Clinical Trial Protocol

	Document Number:	**c36040039-02**
EudraCT No.	2021-003389-10	
BI Trial No.	1346-0017	
BI Investigational Medicinal Product	BI 425809	
Title	Effect of fluconazole on the pharmacokinetics of a single oral dose of BI 425809 in healthy male subjects (an open-label, two-period fixed-sequence design study)	
Lay Title	A study in healthy men to test how fluconazole influences the amount of BI 425809 in the blood	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: + Fax: +	
Principal Investigator	[redacted] Phone: + Fax: +	
Status	Final Protocol (Revised Protocol (based on global amendment 1))	
Version and Date	Version: 2.0	Date: 22 September 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	03 August 2021
Revision date	22 September 2021
BI trial number	1346-0017
Title of trial	Effect of fluconazole on the pharmacokinetics of a single oral dose of BI 425809 in healthy male subjects (an open-label, two-period fixed-sequence design study)
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	Based on *in vitro* and *in vivo* data, CYP3A4 is involved in metabolism of BI 425809. It is therefore necessary to investigate whether co-administration of multiple doses of fluconazole, a moderate CYP3A inhibitor, affects single dose pharmacokinetics of BI 425809 in healthy male subjects
Trial objective	To investigate the effect of steady state exposure of fluconazole, a moderate CYP3A inhibitor, on the pharmacokinetics of BI 425809 in healthy subjects
Trial design	Open-label, two-period fixed-sequence trial with 2 treatments (R and T)
Trial endpoints:	Primary endpoints: $AUC_{0\text{-}215h}$ and C_{max} of BI 425809 Secondary endpoint: $AUC_{0\text{-}\infty}$ of BI 425809
Number of subjects **total entered** **each treatment**	 15 15
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Trial product 1 **dose** **mode of admin.**	BI 425809, 10 mg film-coated tablets 10 mg in Treatment Test and in Treatment Reference Oral with 240 mL of water after an overnight fast of at least 10 h

Trial product 2	Fluconazole, 200 mg hard capsules
dose	2x 200 mg (= 400 mg fluconazole) once daily during Treatment Test, only
mode of admin.	Oral with 240 mL of water
Duration of treatment	Treatment Reference: BI 425809, single dose Treatment Test: 2 capsules with 200 mg fluconazole (=400 mg) qd on study day -4 until study day +9 (total of 13 dosing days); on study day 1, BI 425809 (as single dose) will be administered 1 hour after fluconazole The BI 425809 single doses of Treatments Reference and Test will be separated by a wash-out period of at least 16 days.
Statistical methods	The effect of fluconazole on the pharmacokinetics of BI 425809 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 'subject' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to BI 425809 administration [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [8]	PK plasma (BI 425809)	PK plasma (fluconazole)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [5]
SCR	1	-21 to -1			Screening (SCR) [1]	A			x	x	
Treatment R (BI 425809 single dose)	2	1	-2:00	07:00	Admission to trial site	B[2,9]	x[2]	x[2]	x[2]	x[2]	x[2]
			-1:00	08:00	240 mL fluid intake						
			0:00	09:00	Administration of BI 425809						
			0:30	09:30			x				
			1:00	10:00			x				
			1:30	10:30			x				
			2:00	11:00	240 mL fluid intake		x				x
			3:00	12:00			x				
			4:00	13:00	240 mL fluid intake, Lunch [3]		x				x
			5:00	14:00			x				
			6:00	15:00			x				
			7:00	16:00	Light snack (voluntary)						
			8:00	17:00			x				
			10:00	19:00	Dinner						
			12:00	21:00			x				x
		2	24:00	09:00	Breakfast (voluntary) [3], discharge from trial site	B	x				x
		3	47:00	08:00	Ambulatory visit		x				x
		4	71:00	08:00	Ambulatory visit		x				x
		6	119:00	08:00	Ambulatory visit		x				x
		8	167:00	08:00	Ambulatory visit		x				x
		10	215:00	08:00	Ambulatory visit	C	x				x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to BI 425809 drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. See Flow Chart (cont.) on next page
5. 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.
6. Only applicable for Flow Chart for Treatment T
7. Only applicable for Flow Chart for Treatment T
8. Letters A, B, C and D (in Flow Chart below) define different sets of safety laboratory examinations (for details refer to Section 5.2.3).
9. Including urine drug screening and alcohol breath test

FLOW CHART (cont.)

Period	Visit	Day	Planned time (relative to BI 425809 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [8]	PK plasma (BI 425809)	PK plasma (fluconazole)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [5]
Treatment T (Fluconazole multiple dose + BI 425809 single dose)	3	-4	-97:00	08:00	Fluconazole administration				x		x
		-3	-73:00	08:00	Fluconazole administration						x
		-2	-49:00	08:00	Fluconazole administration						x
		-1	-25:00	08:00	Fluconazole administration	C					x
		1	-2:00	07:00	Admission to trial site	B[2,9]	x[2]		x[2]	x[2]	x[2]
			-1:00	08:00	Fluconazole administration			x[7]			
			0:00	09:00	Administration of BI 425809						
			0:30	09:30			x				
			1:00	10:00			x				
			1:30	10:30			x				
			2:00	11:00	240 mL fluid intake		x				
			3:00	12:00			x			x	
			4:00	13:00	240 mL fluid intake, Lunch [3]		x				x
			5:00	14:00			x				
			6:00	15:00			x				
			7:00	16:00	Light snack (voluntary)						
			8:00	17:00			x				x
			10:00	19:00	Dinner						
			12:00	21:00			x				x
		2	23:00	08:00	Fluconazole administration			x[7]			x
			24:00	09:00	Breakfast (voluntary) [3], discharge from trial site	B	x		x	x	x
		3	47:00	08:00	Fluconazole administration [6]		x	x			x
		4	71:00	08:00	Fluconazole administration [6]	C	x				x
		5	95:00	08:00	Fluconazole administration						x
		6	119:00	08:00	Fluconazole administration [6]	C	x				x
		7	143:00	08:00	Fluconazole administration						x
		8	167:00	08:00	Fluconazole administration [6]	C	x		x		x
		9	191:00	08:00	Fluconazole administration						x
		10	215:00	08:00	Ambulatory visit		x				x
FU	4	16 to 30			End of trial (EoTrial) examination [4]	D			x	x	x

