing and depleting cysteine, resulting in increased oxidative stress, endoplasmic reticular stress, and disruption and eventual destruction of tissue. Therefore, it is expected that vanin inhibition will directly restore tissue metabolite homeostasis and redox balance leading to tissue repair in CD-patients.

As described in Section 1.2.1, the human missense SNP (rs2272996) in the gene, encoding vanin-1, is associated with decreased blood pressure (R18-2692). Considering this data as well as the findings from the dog telemetry study, blood pressure and heart rate will be closely monitored after BI 1595043 administration.

In toxicology studies with BI 1595043, there were no adverse histological pancreas findings or a lack of glycemic control. However, considering the conflicting literature, described in Section 1.2.1 about pancreatic islet cell survival, fasting blood glucose levels will be closely monitored as a precautious measure.

Since there might be a relationship between vanin inhibition and acetaminophen (paracetamol) induced liver toxicity, in this study, acetaminophen will be strictly prohibited as concomitant medication.

1.4.3.2 Relevance of animal models

Vanin-1 is expressed in preclinical species including mouse, rat, and dog. Rat and Beagle dog were chosen as the rodent and non-rodent toxicology species due to the conserved amino acid sequence for vanin-1 (>78% compared to human) and previously demonstrated pharmacological activity of vanin inhibitors in these species (n00261263, n00261387). However, as rodents lack vanin-2, there is a considerable discrepancy between species. In dogs, vanin-1 mRNA levels are high in the lung, liver, spleen and kidney. Comparative expression in tissues is generally lower in the rat, although tissue distribution is comparable. While dogs possess a vanin-2 gene, its expression in dog tissues is not characterized. Target risk assessments generated for vanin-1 and vanin-2 did not reveal any unique on target concerns for vanin-2 when compared to vanin-1. However, any unique effects mediated by vanin-2 may not be evaluated in rodent studies, but dog toxicity studies would inform on potential vanin-2 effects. Potency of BI 1595043 in dog whole blood was comparable to human; while in mouse whole blood, BI 1595043 displayed twenty-five-fold lower potency.

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.

In the rat 13-week study (n00268703), signs of reproductive toxicity were seen in male rats at 300 mg/kg/day (adverse microscopic effects on the testis and epididymis), not considered relevant in humans at planned clinical doses due to large safety margins. Under the conditions of this study the NOAEL at steady state was considered to be 50 mg/kg/day, which corresponded to a C_{max} of 39,900 nM and AUC_{0-24} of 188,000 nM•h in males and C_{max} of 50,500 nM and AUC_{0-24} of 240,000 nM•h in females. With regard to the non-adverse ophthalmology findings (visualization of cataract, descriptively synonymous with a change in lens opacity), no microscopic evidence of correlating cataract formation was observed upon thorough histologic examination in any rat. Likewise, no ophthalmology findings were observed in 1-week repeat-dose toxicity study in rats (n00266340) and in the 2-week and 13-week studies in dogs (most sensitive toxicological species) (n00266444, n00270419), which suggests an unlikely clinical relevance for human subjects receiving two isolated doses in the planned dose range.

In the dog 13-week study (n00270419), once daily oral administration of BI 1595043 resulted in moribundity at 100 mg/kg/day in one male dog. Based on reversible adverse effects on the liver in male dogs at 30 mg/kg/day, liver enzymes parameters will be closely monitored after BI 1595043 administration. Under the conditions of this study the NOAEL at steady state was considered to be 10 mg/kg/day, which corresponded to a C_{max} of 8,550 nM and AUC_{0-24} of 81,700 nM•h in males and C_{max} of 10,700 nM and AUC_{0-24} of 81,400 nM•h in females.

BI 1595043 has a low risk for QT prolongation based on results of the dog telemetry study (n00271655). The observed decreases in blood pressure with accompanying increases in heart rate in dogs may be related to the pharmacological inhibition of vanin (R18-2692). Based on these findings, blood pressure and heart rate will be closely monitored after BI 1595043 administration.

Embryo-fetal development toxicity studies have been completed in rat and rabbit (n00278622, n00278281). Maternal and embryo-fetal toxicity were not observed in these studies (rat NOAEL AUC 125,000 nM•h and C_{max} 25,500 nM, rabbit NOAEL AUC 323,000 nM•h and C_{max} 97,400 nM). Teratogenicity (digit malformations) was observed in rat (LOAEL AUC 6,900 nM•h and C_{max} 2,270 nM) (n00278622). There is a very low risk of relevant systemic exposure through exposure to seminal fluid in women of child-bearing potential (WOCBP) partners of male subjects dosed with BI 1595043. Given the results of the embryo-fetal development study in rats, BI 1595043 currently falls into a category of possible human teratogenicity [R20-3402] for which additional birth barrier contraception (condom) is not strictly required. However, considering the limited clinical data available for

BI 1595043, study subjects will be conservatively required to follow the birth control measures as specified in inclusion criterion No. 5. In addition, unprotected sexual intercourse with a pregnant female partner and sperm donation is not allowed throughout the study and until 30 days after trial completion.

The risk of genotoxicity and phototoxicity is low. Carcinogenicity and local tolerance has not yet been examined. Reproductive studies have not yet been completed.

Overall, it should be highlighted that all toxicological findings occurred at exposures far beyond the estimated therapeutic exposure (C_{max} of 678 nM and AUC_{0-24} of 3,494 nM•h at 30 mg of BI 1595043) supporting 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 the study dose, as described in Section 4.1.2.
- If dosing of several subjects is scheduled on a same day, subjects will be dosed at least 5 min apart.
- Application of the second single dose of BI 1595043 to each subject, only if the first single dose of BI 1595043 is safe, shows acceptable tolerability, and no stopping criterion is met (see Sections 3.3.4.1 and 3.3.4.3). At least 8 days will be maintained between the two drug administrations to each subject.
- A monitoring of safety laboratory with specific focus on plasma glucose levels and liver enzymes (see Flow Chart).
- Safety monitoring (including e.g. vital signs, 12-lead ECGs 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 29.3 h (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.

- 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 first-in-class vanin inhibitor, has been thus far administered to 42 healthy subjects in the preceding FIH SRD study. This is the third trial with BI 1595043 and the first with administration under fed condition. Despite the novelty of the target, non-clinical safety data in relevant animal species, preliminary clinical data obtained in 1445-0001 SRD study, the inhibitory mode of action as well as the comprehensive risk assessment suggest that BI 1595043 is not a high-risk compound and support the application of BI 1595043 under fed condition in this trial.

Based on the risk mitigation strategy, 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 CD, 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 objective of this trial is to investigate the relative bioavailability of 30 mg of BI 1595043 under fed state (Test, T) compared with 30 mg of BI 1595043 under fasted state (Reference, R) following oral administration.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 1595043:

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for BI 1595043:

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

[redacted]

[redacted]

2.2.2.2 Safety and tolerability

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

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open-label, two-way cross-over trial in healthy male subjects in order to compare test treatment T (fed) and reference treatment R (fasted). The treatments will be one single dose of 30 mg of BI 1595043 administered as tablets in the fasting state (R) and one single dose of 30 mg of BI 1595043 administered as tablets in the fed state (T). The subjects will be randomly allocated to the 2 treatment sequences (T-R or R-T). For details, refer to Section 4.1.

There will be a washout period of at least 8 days between the treatments.

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

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

For relative bioavailability trials, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between treatments [R94-1529].

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that 14 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the trial (refer to Section 1.4.3.3).

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, body temperature), 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, i.e. 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 (i.e. condom)

   Unprotected sexual intercourse (i.e. without use of condom) 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 1.2.3), 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.

Due to teratogenicity observed in embryo-fetal development study in rat and the theoretically possible risk that relevant systemic concentrations being achieved in women of child-bearing potential (WOCBP) from exposure to seminal fluid of subject receiving BI 1595043, adequate contraception as outlined in Section 3.3.2 is a prerequisite for participation in the study.

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 <u>and</u> 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
7. The subject has a serious adverse event or a severe non-serious adverse reaction considered at least possibly related to the IMP administration.

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 (item No. 2 describes mandatory discontinuation criteria):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events (SAE), or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if 2 or more subjects experience an adverse event of moderate or greater intensity within the same system organ class (SOC), unless they have been demonstrated to be unrelated to study drug; or if any subject experiences a SAE, unless the SAE has been demonstrated to be unrelated to study drug.
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.

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item No. 3 applies).

3.3.5 Replacement of subjects

If more than 2 subjects do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number and will be assigned to the same treatment as the subject 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:	film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	**5 mg**
Posology:	1-0-0
Route of administration:	oral
Duration of use:	2 single doses separated by a washout period of at least 8 days

Substance:	**BI 1595043**
Pharmaceutical formulation:	film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	**25 mg**
Posology:	1-0-0
Route of administration:	oral
Duration of use:	2 single doses separated by a washout period of at least 8 days

4.1.2 Selection of doses in the trial

BI 1595043 dose selected in this trial is at the current predicted therapeutic dose of 30 mg (see Section 1.2.4).

BI 1595043 is a BCS class I compound with high permeability and high solubility. In SRD study (1445-0001), BI 1595043 was administered as oral solution and was rapidly absorbed with t_{max} of 0.75 or 1 hour, which is in line with BCS class I properties. In pre-clinical testing, tablet formulation had fast disintegration (1-3 min). Thus, no substantial difference in bioavailability is expected between oral solution and tablet formulation. Based on BCS class I properties, BI 1595043 exposures are expected to be minimally affected by food.

The selected dose of 30 mg is 3-fold lower than the maximum tested dose to date (90 mg) in the ongoing SRD study. At the dose of 30 mg, C_{max} is predicted to be 678 nM and AUC_{0-24} – 3,494 nM•h; these are about 3.7-fold and 3.3-fold lower, respectively, than the observed exposure after a single dose of 90 mg (C_{max} of 2,500 nM and AUC_{0-24} of 11,400 nM•h).

Overall, based on physical, chemical and PK properties, the exposure of 30 mg of BI 1595043 as tablet formulation under fed condition will unlikely exceed the observed exposure of 90 mg administered as oral solution in fasted state.

4.1.3 Method of assigning subjects to treatment sequences

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

The randomisation list will be provided to the trial site in advance.

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, numbers of the randomisation list will be allocated to the subjects by the method 'first come - first served' at the time of registration. Therefore, the allocation of subjects to treatment sequences is not influenced by trial personnel, but only by subjects' temporal availability. Subjects are then assigned to a treatment sequence 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

This trial is a two-way cross-over study. All subjects will receive the 2 treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R (Reference)	BI 1595043	film-coated tablet	5 and 25 mg	1 tablet 5 mg and 1 tablet 25 mg under **fasted** condition (single dose)	30 mg
T (Test)	BI 1595043	film-coated tablet	5 and 25 mg	1 tablet 5 mg and 1 tablet 25 mg under **fed** condition (single dose)	30 mg

In treatment R (in the fasted state), 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.

In treatment T (in the fed state), a high-fat, high-calorie meal will be served 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 2; this meal is in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269]. For restrictions with regard to diet, see Section 4.2.2.2.

Table 4.1.4: 2 Composition of the high-fat, high-calorie meal

Ingredients	kcal
2 chicken eggs (whole content) for scrambled eggs	192
10 g butter for frying scrambled eggs	75
35 g fried bacon	186
2 toasted slices of wheat bread	130
15 g butter for buttering toast slices	113

Ingredients	kcal
115 g hash brown potatoes	132
240 mL whole milk (3.5% fat)	156
Sum[1]	984

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

In each treatment period, 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 administration of trial medication, and – if applicable – its preparation (dispensing of BI 1595043), if correct dosage cannot be ensured otherwise.

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.

The treatments will be separated by a wash-out phase of at least 8 days.

4.1.5 Blinding and procedures for unblinding

This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

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

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

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.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

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 milk served with breakfast (see Table 4.1.4: 2), the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects).

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 of each study period is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 10 h before 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.

Subjects with pregnant or non-pregnant WOCBP partners should use male contraception (i.e. condom) to avoid exposure of an existing embryo/fetus. Additional contraception requirements detailed in Inclusion Criterion No. 5 must be considered.

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 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, body temperature), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of weight.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) 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.

Body temperature will be measured orally or under the armpit (axillary method) or in the ear (tympanic method) at each ambulatory visit, at admission to the trial site, and each day in the morning during in-house stay (refer to Flow Chart).

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 Haemoglobin Red Blood Cell Count (Erythrocytes), absol. Reticulocytes, absol. White Blood Cells (Leucocytes), absol. Platelet Count (Thrombocytes), absol.	X X X X X X	X X X X X X	X X X 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 Prothrombin time – INR (International Normalization Ratio) Fibrinogen	X X X	X X X	X X X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT ALT [Alanine transaminase] /GPT, SGPT Alkaline Phosphatase Gamma-Glutamyl Transferase Creatine Kinase [CK] Creatine Kinase Isoenzyme MB [only if CK is elevated] Lactic Dehydrogenase Lipase Amylase	X X X X X X X X X	X X X X X X X X X	X X X X X X X X X
Substrates	Glucose (Plasma) Creatinine Bilirubin, Total Bilirubin, Direct Protein, Total Albumin Albumin (Protein Electrophoresis) Alpha-1-Globulin (Protein Electrophoresis) Alpha-2-Globulin (Protein Electrophoresis) Beta-Globulin (Protein Electrophoresis) Gamma-Globulin (Protein Electrophoresis) C-Reactive Protein (Quant) Uric Acid Cholesterol, total Triglyceride	X X X X X -- X X X X X X X X X	X X X X X X -- -- -- -- -- X X X X	X X X X X X -- -- -- -- -- X X X X

Table 5.2.4.: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Hormones	Thyroid Stimulating Hormone Free T3 - Triiodothyronine Free T4 – Thyroxine	X X X	-- -- --	-- -- --
Electrolytes	Sodium Potassium Calcium	X X X	X X X	X X X
Urinalysis (Stix)	Urine Nitrite (qual) Urine Protein (qual) Urine Glucose (qual) Urine Ketone (qual) Urobilinogen (qual) Urine Bilirubin (qual) Urine RBC/Erythrocytes (qual) Urine WBC/Leucocytes (qual) Urine pH	X X X X X X X X X	X X X X X X X X X	X X X X X X X X X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 1 on Day -3 to -1; and on Day 2 and Day 5 in each treatment period (i.e. at Visits 2 and 3) (for time points refer to Flow Chart)
C: parameters to be determined at Visit 4 (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 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 in each treatment period 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

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

All ECGs will be stored electronically at the site.

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

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

5.2.6 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 Section 5.2.7.1.9 and Section 5.2.7.1.10, 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 5.2.7.1.10.

The following are considered as AESIs:

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

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

5.2.7.1.5 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 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 sufficiently assessed as 'chronic' or 'stable', or no further information can be obtained.

5.2.7.2.4 Pregnancy

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

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

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.

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 90 min, with interim storage of blood samples and aliquots at room temperature. 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.

Plasma samples will be transferred to [redacted].

After completion of the trial, the plasma samples may be used for further methodological investigations (e.g., assessment of metabolites). However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

[redacted]

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.

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.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods. At least 8 days will separate drug administrations in the first and second treatment periods.

On Day 1 of each treatment period, study participants will be admitted to the trial site 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. On all other study days, subjects will be treated in an ambulatory fashion.

For details on time points and procedures for collection of plasma 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 objective of this trial is to investigate the relative bioavailability of 30 mg of BI 1595043 in the fed state (Test, T) compared with 30 mg of BI 1595043 in the fasting state (Reference, R) following oral administration on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

[redacted]

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 1595043 in the fed state compared with BI 1595043 in the fasted state will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for BI 1595043 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

Relevant protocol deviations may be

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

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

- 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),
- The subject experiences emesis at any time during the labelled dosing interval.
- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

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

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

7.3.1 Primary endpoint analyses

Primary analyses

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

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

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

μ = the overall mean,

ζ_i = the ith sequence effect, i = 1, 2,

s_{im} = the effect associated with the mth subject in the ith sequence, m = 1, 2, ..., n_i

π_j = the jth period effect, j = 1, 2,

τ_k = the kth treatment effect, k = 1, 2,

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

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

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

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

[redacted]

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics’ (001-MCS-36-472) and will be assessed statistically using the same methods as described for the primary endpoints.

[redacted]

7.3.4 Safety analyses

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

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.6) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and follow-up 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 values defined as possibly clinically significant will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Subjects will be randomised to one of the 2 treatment sequences in a 1:1 ratio. The block size will be documented in the CTR.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation 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 enter a total of 14 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

Based on the previous SRD trial (see Section 1.2.5.2), the intra-individual coefficient of variation (gCV) for BI 1595043 is assumed to be roughly 23%.

For various assumptions around the gCV of 23%, Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for a value of 100% for the ratio T/R of geometric means.

Table 7.7: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratio of geometric means (T/R) for different gCVs and sample sizes N in a 2x2 crossover trial

gCV [%]	N	Precision**	Ratio [%]*	Lower CL [%]	Upper CL [%]
20	10	1.258	100	79.51	125.77
	12	1.219		82.01	121.93
	14	1.193		83.81	119.31
	16	1.174		85.18	117.40
23	10	1.301	100	76.88	130.07
	12	1.255		79.67	125.52
	14	1.224		81.67	122.44
	16	1.202		83.20	120.19
27	10	1.360	100	73.56	135.95
	12	1.304		76.68	130.42
	14	1.267		78.94	126.69
	16	1.240		80.67	123.97

*Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.
**Defined as ratio of upper CL and relative BA estimate.

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

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

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

The calculation was performed as described by Julious [R11-5230] using R Version 4.0.2.

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

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

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site:
The trial site(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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

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

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

The trial medication (BI 1595043) 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 will be performed at [redacted].

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

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n00271724	BI 1595043: In vivo mammalian erythrocyte micronucleus assay in rats. 05Mar2020.
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n00271739	BI 1595043: In vitro mammalian cell micronucleus assay in human peripheral blood lymphocytes (HPBL) cells. 09Mar2020.
n00272671	BI 1595043: neutral red uptake phototoxicity assay in BALB/c 3T3 mousefibroblasts. 24Feb2020.
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n00278622 A GLP Embryo-fetal Development Study of BI 1595043 by Oral Gavage in Rats.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		11 March 2021
EudraCT number **EU number**		2020-004924-40
BI Trial number		1445-0011
BI Investigational Medicinal Product(s)		BI 1595043
Title of protocol		A randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 1595043 as tablets with and without food 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. Section 1.4.3.3 2. Section 1.4.3.6 3. Section 3.3.2 4. Section 4.1.2 5. Section 4.2.2.2 6. Section 5.2.2
Description of change		1. Clinical relevance of the toxicology ophthalmology findings clarified to reflect two planned doses. 2. The data duplicating Section 4.1.2 removed. 3. Use of male contraception (i.e. condom) explicitly defined in study Inclusion Criterion No. 5 4. Section expanded to describe relevance of possible food effect and possible difference in bioavailability between oral solution and tablets. 5. Use of male contraception (i.e. condom) explicitly defined in the study restrictions for subjects with pregnant or non-pregnant WOCBP partners.6. Oral measurement of body temperature added.

Rationale for change		Changes are based on the regulatory feedback from FAMHP after review of the study protocol as part of the approval procedure. With this amendment minor inconsistencies in the study protocol have been corrected.

11.2 GLOBAL AMENDMENT 2

Date of amendment		08 April 2021
EudraCT number **EU number**		2020-004924-40
BI Trial number		1445-0011
BI Investigational Medicinal Product(s)		BI 1595043
Title of protocol		A randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 1595043 as tablets with and without food 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 3.3.4.3
Description of change		Item No. 2 of Discontinuation of the trial by the sponsor updated
Rationale for change		The change is based on FDA feedback after review of the trial protocol as part of the IND opening trial approval procedure.

11.3 GLOBAL AMENDMENT 3

Date of amendment		30 June 2021
EudraCT number **EU number**		2020-004924-40
BI Trial number		1445-0011
BI Investigational Medicinal Product(s)		BI 1595043
Title of protocol		A randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 1595043 as tablets with and without food 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		Title Page Clinical Trial Protocol Synopsis
Description of change		The Principal Investigator was changed to [redacted].
Rationale for change		The study has been handovered to the new Principal Investigator [redacted].

Boehringer Ingelheim

APPROVAL / SIGNATURE PAGE

Document Number: c34388550 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-version-04

Title: A randomised, open-label, single-dose, two-way cross-over relative bioavailability comparison of BI 1595043 as tablets with and without food in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	01 Jul 2021 09:50 CEST
Author-Trial Statistician		01 Jul 2021 09:52 CEST
Verification-Paper Signature Completion		01 Jul 2021 10:36 CEST
Approval-Team Member Medicine		01 Jul 2021 13:37 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed