Clinical Trial Protocol

	Document Number:	**c21363182-03**
EudraCT No.	2018-001194-24	
BI Trial No.	1346-0015	
BI Investigational Medicinal Product	BI 425809	
Title	Investigation of pharmacokinetics and absolute oral bioavailability of BI 425809 administered as an oral dose with an intravenous microtracer dose of [C-14]-BI 425809 in healthy male volunteers	
Lay Title	A study in healthy men to measure the amount of BI 425809 in the blood when taken as a tablet	
Clinical Phase	I	
Clinical Trial Leader	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol	
Version and Date	Version: 2.0	Date: 07 Jan 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	26Nov2018
Revision date	07Jan2019
BI trial number	1346-0015
Title of trial	Investigation of pharmacokinetics and absolute oral bioavailability of BI 425809 administered as an oral dose with an intravenous microtracer dose of [C-14]-BI 425809 in healthy male volunteers
Principal Investigator:	
Trial site	
Clinical phase	I
Trial rationale	This trial is intended to examine the absolute oral bioavailability of BI 425809 as tablet formulation for oral administration. The data are considered necessary to further support the understanding of the pharmacokinetics of BI 425809.
Trial objective	To determine the absolute oral bioavailability of BI 425809
Trial design	Non-randomized, open-label, single period, single arm
Trial endpoints:	*Primary endpoints:* $AUC_{0-\infty}$ of [^{14}C]-BI 425809 i.v. $AUC_{0-\infty}$ of BI 425809 p.o. *Secondary endpoints:* Oral route: C_{max} of BI 425809 p.o.
Number of subjects	
total entered	6
each treatment	6
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 65 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Trial product 1	BI 425809 film-coated tablet (Treatment Test (T))
dose	25 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Trial product 2	BI 425809 (C-14) as intravenous solution (Treatment Reference (R))
dose	30 µg BI 425809 consisting of 27 µg unlabelled BI 425809 mixed with 3 µg labelled [C-14]-BI 425809 in 10 mL intravenous solution (3 µg BI 425809 (C-14) /mL) The radioactive dose per infusion will be ~0.011 MBq
mode of admin.	Intravenous infusion of 15 min at ~ t_{max} (4 h) of 25 mg tablet after an overnight fast of at least 10 h

Duration of treatment	Intravenous dose (Treatment R): Single intravenous infusion of microtracer over 15 min, Day 1 Oral dose (Treatment T): Single oral dose, Day 1
Statistical methods	Absolute bioavailability (F) will be estimated by the ratios of the geometric means (test/reference) for the primary endpoints $AUC_{0-\infty}$ (dose normalized). Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range is not specified. The statistical model will be an ANOVA on the logarithmic scale including the fixed effect for 'formulation' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	$PK_{plasma\ BI\ 425809}$	$PK_{plasma\ [C-14]-BI\ 425809}$	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[2]
1	-21 to -2			Screening (SCR)[1]	x			x	x	
2	-1	-18:00	14:00	Admission to trial site	x[5]					x
		-14:00	18:00	Dinner						
		-10:30	21:30	Snack (voluntary)						
	1	-2:00	06:00			x[3]		x[3]	x[3]	x[3]
		0:00	08:00	**Drug administration (BI 425809, 25 mg tablet, oral)**						
		1:00	09:00			x		x		
		2:00	10:00	240 mL fluid intake		x		x		
		3:00	11:00			x	x			x
		4:00	12:00	**Start of IV infusion containing [C-14]-BI 425809** 240 mL fluid intake						
		4:05	12:05			x	x			
		4:10	12:10				x			
		4:15	12:15	**Stop of IV infusion containing [C-14]-BI 425809**			x			
		4:30	12:30	Lunch[4]			x			
		5:00	13:00				x			
		6:00	14:00			x	x			
		7:00	15:00				x			
		8:00	16:00	Snack (voluntary)[4]		x	x	x	x	x
		11:00	19:00	Dinner						
		12:00	20:00			x	x			x
		16:00	24:00				x			
	2	24:00	08:00	Breakfast (voluntary)[4], discharge from trial site	x	x	x	x	x	x
	4	72:00	08:00	Ambulatory visit		x	x			x
	6	120:00	08:00	Ambulatory visit	x	x	x			x
	8	168:00	08:00	Ambulatory visit		x	x			x
3	12 to 15			End of trial (EOT) examination[6]	x			x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy, and review of inclusion/exclusion criteria.
2. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
3. The time is approximate; the procedure is to be performed and completed within 2 h prior to drug administration.
4. If several actions are indicated at the same time point, the intake of meals will be the last action.
5. Including urine drug screening and alcohol test.
6. End of trial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.

TABLE OF CONTENTS

ABBREVIATIONS

AD	Alzheimer's Disease
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	Attributable, legible, contemporaneous, original, accurate
AMS	Accelerator mass spectometry
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
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
aVR	Augmented Voltage Right
aVL	Augmented Voltage Left
aVF	Augmented Voltage Foot
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CI	Confidence interval
CIAS	Congnitive impairment associated with schizophrenia
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CRO	Contract Research Organisation
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supplies Unit
DILI	Drug induced liver injury

ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FDA	Food and Drug Administration
Fp.o.(%)	Absolute bioavailability after oral administration
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GlyT1	Glycine transporter 1
gMean	Geometric mean
HR	Heart rate
IB	Investigator's brochure
ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IQRM	Integrated Quality and Risk Management Process
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MBq	MegaBequerel
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time of the analyte in the body after intravenous bolus administration
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
NMDA	N-methyl-D-aspartate
PEG	PolyEthylene Glycol
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
qd	quaque die

QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
ss	(at) steady state
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
Vdss	Volume of distribution at steady state after single intravenous administration
Vdz	Volume of distribution after single intravenous administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
XTC	Ecstasy

1. INTRODUCTION

BI 425809 is a glycine transporter 1 (GlyT1) inhibitor that is being developed for symptomatic treatment of Alzheimer's Disease (AD) and cognitive impairment associated with schizophrenia (CIAS).

1.1 MEDICAL BACKGROUND

Schizophrenia and AD are chronic, severe, and disabling brain disorders affecting both men and women. Both disorders are characterized by abnormalities in glutamatergic pathways related to N-methyl-D-aspartate (NMDA) receptor hypofunction in cortical and hippocampal brain areas. These abnormalities are hypothesized to lead to negative symptoms and cognitive impairment in schizophrenia and cognitive impairment in AD. Inhibition of GlyT1 aims at improving NMDA receptor hypoactivation in patients with schizophrenia and AD by increasing the concentration of the NMDA receptor co-activator glycine in the synaptic cleft, thereby leading to improvement of negative and cognitive symptoms in patients with schizophrenia (as add-on therapy to antipsychotics) as well as to cognitive improvement in AD patients (as add-on therapy to acetylcholinesterase inhibitors).

1.2 DRUG PROFILE

1.2.1 Non-clinical pharmacokinetics

1.2.2 Non-clinical safety pharmacology and toxicology

For a more detailed description of the BI 425809 profile, please refer to the current Investigator's Brochure (IB) [c02155957-08].

1.2.3 Residual Effect Period

1.2.4 Clinical experience in humans

For a more detailed list of observed AEs and safety measures please refer to the current Investigator's Brochure, section 6 [c02155957-08].

1.2.5 Clinical pharmacokinetics

For a more detailed description of the BI 425809 profile please refer to the current Investigator's Brochure [c02155957-08].

1.3 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the absolute oral bioavailability of BI 425809 using an intravenous [C-14]-microtracer approach. The data are considered necessary to further support the understanding of the pharmacokinetics of BI 425809.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of BI 425809. The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling or intravenous infusion may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venepuncture for blood sampling.

The solvent for the intravenous infusion containing a mixture of labelled and unlabelled BI 425809 is 20% PEG 400 in saline. Therefore, in case of inadvertent paravenous drug administration apart from local swelling no tissue damage is expected.

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

Drug-related risks and safety measures

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and

follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety, see also Section 5.2.6.1.4, adverse events of special interest.

Risks related to oral BI 425809 administration

The currently available data from 7 phase I trials in healthy young and elderly subjects with single oral administration of up to 150 mg BI 425809 and multiple doses of up to 75 mg BI 425809 twice daily (150 mg/d), indicate that BI 425809 has a broad safety margin and is generally well tolerated. The most frequent AEs were adverse CNS symptoms, most commonly headaches that showed a trend for dose dependency, were reversible and can be clinically monitored. In addition, BI 425809 may be associated with visual disturbances, and somnolence (drowsiness). These effects are understood to be mostly mild to moderate and transient. Decreased haemoglobin is a potential risk based on preclinical data and class effect; however, no clear decrease in haemoglobin was seen in BI 425809 treated subjects compared to placebo in phase I trials so far.

Risks related to M232 (BI 761036) and M530

The major human metabolites of BI 425809, M530 and M232, have been evaluated in nonclinical studies with no evidence of pharmacological activity, genotoxicity, effects on embryo-foetal development, or adverse effects in repeat-dose toxicity in studies of 13 – 15 weeks duration.

Furthermore, available clinical data with multiple doses of up to 75 mg twice daily (150 mg/d), were well tolerated, and suggest that there is no metabolite-mediated safety concern after single oral dose administration of 25 mg BI 425809 in the present trial.

Risks related to intravenous administration of BI 425809(C-14) solution

No therapeutic intravenous use is planned for BI 425809. Therefore, in accordance to the guideline on non-clinical safety studies ICH-M3(R2) [R15-0594], the intravenous microtracer dose of 30 µg BI 425809 (C-14) is considered adequately qualified by the existing oral toxicity studies and investigation of intravenous local tolerance of the drug substance is not recommended in this situation because the administered dose is very low (< 100 µg) and no novel solvent is used.

BI 425809 is labelled with the isotope [^{14}C] which is necessary for the purposes of this microtracer trial to distinguish the intravenously administered labelled drug from the unlabelled oral drug. The radioactive dose per infusion will be approx. 0.011 MBq and thereby falls into the ICRP 1 category (trivial level of risk) based on the calculated ICRP Category I limit for administration of [^{14}C]-BI 425809 of 0.9 MBq [c25192159][R15-3219].

Summary of benefit-risk assessment

In previous trials in healthy subjects, single oral doses up to 150 mg BI 425809 and multiple oral doses up to 75 mg BI 425809 once or twice daily were safely administered. In the current

trial, healthy male volunteers will receive a single oral dose of 25 mg BI 425809 and an intravenous microtracer dose of 30 µg BI 425809 (C-14). Each participating subject will receive only one infusion containing a radioactive dose <0.9 MBq (ICRP 1 category, trivial level of risk).

The trial design is optimized to collect as much relevant information as possible on the pharmacokinetics of BI 425809 without exposing participating volunteers to undue risk. However, there is always the potential of serious adverse events (SAEs) occurring with intake of trial medication. Risks to subjects will be minimized and addressed by eligibility criteria, safety laboratory examinations, ECG and vital sign measurements, in-house observation periods and verbal communication concerning AEs.

If the investigator should have any clinical concern, the safety of the subjects will be of paramount importance. The investigator has the discretion to remove subjects from the study should there be any safety concerns or if the subject's wellbeing is at jeopardy.

The investigation of the absolute bioavailability of this BCS class 2 compound contributes substantially to a better understanding of its pharmacokinetics. The results of this trial are necessary for the further development of BI 425809. Successful development of BI 425809 is expected to provide a new valuable treatment to improve cognitive functioning in patients with AD and CIAS.

The risks of the participating volunteers are minimized and justified when compared to the potential benefits of a successful clinical development of BI 425809 for patients with AD, and CIAS.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to investigate the absolute oral bioavailability of 25 mg BI 425809 administered as tablet (Test, T) compared to 3 µg of [C-14]-BI 425809 administered as intravenous microtracer (the total dose administered iv is a mixture of 3 µg labelled [C-14]-BI 425809 and 27 µg unlabelled BI 425809) (Reference, R).

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined in plasma for [^{14}C]-BI 425809 after intravenous administration as well as for BI 425809 after oral administration:

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for BI 425809 after oral administration:

- C_{max} (maximum measured concentration of the analyte in plasma)

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.2 Further endpoints

2.2.2.2 Safety and tolerability

Safety and tolerability of the investigational drug 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, single period and single arm trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The test treatment (T) will be one oral tablet of 25 mg BI 425809 (intended clinical formulation (ICF)) and the reference treatment (R) will be an intravenous microtracer infusion of 30 µg BI 425809 (14-C) (consisting of 27 µg unlabelled BI 425809 mixed with 3 µg labelled [C-14]-BI 425809 in 10 mL intravenous solution (3 µg BI 425809 (C-14)/mL)). Both treatments will be given in the fasted state. For details refer to Section 4.1.

Drug administration in Treatment R will start 4 h 00 min after drug administration in Treatment T, i.e. at the time of expected T_{max} of treatment T.

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 Section 6.2, respectively.

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

To investigate the absolute bioavailability, a single arm, single period trial design using a microtracer approach* was considered to be the favourable design also in comparison to the traditional cross-over design used for absolute bioavailability studies for the following reasons:

- As in a traditional cross-over design each subject serves as his own control removing inter-subject variability. However, additionally day to day variability within a subject is also eliminated as potential confounding variable as each subject is exposed to the two treatments in parallel, i.e. treatment R will be administered at T_{max} of Treatment T
- Expected favourable safety due to very low exposures after an intravenous microdose
- The radioactive dose per infusion has been calculated to be 0.011 MBq thereby not exceeding the ICRP 1 limit for administration of [^{14}C]-BI 425809 of 0.9 MBq, i.e. trivial level of risk [c25192159].
- Reduced duration of the clinical trial

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analyte.

*In this context ‘microtracer’ is defined as an intravenous dose of an isotopically labelled drug in an absolute bioavailability study administered as 1% of the pharmacologic dose or 0.1 mg, whichever is the lower. [R17-1799]

3.3 SELECTION OF TRIAL POPULATION

It is planned that 6 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site or, if necessary, via advertisement.

The current trial is designed to investigate the absolute oral bioavailability of BI 425809. Healthy male subjects are an ideal population for the objectives of this trial, since they provide relatively stable physiological, biochemical and hormonal conditions, i.e. the absence of disease-related variations and relevant concomitant medications.

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, 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 65 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
5. Subjects who are sexually active must use, with their partner, highly effective contraception from the time of administration of trial medication until 4 months after administration of trial medication. Adequate methods are:
   - Condoms *plus* use of hormonal contraception by the female partner that started at least 2 months prior to administration of trial medication (e.g., implants, injectables, combined oral or vaginal contraceptives, intrauterine device) *or*
   - Condoms plus surgical sterilization (vasectomy at least 1 year prior to enrolment) or
   - Condoms plus surgically sterilised partner (including hysterectomy) or
   - Condoms plus intrauterine device or
   - Condoms plus partner of non-childbearing potential (including homosexual men)

   Subjects are required to use condoms to prevent unintended exposure of the partner to the study drug via seminal fluid.

   Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes

active, with their partner, they must comply with the contraceptive requirements detailed above.

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) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 139 mmHg, diastolic blood pressure outside the range of 45 to 89 mmHg, or pulse rate outside the range of 40 to 100 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 judged as clinically relevant by the investigator
5. Clinically significant gastrointestinal, hepatic, renal, respiratory (including but not limited to interstitial lung disease), cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation). Use of CYP3A4 inhibitors and inducers 1 week prior to administration of trial medication
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Smoker (more than 5 cigarettes or 1 cigar or 1 pipe per day)
14. Inability to refrain from smoking on specified trial days
15. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 35 ml of spirits)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within 4 days prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of 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 Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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 Section 3.3.4.1 and Section 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 and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. 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, or the contract with BI impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product

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

3.3.5 Replacement of subjects

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational unlabelled product (Trial product 1) has been manufactured by BI Pharma GmbH & Co. KG. BI 425809 XX is a neutral molecule exhibiting no ionizing centre. Therefore 25 mg BI 425809 equal to 25 mg BI 425809 XX.

Radiolabelled BI 425809 (C-14) is administered as an intravenous solution. The powder used for intravenous solution contains [C-14] BI 425809 and unlabelled BI 425809 are both manufactured by BI Pharma GmbH & Co. KG. The mixture of [C-14] BI 425809 and unlabelled BI 425809 and the solution from this mixture are made by

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of Trial Product 1 (Treatment T) are given below:

Name:	BI 425809 intended Commercial Form (iCF)
Substance:	BI 425809
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	25 mg
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	single dose

The characteristics of Trial Product 2 (Treatment R) are given below:

Name:	BI 425809 (C-14) intravenous solution
Substance:	BI 425809 mixed with [C-14]-BI 425809
Pharmaceutical formulation:	intravenous solution
Source:	
Unit strength:	30 µg BI 425809 - consisting of 3 µg [^{14}C]-labelled BI 425809 mixed with 27 µg unlabelled BI 425809 - in 20% PEG 400 in saline solution of 10 mL volume (Concentration of BI 425809 (C-14): 3 µg/mL)
Posology:	1-0-0
Route of administration:	i.v.
Duration of use:	single infusion over 15 min

4.1.2 Selection of doses in the trial

The dose of 25 mg BI 425809 is below the already tested highest doses (single doses up to 150 mg, multiple doses up to 75 mg bid (150 mg/d)) of BI 425809 in healthy subjects. In healthy volunteers, a single dose of 25 mg was safe and well-tolerated (Section 1.2.4). A dose of 25 mg corresponds to the maximum dose tested in the ongoing phase II studies 1346-0023 [c03632269-05], 1346.9 [c03559983-03] and is considered adequate for the objectives of the current trial.

Using the microtracer approach to investigate the absolute bioavailability the intravenously administered dose is not expected to significantly add to the systemic drug concentrations arising from the oral administration [R17-1799].The oral dose (25 mg BI 425809) is more than 800 fold higher than the intravenously infused dose (0.03 mg BI 425809 (C-14)). Therefore the exposure of BI 425809 (C-14) originating from the infused microtracer is considered negligible (see Section 1.4).

4.1.3 Method of assigning subjects to treatment groups

This is an open-label, phase I, single-dose study. All subjects receive the same treatment. Once a subject number has been assigned, it cannot be reassigned to any other subject. The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a non-randomised, open-label, single period, single arm trial. All subjects will receive the same treatment. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose of BI 425809
T (Test)	BI 425809	Tablet	25 mg	1 tablet as single dose on d1	25 mg
R (Reference)	BI 425809 (C-14)	i.v. solution	3 µg /mL	i.v. infusion of 10 ml over 15 min on d1	0.03 mg

The oral medication (Treatment T) will be administered as a single oral dose together with about 240 mL of water to a subject in the sitting/standing position under supervision of the investigating physician or an authorised designee.

After drug administration until the start of the intravenous infusion of BI 425809 (C-14), subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The microtracer (Treatment R) will be administered as a constant intravenous infusion over 15 min to a subject in the semi supine position under supervision of the investigating physician or an authorised designee. Start and end time of the infusion will be recorded. For

the microtracer intravenous an indwelling catheter is placed into an arm vein of the subject and will be kept patent with a saline infusion. A second indwelling catheter used for collection of blood samples will be placed on the contralateral arm.

The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. Administration will be performed following an overnight fast starting no later than 10 h before scheduled dosing.

Subjects will be kept under close medical surveillance until 24 h following drug administration. The in-house stay can be extended in case considered medically necessary by the investigator.

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

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to the Local Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers.

Radiolabelled drug product manufacturing is done by The final container used for administration of the radiolabelled drug product will be a syringe for intravenous infusions and will be labelled according to GMP Annex 13 / EU GMP Guideline and local drug law.

BI 425809 tablets are provided in blisters within the clinical trial supply containers and will be labelled according to GMP Annex 13 / EU GMP Guideline and local drug law.

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

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

pharmacy will receive Trial product 1 (25 mg tablet of BI 425809) delivered from the sponsor once the below mentioned requirements are fulfilled. pharmacy will deliver trial product 1 and 2 to the investigator upon availability of a valid prescription from the investigator. The investigator will also not order the investigational drugs from the pharmacy before these requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of a signed and dated clinical trial protocol
- Availability of licence for clinical research using radioactive isotopes

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 all unused or partially used drug supplies have been returned by the clinical trial subject and 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 except for paracetamol. Limited doses of paracetamol (up to 2 grams per day) are allowed prior to entry in the clinic and during the clinical stay after prescription by a physician to treat aches and pains. However, in case of adverse events in need of treatment, a concomitant therapy will be permitted. The use of moderate or potent CYP3A4 inhibitors should be avoided. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.
In the case of AEs the volunteers will be treated as necessary and if required kept under constant supervision at the trial centre or transferred to hospital until such time that all the results of the evaluations have returned to a medically acceptable level.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed for at least 4,5 h after intake of BI 425809 as tablet. On day 1 all subjects will receive the same standardized meals.

From 1 h before intake of BI 425809 as tablet until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, subjects will be advised that total fluid intake should be within about 1000 to 3000 mL.

On Day 1 subjects will receive a 15 minutes microtracer infusion starting at 4 h after intake of BI 425809 tablets (i.e., t_{max} for oral dose). The handling instructions will be filed in the ISF.

Poppy-seed containing products should not be consumed starting 2 days before first trial drug administration until last PK sampling of the trial.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed 24 hours before first dose and at the day of in-house confinement.

Alcoholic beverages are not allowed 48 hours before administration of the compound, before each admission and during the clinic period. During the ambulatory phase alcohol consumption is restricted to a maximum of 24 units per week.

Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the administration of trial medication until after the last PK sample of each study period is collected.

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

Excessive physical activity (such as competitive sport) should be avoided starting 4 days before the 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 CareScape VC150 from GE Healthcare) 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 except for the Screening safety laboratory evaluation where a 4 h fast is sufficient. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	**BI test name [comment/abbreviation]**	**A**	**B**	**C**
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	Reticulocytes/Erythrocyte	X	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	X	X	X
	INR (International Normalization Ratio)	X	X	X
	Fibrinogen	X	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Glutamate Dehydrogenase (GLDH)	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X
	Lactic Dehydrogenase	X	X	X
	Lipase	X	X	X
	Amylase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	X
	Free T3 - Triiodothyronine	X	--	--
	Free T4 – Thyroxine	X	--	--
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	--	X
	Cholesterol, total	X	--	X
	Triglyceride	X	--	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	**BI test name [comment/abbreviation]**	**A**	**B**	**C**
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Magnesium	X	X	X
	Calcium	X	X	X
Urinalysis[1] (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 haemoglobin (qual)	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment[1] (microscopic examination if erythrocytes, leukocytes, nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Day -1, 2, and 6 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (end of trial examination)

The tests listed in Table 5.2.3: 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 on Day-1 prior to the 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 Alcohol
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, an alcohol test in urine will be performed at screening and on Day-1 prior to the treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.3: 1 and Table 5.2.3: 2 will be performed at the safety laboratory of

The drug and alcohol screening tests will be performed using the ADVIA Chemistry XPT 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 (Mortara ELI 250 Rx) 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. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be

carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

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

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

Local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings and reported as AE in case of clinical relevant findings.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

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

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

5.2.6.1.2 Serious adverse event

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

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

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

5.2.6.1.3 AEs considered 'Always Serious'

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

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

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

5.2.6.1.4 Adverse events of special interest

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

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.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

5.2.6.1.6 Causal relationship of AEs

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

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced)

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned)
- Disappearance of the event even though the trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

Subjects will be required to report spontaneously any AEs as well as the time of onset, end time, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

5.3 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

For quantification of BI 425809 plasma concentrations, approx. 3 mL of blood will be taken from an antecubital or forearm vein into a K_2-EDTA (tripotassium ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart

For quantification of [C-14] BI 425809 plasma concentrations, an additional 3 mL K_2-EDTA tube needs to be collected as 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 aliquots should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min, with interim storage of blood samples and aliquots on ice. The time each aliquot was placed in the freezer will be documented.

Until transfer on dry ice to the analytical laboratory, the plasma samples will be stored frozen and in upright position at about –20°C or below at the clinical site and at the analytical laboratory until analysis.

For detailed description of blood sampling, sample handling, sample preparation, sample

storage, tube labelling and sample shipment refer to the laboratory manual.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

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

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte plasma concentrations

Cold BI 425809 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay.

The analysis will be performed at:

[C-14] BI 425809 will be determined by a validated AMS (accelerator mass spectrometry) assay.

The analysis will be performed at:

Since this is an open study, the bioanalyst will be unblinded during sample analysis.

5.4 BIOBANKING

Not applicable.

5.5 OTHER ASSESSMENTS

Not applicable.

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 and intravenously administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.4 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min on Day 1 and ± 90 min on the following days of Visit 2.

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

Each subject is expected to participate in one treatment period (Visit 2).

On Day -1 of Visit 2 study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other study days, subjects will be treated in an ambulatory fashion.

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

If several activities, including 12-lead ECG and meal intake, are scheduled at the same time

point in the Flow Chart, ECG should be the first and meal intake the last activity. 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.

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

6.2.3 Follow-up period and trial completion

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The primary objective of this trial is to investigate the absolute oral bioavailability of 25 mg BI 425809 administered as tablet (Test, T) compared to 3 µg of [C-14]-BI 425809 administered as intravenous microtracer (mixed with 27 µg unlabelled BI 425809) (Reference, R) on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and Section 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of an appropriate linear model.

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 absolute bioavailability of 25 mg orally administered BI 425809 compared to 3 µg of [C-14]-BI 425809 administered as intravenous microtracer (mixed with 27 µg unlabelled BI 425809) will be estimated by the ratios of the geometric means (test/reference) for the dose normalized primary PK endpoints. Additionally, their 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.

Confidence intervals and p-values will be computed, but have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects, while p-values are considered as an exploratory measure of evidence for effects in the present data.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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 IQRM plan. IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug BI 425809 will be calculated according to the relevant SOP of the Sponsor [001-MCS-36-472].

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

Relevant protocol deviations may be

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

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- A predose concentration is >5% of the C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

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

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

7.3.1 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-

transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: 'subjects' and 'formulation'. The effect 'subjects ' will be considered as random, whereas 'formulation' will be considered as fixed. The model is described by the following equation:

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

y_{km} = logarithm of response (dose normalized primary endpoint, see Section 7.2)

measured on subject m receiving formulation k,

μ = the overall mean,

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

τ_k = the k^{th} formulation effect (either tablet or i.v.), k = 1, 2,

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

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

As a sensitivity analysis, the same statistical model as stated above will be repeated for the primary endpoints but with subject as fixed effect instead of random effect. This result will be presented in the same manner as for the primary analyses.

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 BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' [001-MCS-36-472] and will be assessed statistically using the same methods as described for the primary endpoints.

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 7.3) 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 (test treatment) and beginning of reference treatment will be assigned to the test treatment period. Those between the start of infusion until the end of REP (see Section 1.2.3) will be assigned to the combined test/reference treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before 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 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

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

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

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Randomization is not applicable in this open-label and single group clinical study. All subjects will receive the same treatment. Consecutive subject numbers will be assigned via the EDC system.

7.7 DETERMINATION OF SAMPLE SIZE

For this exploratory trial, no prospective calculations of statistical precision or power have been made. The planned sample size of 6 evaluable subjects has been selected for practical reasons and is judged as being adequate to get reliable results regarding the trial objectives.

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 directive 2001/20/EC and other relevant regulations. Investigators and site staff must adhere to these principles.

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

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

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

The terms and conditions of the insurance coverage will be described in the ICF and 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 delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

Measures are in place to comply with the applicable rules for the collection, 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 storing 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 (e.g. biomarker proposal, analysis plan and report) ensures compliant usage
- If applicable, 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 of the enrolment of the first subject in the trial.

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

The non-labelled trial medication (intended final formulation of 25 mg BI 425809, IFF) will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany.

The radiolabelled trial medication (intravenous microtracer solution) will be provided by .

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

The analyses of unlabelled BI 425809 concentrations in plasma will be performed at a suitable Contract Research Organisation (CRO) under the responsibility of the Department of the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

The analyses of labelled BI 425809 via Accelerator mass spectrometry (AMS) analysis will be conducted at .

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

Data management and statistical evaluation will be done by BI or a contract research organisation appointed by BI according to BI SOPs.

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

R13-4447 Lane HY, Chang YC, Liu Y, Chiu CC, Tsai GE. Sarcosine or D-serine add-on treatment for acute exacerbation of schizophrenia: a randomized, double-blind, placebo-controlled study. Arch Gen Psychiatry 2005;62:1196-1204

R13-4508 Martin-Facklam M, Patat A, Hofmann C, Boetsch C, Banken L, Biedinger U, Boutouyrie-Dumont B. Safety, tolerability and pharmacokinetics of bitopertin (RG1678), a novel glycine reuptake inhibitor after multiple doses in healthy volunteers. 3rd Biennial Conf of the Schizophrenia International Research Society (SIRS), Florence, 14 - 18 Apr 2012 (Poster). 2012

R15-0594 European Medicines Agency (EMA). ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals: step 5 (December 2009, EMA/CPMP/ICH/286/1995). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002720.pdf (access date: 5 February 2015) ; London: European Medicines Agency (EMA); 2009.

R15-3219 International Commission on Radiological Protection (ICRP). 2007 Recommendations of the International Commission on Radiological Protection (users edition): abstract. http://www.icrp.org/publication.asp?id=ICRP%20Publication%20103%20(Users%20Editi on) (access date: 24 June 2015) ; (ICRP Publication; 103 (Users Edition)) International Commission on Radiological Protection (ICRP); 2007.

R17-1799 Lappin G. Approaches to intravenous clinical pharmacokinetics: recent developments with isotopic microtracers. J Clin Pharmacol 2016;56(1):11-23.

9.2 UNPUBLISHED REFERENCES

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

c02155957-08 BI 425809 Investigators Brochure. 06 Jun 2018

c25192159 . Clinical trial protocol radiation burden calculation report. 1346.16. 14 May 2018

c03632269-05 A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy and safety of orally administered BI425809 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease. 1346.23. 12 Jul 2018

c03559983-03 A phase II randomised, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia. 1346.9. 13 Dec 2017

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		07 Jan 2019
EudraCT number **EU number**		2018-001194-24
BI Trial number		1346-0015
BI Investigational Medicinal Product(s)		BI 425809
Title of protocol		Investigation of pharmacokinetics and absolute oral bioavailability of BI 425809 administered as an oral dose with an intravenous microtracer dose of [C-14]-BI 425809 in healthy male volunteers
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		Flow Chart
Description of change		240 mL fluid intake corrected from 14:15 to 14:00
Rationale for change		Inconsistency between Flow Chart and Section 4.2.2.2 Restriction on diet and life style

APPROVAL / SIGNATURE PAGE

Document Number: c21363182 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol

Title: Investigation of pharmacokinetics and absolute oral bioavailability of BI 425809 administered as an oral dose with an intravenous microtracer dose of [C-14]-BI 425809 in healthy male volunteers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area		07 Jan 2019 13:43 CET
Author-Clinical Trial Leader		07 Jan 2019 14:07 CET
Author-Trial Clinical Pharmacokineticist		07 Jan 2019 14:16 CET
Author-Trial Statistician		07 Jan 2019 15:35 CET
Approval-Team Member Medicine		07 Jan 2019 23:23 CET
Verification-Paper Signature Completion		14 Jan 2019 08:47 CET

(Continued) Signatures (obtained electronically)

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