1. See Flow Chart on previous page.
2. The time is approximate; the procedure is to be performed and completed within the 2 h prior to fluconazole drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. 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.
6. Immediately after PK blood sampling.
7. PK sampling pre-dose (tolerance with respect to planned time: -5 min); fluconazole administration on time.
8. Letters A, B, C and D define different sets of safety laboratory examinations (for details refer to Section 5.2.3).
9. Including urine drug screening and alcohol breath test

TABLE OF CONTENTS

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	attributable, legible, contemporaneous, original, and accurate
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	[redacted]
AUC_{0-215h}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 215 hours
[redacted]	[redacted]
[redacted]	[redacted]
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CIAS	Cognitive impairment associated with schizophrenia
CK	Creatine kinase
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in plasma
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CNS	Central Nervous System
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)

CSF	Cerebrospinal fluid
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
DRESS	Drug reaction with eosinophilia and systemic symptoms
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
GOT	Glutamic oxaloacetic transaminase
[redacted]	
IB	Investigator's brochure
IEC	Independent Ethics Committee
Ikr	Inward rectifier K+ current
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
[redacted]	[redacted]
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MCHC	Mean cell haemoglobin concentration
MCV	Mean corpuscular volume
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
NMDA	N-methyl-D-aspartate
NOAEL	No observed adverse event level
NSFS	Negative Symptom Factor Score
PANSS	Positive and Negative Syndrome Scale

PBPK	Physiologically-based pharmacokinetics
PD	Pharmacodynamic(s)
PE	Polyethylene
PfOS	Powder for reconstitution of an oral solution
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
qd/QD	once daily
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
RDW	Red cell distribution width
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
T	Test product or treatment
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAS	Visual analogue scale
[redacted]	[redacted]
XTC	Ecstasy

1. INTRODUCTION

BI 425809 is a glycine transporter 1 (GlyT1) inhibitor under development for treatment of cognitive impairment associated with schizophrenia (CIAS).

1.1 MEDICAL BACKGROUND

Schizophrenia is a chronic, severe, and disabling brain disorder affecting both men and women. The disease is characterised by abnormalities in glutamatergic pathways related to N-methyl-D-aspartate (NMDA) receptor hypofunction in cortical and hippocampal brain areas [R13-4518, R13-4521]. These abnormalities are hypothesised to lead to negative symptoms and cognitive impairment in schizophrenia. Existing treatment options for schizophrenia (i.e. first- and second-generation antipsychotics) primarily affect positive symptoms but have a limited effect on cognitive and negative symptoms [R15-0595]. Inhibition of GlyT1 aims at improving NMDA receptor hypoactivation by increasing the concentration of the NMDA receptor co-activator glycine in the synaptic cleft.

GlyT1 inhibitors have been tested in healthy volunteers and no serious adverse effects have been noted [R13-4450, R13-4451, R13-4508]. Proof of clinical concept has been reported for treatment of negative symptoms of schizophrenia in a Phase II clinical trial with the GlyT1 inhibitor Bitopertin (RG1678). In this trial, patients exhibited a larger reduction in the Positive and Negative Syndrome Scale (PANSS) Negative Symptom Factor Score (NSFS) compared with placebo [R15-1266]. However, subsequent Phase III clinical trials failed to demonstrate a significant effect on negative symptoms of schizophrenia [R18-1054]. The GlyT1 inhibitor prototype sarcosine also has been shown to improve positive, negative, and cognitive symptoms in patients with schizophrenia [R13-4447, R13-4524].

[redacted]

1.2 DRUG PROFILE

1.2.1 BI 425809

BI 425809 is a potent and selective inhibitor of GlyT1.

1.2.1.1 Non-clinical drug safety

[redacted]

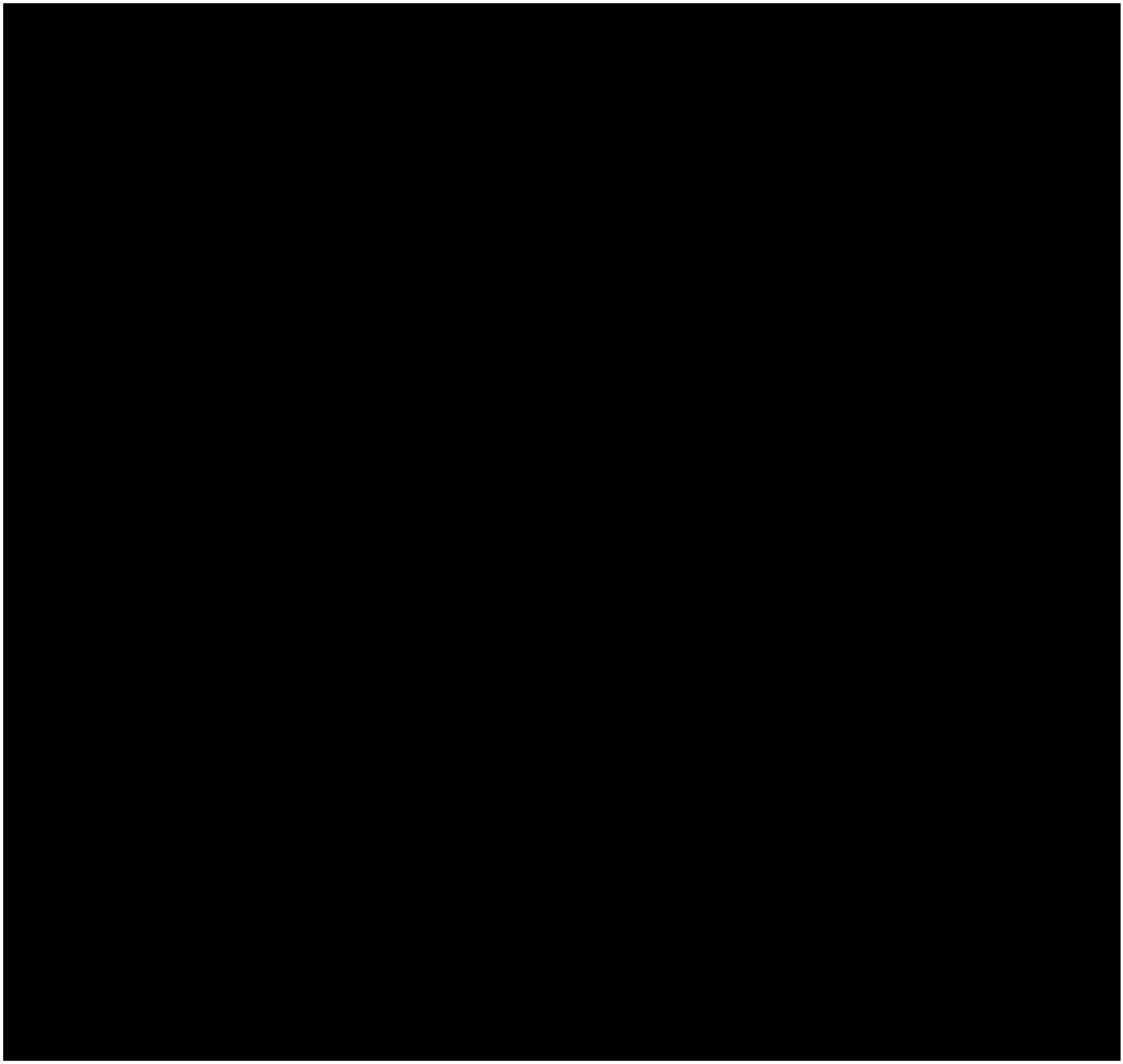
For details on the non-clinical pharmacology, pharmacokinetics in animals and toxicology results and for a detailed description of the BI 425809 PK profile please refer to the current IB [c02155957].

[redacted]

For a more detailed description of the BI 425809 profile, please refer to the current IB [c02155957].

1.2.1.3 Expected exposure of BI 425809 in this trial

[redacted]



1.2.2 Fluconazole

Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole [R21-2282].

Pharmacokinetics and drug metabolism

After oral administration fluconazole is well absorbed, and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose. Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing.

Fluconazole achieves good penetration in all body fluids studied. High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum.

Fluconazole is metabolised only to a minor extent. Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicinal product. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

Fluconazole is a moderate inhibitor of the isozymes CYP2C9 and CYP3A4: Concomitant intake of fluconazole 200 mg and midazolam (a CYP3A4 substrate) 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively [R21-2282], similar results were found in [R03-2551]. Fluconazole is also a strong inhibitor of the isozyme CYP2C19 [R21-2282].

Clinical safety in healthy volunteers:

For an overview of safety when fluconazole was used as a moderate inhibitor in healthy volunteer trials, a number of publications is cited here which use different treatment schedules for fluconazole ranging from

- administration of fluconazole (400 mg on day 1 and 200 mg qd on subsequent days) over 4 days in Scott et al. [R21-2438], over 7 days in Gupta et al. [R21-2439] or over 20 days in Gardin et al. [R21-2467],
- administration of fluconazole (400 mg qd) over 6 days in Mueck et al. [R13-3004] *to*
- administration of fluconazole (400 mg qd) over 11 days in Poggesi et al. [R21-2461] and Brings et al. [R21-2447], the latter including a loading dose of 800 mg fluconazole.

In these studies, fluconazole was - overall - safe and well tolerated. The adverse event most often described was headache of mostly mild, sometimes moderate intensity. However, due to the study designs, where other drugs under investigation were co-administered with fluconazole, proof of causality is challenging. Please find a more detailed description of the safety observed in the cited trials below.

- Scott et al. [R21-2438]: Trial medication lumiracoxib and fluconazole; 13 subjects included, 1 adverse event (headache in a subject receiving lumiracoxib plus fluconazole), starting 10 days after study drug administration, not considered drug-related
- Gupta et al. [R21-2439]: Trial medication tofacitinib and fluconazole; 12 subjects included, a total of six subjects reported 15 AEs. All were mild with the exception of 1 moderate case of headache during fluconazole treatment. The most frequently reported

treatment-emergent, all-causality AE was headache (reported in fours subjects). No deaths, severe AEs, SAEs or discontinuations. No clinically important changes in vital signs, clinical laboratory parameters or ECG.

- Gardin et al. [R21-2467]: Trial medication siponimod and fluconazole; 14 subjects enrolled of which 11 completed the study, two withdrew consent, and one discontinued due to an upper respiratory tract infection. In period 1 (siponimod alone), 11 subjects (79%) experienced AEs compared with eight subjects (73%) in period 2 (Siponimod + fluconazole). The most commonly reported AEs (≥ 10% of subjects) were headache, dizziness, somnolence, bradycardia, fatigue, seasonal allergy, and upper respiratory tract infection. The majority of AEs reported in the study were of mild intensity. The AEs of moderate intensity reported in the treatment groups were bradycardia and abdominal discomfort (siponimod alone) and headache and disturbance in attention (siponimod + fluconazole), all of which were resolved without any treatment. No deaths or SAEs were reported during the study. No clinically significant changes were observed in vital signs throughout the study. The most common ECG abnormality observed during the study was bradycardia. None of these events were considered clinically significant.

- Poggesi et al. [R21-2461: Trial medication erdafitinib and fluconazole; a total of 13/18 subjects experienced at least one treatment-emergent adverse event (TEAE), the most commonly reported one was headache. All TEAEs were Grade 1 or 2 in severity, no serious TEAE reported, no clinically significant laboratory safety abnormalities, no clinically meaningful ECG, physical examination, or vital signs observations reported during the study.

- Brings et al. [R21-2447]: Trial medication rivaroxaban, ciclosporin and fluconazole; 12 subjects included. Non-serious adverse events with possible, probable, or certain causal relationship to the trial drugs were hypomagnesemia (n=9), dry mouth (n=3), sensation of heat or cold in hands or feet (n=3), decline in plasma magnesium not reaching criteria for hypomagnesemia (n=2), headache (n=2), gastric pain (n=1), heartburn (n=1), muscle ache (n=1), flank pain (n=1), pruritic lower arm exanthema (n=1), hypertrichosis (n=1), hyperkalemia (n=1), isolated increase in bilirubin (n=1), increase in creatine kinase (CK) and glutamic oxaloacetic transaminase (GOT) (n=1), anemia (n=1). All adverse events were mild and resolved or were resolving at the end of trial.

  QTcF increased during fluconazole by 11.4 ± 6.0 ms (range 5-23 ms, $P < 0.01$). QTcF or relative change in QTcF did not correlate with fluconazole concentration. However, in the present trial ECGs were done primarily for safety reasons and not to evaluate effects on QTc. Thus, the authors obtained only single ECG recordings, the screening ECG could be obtained later in the day, and participants were not required to be fasting at screening and on the fifth day of fluconazole. Thus, also circadian variability or food effects may have influenced QTc.

Clinical safety in patients:

According to the German "Fachinformation", the most frequently (≥1/100 to <1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash (see also Section 1.4.3.2).

Fluconazole (Diflucan®) has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking Diflucan. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant treatment that may have been contributory.

Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

For a detailed description of the fluconazole profile, please refer to the German 'Fachinformation' [R21-2282].

1.2.3 Residual Effect Period

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

[redacted]

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Expected benefit for the target population

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 425809 which

may help to treat patients suffering from CIAS. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

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.

ECG electrodes may cause local and typically transient skin reactions.

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

1.4.3.1 Risks related to the administration of BI 425809

For clinical safety in healthy subjects observed so far upon administration of BI 425809 please refer to Section 1.2.1.2. [redacted]

[redacted]

1.4.3.2 Risks related to the administration of fluconazole

Fluconazole (Diflucan®) is a market-approved drug. The dose used in this trial (400 mg qd for 13 days) is within the therapeutic range used for patients to treat fungal infections [R21-2282] .

Based on the German 'Fachinformation' for Diflucan®, the following adverse reactions have been observed and reported during treatment with Diflucan with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Common: Headache, abdominal pain, vomiting, diarrhea, nausea, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, rash

Uncommon: Anaemia, decreased appetite, somnolence, insomnia, seizures, paraesthesia, dizziness, taste perversion, vertigo, constipation, dyspepsia, flatulence, dry mouth, cholestasis, jaundice, bilirubin increased, drug eruption, urticarial, pruritus, increased sweating, myalgia, fatigue, malaise, asthenia, fever

Rare: Agranulocytosis, leukopenia, thrombocytopenia, neutropenia, anaphylaxis, hypercholesterolaemia, hypertriglyceridaemia, hypokalemia, tremor, torsade de pointes, QT prolongation, hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous-pustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Risk mitigation hepatic injury:

- During fluconazole dosing phase laboratory liver parameters will be regularly assessed
- Only subjects with liver parameters AST, ALT and GGT within normal range will be allowed to participate in the trial (see Section 3.3.3)
- In case of relevant increase in liver enzymes or hepatic injury (DILI), subjects will discontinue trial treatment (see Section 3.3.4.1)

Risk mitigation QT prolongation:

- Subjects with baseline disease (such as pro-arrhythmic conditions) will be excluded from the trial
- No concomitant therapy prolonging the QT interval will be allowed
- During fluconazole dosing phase ECG will be assessed regularly for potential QT prolongation
- Laboratory tests (including determination of potassium levels) will be performed

Risk mitigation dermatological reaction:

- In case a rash occurs during the fluconazole dosing phase which is attributable to fluconazole treatment, the respective subject will discontinue study treatment (see Section 3.3.4.1)

For further risks and side-effects associated with the administration of Diflucan® please refer to the German 'Fachinformation' [R21-2282].

1.4.3.3 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 5.2.5.1.4, adverse events of special interest.

1.4.3.4 Risk assessment in the context of SARS-CoV-2 pandemic

This Phase I study is planned to be conducted in healthy volunteers, aged 18-55 years. These healthy subjects do not belong to the population at higher risk for severe illness from COVID-19. This population is not at higher risk of severe COVID-19 infection, and study participation would not increase the risk of becoming infected with SARS-CoV-2 beyond the potential risk associated with any need for the study participant to leave his home for study related activities [adapted from c32354247, "Benefit-Risk assessment in context of COVID-19 injection"].

Risk mitigation SARS-CoV-2 pandemic:

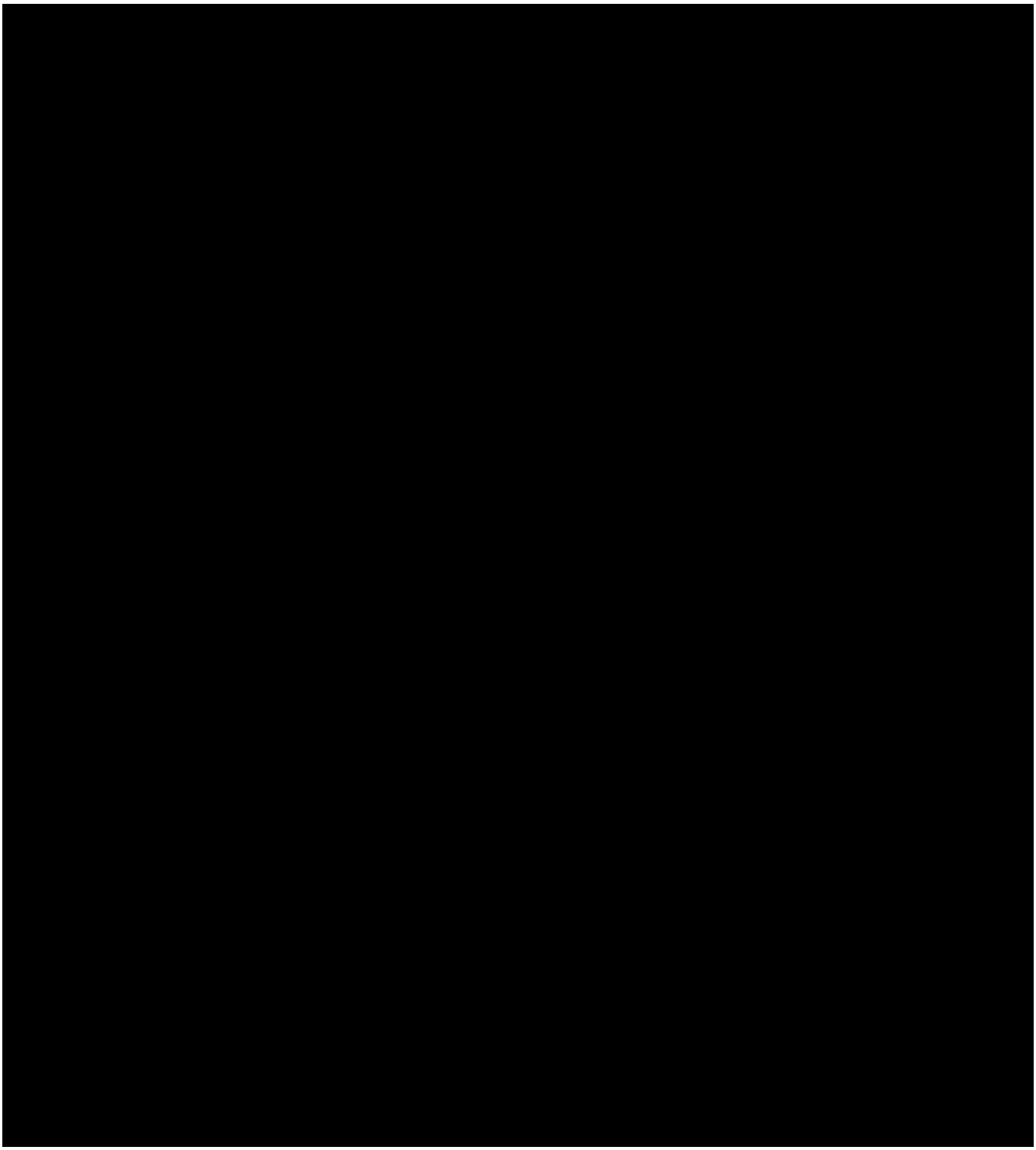
- A risk management plan has been set up at the clinical site that details specific precautionary measures (e.g. hygienic rules, wearing of face masks, physical distancing), which will be filed in the ISF. These measures were implemented per local requirements in Baden-Württemberg and recommendation by the Robert Koch Institute. The local requirements may be subject to change and the trial procedures will be adapted accordingly, if applicable
- AEs will be closely monitored and guidance pertaining to treatment and management of acute infections occurring during the trial will be provided
- Trial participants will be screened for SARS-CoV-2, e.g. via polymerase chain reaction (PCR) test, prior to screening (see also exclusion criterion #23) and at various time points during the trial
- During the ambulatory visits, subjects are allowed to enter the site only after it was confirmed that subjects do not have any signs or symptoms of infection (e.g. fever)
- In case SARS-CoV-2 infection is suspected in a subject during trial participation, PCR testing will be initiated without delay to enable the investigator to take decisions about the next steps (e.g. according to Section 3.3.4.1)
- Any subject with suspected or diagnosed COVID-19 will be referred to health care professionals in charge to receive treatment according to standard of care

SARS-CoV-2 vaccination

Diminished response to the vaccine in subjects receiving BI 425809 is unlikely as there is no immunocompromised condition or immunosuppressant treatment present in healthy volunteers. It is not expected that there would be any interaction between vaccinations and the use of BI 425809 ["bi-425809-cias-sars-cov-2-vaccination-statement-letter-for-sites", document on file]. However, potential side effects of a vaccination may be hard to distinguish from adverse events induced by BI 425809 or fluconazole. Therefore, exclusion criterion #11 includes a statement to avoid SARS-CoV-2 vaccination during this rather short trial.

1.4.4 Overall assessment of benefit-risk ratio

BI 425809 is a potent and selective inhibitor of GlyT1 that has been adequately characterized in pre-clinical studies. [redacted]



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 effect of a moderate CYP3A inhibitor, fluconazole, under steady state conditions on the pharmacokinetics of BI 425809 (Reference Treatment R: BI 425809 alone; Test Treatment T: BI 425809 given under steady state conditions of fluconazole).

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 425809:

- $AUC_{0\text{-}215h}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 215 hours post administration of BI 425809)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for BI 425809:

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

2.2.2.3 Safety and tolerability

Safety and tolerability of BI 425809 and fluconazole 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 non-randomised, open-label, 2-period fixed-sequence crossover trial in healthy male subjects in order to compare the Test Treatment (T) to the Reference Treatment (R). An overview of both treatments is given below, for details refer to Section 4.1.

Reference Treatment, R

- One 10 mg tablet BI 425809 given alone on Day 1 of period 1

Test Treatment T

- One 10 mg tablet BI 425809 given one hour after the administration of fluconazole on Day 1 of period 2; dosing with fluconazole will start from Day -4 (pre administration of BI 425809) and will continue through Day 9 (post administration of BI 425809); dosing regimen for fluconazole is 400 mg qd

Treatments with BI 425809 will be given under fasting conditions. Reference Treatment will always be followed by the Test Treatment in a fixed sequence. The treatment periods will be separated by a wash-out phase of at least 16 days between the administrations of BI 425809.

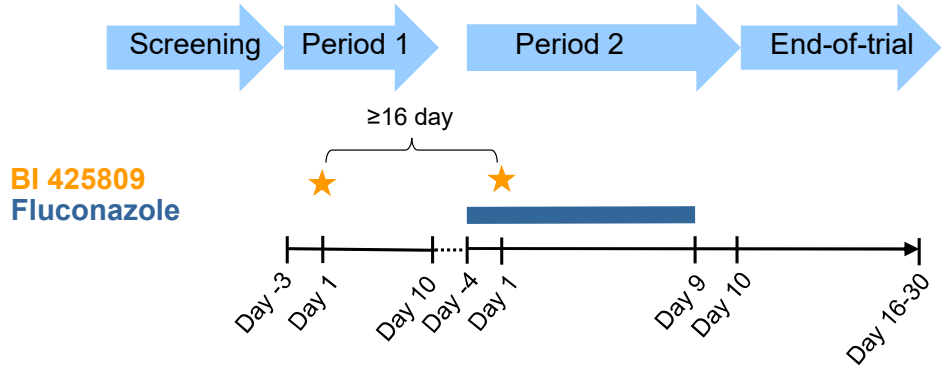


Figure 3.1: 1 Trial design

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 GROUPS

For this relative bioavailability trial, 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].

Because of the long (~ 44 hours) half-life of BI 425809 (10 mg) and because of the different treatment time schedules and in order to avoid overlapping inhibitory effects, a fixed-sequence design is selected, in which fluconazole will be administered in the second study period only. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects since nonspecific time-effects are unlikely due to the short trial duration.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 15 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including 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. Relevant gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders

6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medications or their excipients, and to azole derivates)
11. Use of drugs within 21 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation) or vaccination of any kind within 21 days of planned administration of trial medication or any vaccination requiring re-vaccination during the course of the trial
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 24 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection
24. Known hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption
25. Liver enzymes (ALT, AST, GGT) or serum creatinine above upper limit of normal range at screening examination, confirmed by a repeat test; creatinine clearance (according to CKD EPI formula) is lower than 80 ml/min confirmed by a repeat test
26. Subjects with any other condition that would preclude administration of fluconazole as per German SmPC

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.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN
6. The subject has an elevation of AST and/or ALT ≥ 1.5-fold ULN and a control blood sample, which will be withdrawn on the next day, confirms further meaningful increase of the respective parameter. It is with the investigator to evaluate the clinical significance of this increase taking into account its occurrence in relation to the 13 days of fluconazole treatment
7. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
8. In case a rash occurs during the fluconazole dosing phase which is attributable to fluconazole treatment, the respective subject will discontinue study treatment

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported
3. Violation of GCP or the CTP impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product

3.3.5 Replacement of subjects

In case more than 3 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.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 425809 will be provided by BI Pharma GmbH & Co. KG, Germany. Fluconazole (Diflucan®) will be obtained from a public pharmacy.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the investigational medicinal product fluconazole are:

Name:	Diflucan®
Substance:	Fluconazole
Pharmaceutical formulation:	Hard capsule
Source:	[redacted]
Unit strength:	200 mg
Posology:	2-0-0
Route of administration:	oral
Duration of use:	13 days (Day -4 to Day 9) in Visit 3 (Test Treatment)

4.1.2 Selection of doses in the trial

The clinically recommended dose of fluconazole is 200 to 400 mg qd. Only in exceptional cases, for treatment of severe or life-threatening conditions daily dose may be increased to 800 mg. Thus, fluconazole 400 mg qd reflects the highest standard clinical dose and is considered sufficient to result in a moderate CYP3A4 inhibition. In the absence of a publication clearly showing that maximum fluconazole-induced inhibition of CYP3A can be induced by 200 mg daily already and guided by literature suggesting that 400 mg fluconazole qd may have a stronger inhibitory effect than 200 mg qd [R21-2447], a dosing regimen for this trial with 400 mg fluconazole qd was chosen. This dosing regimen also fulfils regulatory requirements that the highest generally recommended clinical dose be used for interaction

studies [R20-2271, P15-06991]. A dosing period of 13 days has been chosen for fluconazole 400 mg qd which is in accordance with Liu et al. [R17-3744] suggesting (for itraconazole) that subchronic dosing (i.e. ≤ 14 days) may have a lower risk of liver injury as opposed to chronic dosing. At the same time this period is long enough to cover the long half-life of BI 425809.

[redacted]

4.1.3 Method of assigning subjects to treatment groups

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable (for safety margin to exposure reached in previous single and multiple rising dose trials refer to Section 1.2.1.3; for discussion of study-associated risks and safety measures see Section 1.4.3).

Prior to the start of the study, subjects willing to participate will be recruited to cohorts according to their temporal availability. There will only be one treatment sequence investigated in this trial, i.e., each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a study subject number by drawing lots prior to first administration of trial medication in the morning of Day 1 of Visit 2.

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

4.1.4 Drug assignment and administration of doses for each subject

This trial is a non-randomised 2-period fixed-sequence crossover study. All subjects will receive the 2 treatments in a fixed sequence (Reference always followed by Test)

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 daily dose
R (Reference)	BI 425809	Film-coated tablet	10 mg	1 tablet as single dose	10 mg
T (Test)	BI 425809	Film-coated tablet	10 mg	1 tablet as single dose	10 mg
	Fluconazole	Hard capsule	200 mg	2 capsules (=400 mg) qd for 13 days **On Day 1 the dose is given 1 h prior to BI 425809**	400 mg

Administration of BI 425809 will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. For intake of fluconazole no fasting

is required (with exception of intake of fluconazole on Day 1 of period 2 where fasting is applicable due to subsequent administration of BI 425809 and on Day 2 of period 2 where fasting is applicable due to safety lab).

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 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 (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until 24 h after administration of BI 425809. During the first 4 h after administration of BI 425809, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture), unless required for medical procedures. For restrictions with regard to diet, see Section 4.2.2.2.

The administrations of BI 425809 will be separated by a wash-out phase of at least 16 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.

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

BI 425809

BI 425809 tablets 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.

Fluconazole

Fluconazole will be obtained by the clinical trial site from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.

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
- 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 Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. In particular, concomitant use of drugs known to be metabolized via CYP3A4 or drugs known to prolong the QT interval, are

prohibited. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after intake of BI 425809.

On Day 1 of both treatment periods, starting from 1 h before intake of BI 425809 (i.e. from planned time -1:00) until lunch, fluid intake is restricted to 240 mL of water at planned time -1:00 either with [period 2] or without [period 1] intake of fluconazole), 240 mL with intake of BI 425809, and an additional 240 mL of water at 2 h and 4 h after administration of BI 425809.

In both periods, total fluid intake on Day 1 is restricted to 3000 mL from lunch until 24 h post administration of BI 425809.

Green tea, 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 sampling of the trial.

Alcoholic beverages are not permitted starting 48 h before first trial drug administration until last PK sampling of the trial.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed during in-house confinement at the trial site.

Smoking is not allowed during in-house confinement at the trial site.

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

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

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

5.2.2 Vital signs

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

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required. Fasting is not required for safety lab C (see Flow Chart and Table 5.2.3: 1).

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]	D[1]
Haematology	Haematocrit	X	X	--	X
	Haemoglobin	X	X	--	X
	Red Blood Cell Count/Erythrocytes	X	X	--	X
	Reticulocytes, absol.	X	--	--	X
	Reticulocytes/Erythrocyte	X	--	--	X
	White Blood Cells/Leucocytes	X	X	--	X
	Platelet Count/Thrombocytes (quant)	X	X	--	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	--	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	--	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.				
Coagulation	Activated Partial Thromboplastin Time	X	X	--	X
	Prothrombin time – INR (International Normalization Ratio)	X	X	--	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X	X
	Alkaline Phosphatase	X	X	X	X
	Gamma-Glutamyl Transferase	X	X	X	X
	Creatine Kinase [CK]	X	--	--	--
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	--	--	--
Hormones	Thyroid Stimulating Hormone	X	--	--	--
Substrates	Glucose (Plasma)	X	X	--	X
	Creatinine	X	X	--	X
	GFR/ CKD-EPI[3]	X	--	--	--
	Bilirubin, Total	X	X	--	X
	Bilirubin, Direct	X	X	--	X
	Protein, Total	X	X	--	X
	C-Reactive Protein (Quant)	X	X	--	X
Electrolytes	Sodium	X	X	--	X
	Potassium	X	X	--	X
Urinalysis[2] (Stix)	Urine Nitrite (qual)	X	X	--	X
	Urine Protein (qual)	X	X	--	X
	Urine Glucose (qual)	X	X	--	X
	Urine Ketone (qual)	X	X	--	X
	Urobilinogen (qual)	X	X	--	X
	Urine Bilirubin (qual)	X	X	--	X
	Urine RBC/Erythrocytes (qual)	X	X	--	X
	Urine WBC/Leucocytes (qual)	X	X	--	X
	Urine pH	X	X	--	X
Urine sediment[2] (microscopic examination)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)				

1 A, B, C and D refer to different sets of laboratory parameters. The Flow Chart details at which time point which set is to be investigated
2 Microscopic examination if erythrocytes, leukocytes, nitrite or protein are abnormal in urine
3 Estimated glomerular filtration rate according to CKD-EPI formula [R12-1392]

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

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. [redacted], [redacted]) will be performed prior to each the study at the discretion of an investigator or designee. The results will not be included in the CTR.

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

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

5.2.4 Electrocardiogram

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

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

All ECGs will be recorded for 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 to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System ([redacted]). Electrode placement will be performed according to the

method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

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

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

5.2.5 Assessment of adverse events

5.2.5.1 Definitions of adverse events

5.2.5.1.1 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.

5.2.5.1.2 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

5.2.5.1.3 AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in 5.2.5.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

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

5.2.5.1.4 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 5.2.5.2.2.

The following are considered as AESIs:

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

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

test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.5.1.5 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

5.2.5.1.6 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

5.2.5.2 Adverse event collection and reporting

5.2.5.2.1 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.

5.2.5.2.2 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 immediately (without undue delay) 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 send 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.

5.2.5.2.3 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.

5.3 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.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis of BI 425809

For quantification of BI 425809 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 x g to 4000 x 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 first aliquot will be used for analysis of BI 425809 ('A1 - BI'), the second aliquot ('A2 - BI') may be used for analysis of fluconazole (only applicable for PK samples from period 2) if not needed for analysis of BI 425809. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min, with interim storage of blood samples 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. The second aliquot may only be used for fluconazole analysis after the bioanalyst has acknowledged receipt of valid data from BI 425809 analysis (only applicable for PK samples from period 2).

At a minimum, the sample tube labels should list BI trial number, subject number, visit, planned sampling time, and aliquot (‘A1 - BI’ or ‘A2 - BI').

After successful analysis, the samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) and fluconazole 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 has been archived.

5.3.2.2 Blood sampling for pharmacokinetic analysis of fluconazole

For quantification of fluconazole trough 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 x g to 4000 x g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot (‘A1 - FL’) should contain at least 0.5 mL of plasma. The second aliquot (‘A2 - FL’) may contain less. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min, with interim storage of blood samples 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, visit, planned sampling time, and aliquot (‘A1 - FL’ or ‘A2 - FL').

After successful analysis, the samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) and fluconazole 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 has been archived.

[redacted]

5.4 BIOBANKING

Not applicable.

5.5 OTHER ASSESSMENTS

5.5.1 Pharmacogenomic evaluation

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

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the CTR. However, the data may be part of the CTR, if necessary.

5.6 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' BI 425809 administration on Day 1 are to be performed and completed within a 3 h-period prior administration of BI 425809.

In ambulatory visits prior to administration of BI 425809 in period 2, the acceptable deviation from the scheduled time for ECG and laboratory tests will be -15 min.

Following administration of BI 425809, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 45 min until Day 6. From Day 8 onwards, a deviation from the scheduled time for fluconazole administration, safety laboratory tests, and ECG of ± 60 min is acceptable.

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.4.

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.5).

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days 1, 2, 3, 4, 6, 8 and 10 in the treatment period 'Reference' and Days -4 through Day 10 in the treatment period 'Test').

At least 16 days will separate BI 425809 drug administrations in the first and second treatment period.

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 24 h following administration of BI 425809. 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 the Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 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 Section 5.2.
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 10 mg of BI 425809 under steady state exposure of fluconazole (Test, T) compared with 10 mg of BI 425809 alone (Reference, R) following oral administration on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Sections 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 425809 under steady state exposure of fluconazole (Test) compared with BI 425809 alone (Reference) 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 deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

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 and Section 2.2 for BI 425809 and fluconazole will be calculated according to the relevant BI internal procedures.

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)
- A predose concentration of BI 425809 is >5% C_{max} value of that subject in the respective treatment period
- 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 (refer to Section 2.1.2) will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subjects and treatment. The effect 'subjects' will be considered as random, whereas the effect 'treatment' will be considered as fixed. The model is described by the following equation:

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

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

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., 15

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

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

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

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

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

Further exploratory analyses

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

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

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures 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 1.2.3) 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 5.2.5.1.4), 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 BI internal procedures.

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

7.6 RANDOMISATION

This is a non-randomised trial.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 15 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.

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. 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 respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

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

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

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

For subjects enrolled during the COVID-19 pandemic: In addition to the study-specific informed consent, separate written consent will be obtained for testing for SARS-CoV-2 infection.

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.

[redacted] In the [redacted] – the validated [redacted] system is used for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, [redacted] serves as database. Instead of being entered into CRFs, selected data are directly entered into the [redacted] system.

8.3.1 Source documents

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

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

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.

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [redacted] 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 Manager, Clinical Research Associates, and investigators of the participating trial site

The trial medication (BI 425809) will be provided by the [redacted]. Fluconazole (Diflucan®) will be purchased by the clinical site at a public pharmacy.

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

Analyses of BI 425809 concentrations in plasma will be performed at [redacted]. Analyses of fluconazole 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 by BI according to BI SOPs.

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

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		22 September 2021
EudraCT number		2021-003389-10
BI Trial number		1346-0017
BI Investigational Medicinal Product		BI 425809
Title of protocol		Effect of fluconazole on the pharmacokinetics of a single oral dose of BI 425809 in healthy male subjects (an open-label, two-period fixed-sequence design study)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed	--- 1.2.1.3 3.3.4.1 5.2.5.2.2	Flow Chart Expected exposure of BI 425809 in this trial Discontinuation of trial treatment AE reporting to the sponsor and timelines
Description of change	Flow Chart 1.2.1.3 3.3.4.1 5.2.5.2.2	Increased the frequency of safety laboratory assessment for liver enzymes; corrected two errors: Actual clock time at PTM -2:00 and a missing cross for AE questioning on Day 10 of Visit 3 Correction of unit in table 1.2.1.3: 1 Added an additional discontinuation criterion for increase of liver enzymes above ULN Deleted “within 24 hours”, instead adopted the wording from the European Commission guidance document “CT-3”
Rationale for change	Flow Chart 1.2.1.3 3.3.4.1 5.2.5.2.2.	Request by HA and EC (deficiency letter) and correction of 2 errors Errors in unit corrected Request by HA and EC (deficiency letter) Request by HA and EC (deficiency letter)

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	23 Sep 2021 09:48 CEST
Verification-Paper Signature Completion		23 Sep 2021 09:54 CEST
Author-Statistician		23 Sep 2021 12:32 CEST
Approval-Team Member Medicine		23 Sep 2021 21:43 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed