Clinical Trial Protocol

	Document Number: c13723133-03
EudraCT No.:	2016-004862-24
BI Trial No.:	1346-0018
BI Investigational Product:	BI 425809
Title:	Effects of rifampicin on the pharmacokinetics of BI 425809 following oral administration in healthy male subjects (an open-label, two-period, fixed-sequence trial)
Clinical Phase:	I
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]
Principal Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	Version: 3.0 Date: 05 Apr 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 425809			
Protocol date: 20 December 2016	**Trial number:** 1346-0018		**Revision date:** 05 April 2017

Title of trial:	Effects of rifampicin on the pharmacokinetics of BI 425809 following oral administration in healthy male subjects (an open-label, two-period, fixed-sequence trial)
Principal Investigator:	[redacted]
Trial site:	[redacted]
Clinical phase:	I
Objective:	To investigate whether and to what extent co-administration of multiple doses of rifampicin affect single dose pharmacokinetics of BI 425809 in healthy male subjects and to characterize the single dose pharmacokinetics of the metabolite BI 761036
Methodology:	Open-label, fixed-sequence trial with 2 treatments (A and B)
No. of subjects: **total entered:** **each treatment:**	 16 16
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 55 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Trial product 1: **dose:** **mode of admin.:**	BI 425809, 25 mg tablet 25 mg as single dose in treatments A and B Oral administration with 240 mL of water after overnight fast
Trial product 2: **dose:** **mode of admin.:**	Eremfat® 600 mg tablet (1 tablet containing 600 mg rifampicin) 600 mg once daily (qd) for 10 days in treatment A Oral administration with 240 mL of water
Duration of treatment:	Treatment B, Reference (BI 425809 alone): Single dose of 25 mg BI 425809 on Day 1 Treatment A, Test (rifampicin + BI 425809): 10 days of rifampicin (600 mg qd) treatment combined with a single dose of 25 mg BI 425809 on the seventh day of the rifampicin treatment. BI 425809 single doses in treatments B and A will be separated by a wash-out period of at least 49 days.

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 425809			
Protocol date: 20 December 2016	**Trial number:** 1346-0018		**Revision date:** 05 April 2017
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-168} and C_{max} of BI 425809 in plasma Secondary endpoints: $AUC_{0-\infty}$ of BI 425809 in plasma, $t_{1/2}$ of metabolite BI 761036 in plasma [redacted]		
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])		
Statistical methods:	Relative bioavailability will be estimated based on the point estimators of the intra-subject ratio (test to reference treatments) of the geometric means (gMeans) of the primary endpoints and the secondary endpoint $AUC_{0-\infty}$ of BI 425809 in plasma. Additionally their corresponding two-sided 90% confidence intervals will be provided. The statistical model will be a (mixed effects) ANOVA on log transformed parameters, including effects for 'subjects' and 'treatment'. Confidence intervals will be based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.		

FLOW CHART

Period	Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK plasma (BI 425809)	PK plasma (metabolites)	Urine for 6β-OH cortisol	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	x				x	x	
Treatment B, Reference (BI 425809 single dose)	2	1	-2:00	06:00	Admission to trial site[2], allocation to study subject numbers	x[5,2]	x[2]	x[2]	x[2]		x[2]	x[2]
			0:00	08:00	Drug administration BI 425809							
			0:30	08:30			x					
			1:00	09:00			x					
			1:30	09:30			x					
			2:00	10:00	240 mL fluid intake		x					
			2:30	10:30			x					
			3:00	11:00			x	x				
			3:30	11:30			x					
			4:00	12:00	240 mL fluid intake		x					x
			4:30	12:30			x					
			5:00	13.00	Lunch[3]		x					
			6:00	14:00			x	x				
			8:00	16:00			x					
			10:00	18:00			x					
			11:00	19:00	Dinner							
			12:00	20:00			x	x				x
		2	24:00	08:00	Breakfast (voluntary)[3], discharge		x	x			x	x
			34:00	18:00	Ambulatory visit		x	x				x
		3	48:00	08:00	Ambulatory visit		x	x				x
		4	72:00	08:00	Ambulatory visit		x	x				x
		5	96:00	08:00	Ambulatory visit		x	x				x
		8	168:00	08:00	Ambulatory visit		x[7]	x[7]				x[7]
		10	216:00	08:00	Ambulatory visit		x[7]	x[7]				x[7]
		12	264:00	08:00	Ambulatory visit		x[7]	x[7]				x[7]
		15	336:00	08:00	Ambulatory visit	x[7]	x[7]	x[7]				x[7]
		18	408:00	08:00	Ambulatory visit		x[7]	x[7]				x[7]
		22	504:00	08:00	Ambulatory visit		x[7]	x[7]				x[7]
		25	576:00	08:00	Ambulatory visit			x[7]				x[7]
		29	672:00	08:00	Ambulatory visit			x[7]				x[7]
		32	744:00	08:00	Ambulatory visit			x[7]				x[7]
		36	840:00	08:00	Ambulatory visit			x[7]				x[7]
		43	1008:00	08:00	Ambulatory visit	x[7]		x[7]				x[7]

FLOW CHART (cont.)

Period	Visit	Day	Planned time (relative to BI 425809 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK plasma (BI 425809)	PK plasma (metabolites)	Urine for 6β-OH cortisol	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
Treatment A -Test (Rifampicin multiple dose + BI 425809 single dose)	3	-6	-134:30	17:30	Admission to trial site[2]	x[2,8]						x[2]
			-134:00	18:00	Rifampicin administration							
			-133:00	19:00	Dinner							
			-132:00	20:00	Discharge from trial site							x
		-5	-110:00	18:00	Ambulatory visit, rifampicin administration							x
		-4	-86:00	18:00	Ambulatory visit, rifampicin administration							x
		-3	-72:00	08:00	Ambulatory visit	x[7]						x[7]
			-62:00	18:00	Ambulatory visit, rifampicin administration							x
		-2	-38:00	18:00	Ambulatory visit, rifampicin administration							x
		-1	-14:00	18:00	Ambulatory visit, rifampicin administration							x
		1	-2:00	06:00	Admission to trial site[2]	x[2]	x[2]	x[2]	x[2]		x[2]	x[2]
			0:00	08:00	Drug administration BI 425809							
			0:30	08:30			x					
			1:00	09:00			x					
			1:30	09:30			x					
			2:00	10:00	240 mL fluid intake		x					
			2:30	10:30			x					
			3:00	11:00			x	x				
			3:30	11:30			x					
			4:00	12:00	240 mL fluid intake		x					x
			4:30	12:30			x					
			5:00	13.00	Lunch[3]		x					
			6:00	14:00			x	x				
			8:00	16:00			x					
			10:00	18:00	Rifampicin administration[3]		x					x
			11:00	19:00	Dinner							
			12:00	20:00			x	x				x
		2	24:00	08:00	Breakfast (voluntary), discharge		x	x			x	x
			34:00	18:00	Ambulatory visit, rifampicin administration[3]		x	x				x
		3	48:00	08:00	Ambulatory visit		x	x				x
			58:00	18:00	Ambulatory visit, rifampicin administration							x
		4	72:00	08:00	Ambulatory visit	x	x	x				x
			82:00	18:00	Ambulatory visit, rifampicin administration							x
		5	96:00	08:00	Ambulatory visit		x	x				x
		8	168:00	08:00	Ambulatory visit		x[7]	x[7]				x[7]
EOT	4	12 to 23			End of trial (EOT) examination[4]	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. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within 3 h prior to drug administration.
3. If several actions are indicated at the same time point, this will be the last action.
4. End of trial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Including urine drug screening and alcohol breath test.

6. 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.
7. The time is approximate; the procedure is to be performed and completed within ±3 h of planned time.
8. Urine drug screen and alcohol breath test only.

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS

AD	Alzheimer's disease
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	[redacted]
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CIAS	Cognitive impairment associated with schizophrenia
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
ES	Entered set
gCV	Geometric coefficient of variation
GlyT1	Glycine Transporter 1
gMean	Geometric mean
(HP)LC-MS/MS	(High performance) liquid chromatography with tandem mass spectrometry
IEC	Independent Ethics Committee
IRB	Institutional Review Board

ISF	Investigator site file
[redacted]	[redacted]
NC	Not calculated
NMDA	N-methyl-D-aspartate
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetic(s)
PKS	PK analysis set
PR	Pulse rate
qd	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
R	Reference (product or treatment)
REP	Residual effect period
RPM	Report planning meeting
SAE	Serious adverse event
SCR	Screening
SPC	Summary of product characteristics
T	Test (product or treatment)
[redacted]	[redacted]
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This clinical phase I study will be done as an open-label, two period, fixed-sequence trial with 2 treatments in order to compare the test treatment (A) to the reference treatment (B) in a single centre.

The trial will consist of 4 visits. Visit 1 will be the screening investigation.

Each subject will receive treatment B (reference) in Visit 2 and treatment A (test) in Visit 3. The two treatments are described below. The administrations of the single dose of BI 425809 in the first period (Visit 2) and in the following combined treatment period (Visit 3) will be separated by a wash-out period of at least 49 days. For details refer to Section 4.1.

Visit 4 will be the end-of-trial examination.

Reference treatment (BI 425809 alone):

One tablet of 25 mg BI 425809 will be given as a single dose on Day 1 of Visit 2 (treatment B).

Test treatment (rifampicin + BI 425809):

During the second period of the study (Visit 3, treatment A) one tablet of 600 mg rifampicin will be given once daily on Days -6 to Day -1. One tablet of 25 mg BI 425809 will be given as a single dose approximately 10 h before the rifampicin administration on Day 1 (corresponding to the seventh day of the 10-day rifampicin treatment). Rifampicin will be continued for further 3 days (trial days 2, 3 and 4).

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

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, Germany.

BI has appointed a trial clinical monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors, clinical research associates, and participating trial sites.

[redacted]

[redacted]

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

Data management and statistical evaluation will be done by BI according to BI SOPs.

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

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

The study will be performed as a randomized, open-label, two period, fixed-sequence trial in healthy male subjects. This study design is considered to be appropriate to investigate the effect of multiple doses of rifampicin on single-dose PK of BI 425809 and to characterise the PK of its major metabolites.

Full induction effect of rifampicin can be expected after 1 week. The baseline activity after discontinuing rifampicin treatment can be attained within 2 weeks [P03-08008].

Due to the expected long half-life of metabolite BI 761036 a fixed sequence design was selected, with administration of rifampicin in the second study period only. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects, because the trial duration is short enough so that nonspecific time-effects are not expected.

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

Rifampicin must not be used during pregnancy; furthermore oral contraceptives may become ineffective when co-administered with rifampicin. Therefore, the sponsor decided to only include male subjects into the study.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

Subjects will only be included into 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 55 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

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 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm

3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance

4. Any evidence of a concomitant disease judged as clinically relevant by the investigator

5. Gastrointestinal, hepatic, renal, respiratory, 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)

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 10 cigarettes or 3 cigars or 3 pipes per day)

14. Inability to refrain from smoking on specified trial days

15. Alcohol abuse (consumption of more than 20 g per day)

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 one week prior to administration of trial medication or during the trial

19. Inability to comply with dietary regimen of trial site

20. 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

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

21. History of relevant liver diseases such as disturbance of liver function, jaundice, drug induced liver injury, Dubin-Johnson syndrome, Rotor syndrome, or liver tumours

22. Thrombocytes below lower limit of normal or liver enzymes (ALT, AST, GGT, AP) above upper limit of normal at the screening examination

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision

2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication

3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events, or diseases)

4. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with 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.

5. The subject presents with a clinically relevant thrombocytopenia

A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database 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 CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable.

2. The expected enrolment goals overall or at a particular trial site are not met

3. Violation of GCP, or the CTP by a trial site or investigator, disturbing the appropriate conduct of the trial

4. The sponsor decides to discontinue the further development of the investigational product.

[redacted]

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product and comparator products

The characteristics of trial product 1 are given below:

Substance:	BI 425809
Pharmaceutical formulation:	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 (in treatment A and B)

The characteristics of trial product 2 are given below:

Name:	Eremfat® 600 mg
Substance:	Rifampicin
Pharmaceutical formulation:	Film-coated tablet
Source:	Riemser Pharma GmbH, Germany
Unit strength:	600 mg
Posology:	0-0-1
Route of administration:	p.o.
Duration of use:	10 days (in treatment A only)

4.1.2 Method of assigning subjects to treatment groups

This is an open-label, two-period, fixed-sequence trial.

The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication in the morning of Day1 (Visit 2). For this purpose, the subjects will be allocated to a study subject number by drawing lots. Once a subject number has been assigned, it cannot be reassigned to any other subject.

4.1.3 Selection of doses in the trial

Rifampicin given at a dosage of 600 mg once daily reflects standard clinical doses and is considered sufficient to yield significant CYP3A4 induction. To avoid any potential interference with rifampicin effects on transporters, BI 425809 and rifampicin are not administered simultaneously.

The selected dose of BI 425809 (25 mg) corresponds to the estimated therapeutic dose and is expected to provide adequate exposure for the purposes of this trial whilst being safe at the same time.

4.1.4 Drug assignment and administration of doses for each subject

All subjects will receive the two treatments in a fixed sequence order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
B (Reference)	BI 425809	Tablet	25 mg	1 tablet (25 mg) qd as single dose on day1 of Visit 2	25 mg
A (Test)	BI 425809	Tablet	25 mg	1 tablet (25 mg) qd as single dose on day1 of Visit 3	25 mg
	Rifampicin	Tablet	600 mg	1 tablet (600 mg) qd for 10 days (Day -6 to Day 4) of Visit 3	6000 mg

The medication will be administered as oral dose together with about 240 mL of water to a subject in the standing position under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication, if correct dosage cannot be ensured otherwise. Administration of BI 425809 will be performed in the morning of Day 1 following an overnight fast starting no later than 10 h before scheduled dosing. For administrations of rifampicin, subjects are advised to fast for at least 2 hours before and at least 30 minutes after drug administrations.

Subjects will be kept under close medical surveillance until 24 h following drug administration of BI 425809. During the first 5 h after BI 425809 administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture). The first rifampicin administration will be followed by a 2-hour post-administration in-house observation period.

For restrictions with regard to diet see Section 4.2.2.2.

The treatment with BI 425809 will be separated by a wash-out phase of at least 49 days.

4.1.5 Blinding and procedures for unblinding

No blinding was performed because the treatments are distinguishable from each another. 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.

4.1.6 Packaging, labelling, and re-supply

[redacted]

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

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term 'For Clinical Trial Use' (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date
- Batch number

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

No re-supply is planned.

Rifampicin (Eremfat® 600 mg tablets) will be ordered by the investigator from local pharmacy and used as marketed, without repackaging or additional labelling. Documentation on the commercial drug product according to [001-MCS-40-302_RD-24] must be available on-site in the ISF.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

The investigator will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol

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

The investigator 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 products and trial subjects. The investigator will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator must verify that no remaining supplies are in the investigator's possession.

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, in case of adverse events in need of treatment, the investigator can authorise symptomatic therapy (for restrictions see below). 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 medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Paracetamol must be avoided as symptomatic therapy of AEs due to its potential liver toxicity. The same applies to diclofenac. If need be, ibuprofen may be used as analgesic drug.

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 h after intake of BI 425809 and for at least 30 minutes after rifampicin administration.

From 1 h before intake of BI 425809 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, total fluid intake is restricted to 3000 mL.

Alcoholic beverages, 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 first administration of trial medication until after the last PK sample of the trial is collected.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during hospitalisation periods.

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

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

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations 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. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Safety and tolerability of the investigational drugs 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)

These parameters will be evaluated in a descriptive way only, and are therefore considered to be 'further parameters of interest'. A confirmatory analysis is not planned (see Section 7.3).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

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.

Adverse drug reaction

An adverse drug reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse drug reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this 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 or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,

  or
- is to be 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.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. 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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered 'Always Serious'

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

The latest list of 'Always Serious AEs' can be found in the RDC system, a remote 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.

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Adverse events of special interest (AESIs)

The term 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. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

The following are considered as AESIs in this trial:

- Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:
  - o an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or
  - o marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the patients 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 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.

Intensity of AEs

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

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

Causal relationship of AEs

The definition of an adverse drug reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse drug reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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 diminished).

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 study drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AEs 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.

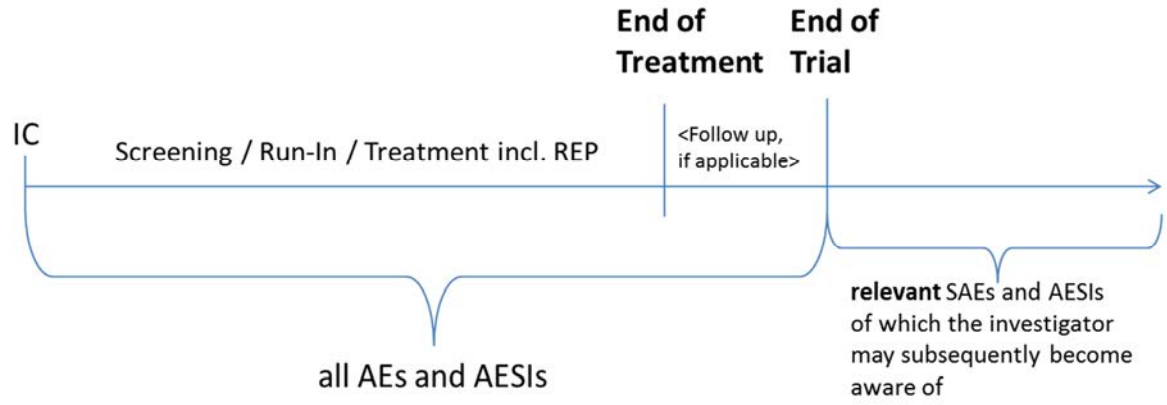
Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will 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 careful 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, and intensity of the event as well as 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 through the residual effect period (REP), 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 relevant SAEs and relevant AESIs of which he may become aware of.



The REP for BI 425809, when measurable drug levels or pharmacodynamic effects are still likely to be present, is defined as 11 days after the last administration of BI 425809.

Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see Section 7.3.3. Events which occurred after the REP will be considered as post treatment events.

The follow-up period describes the period of time from the last administration of trial medication including the REP until the end of trial examination (last per protocol contact).

AE reporting to 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 of awareness) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). In specific occasions the Investigator could inform the sponsor upfront via telephone. The same timeline applies if follow-up information becomes available. 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.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable). The investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF and on the 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 trial inclusion they will be considered as baseline conditions.

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designee for retests and for safety labs "within period".

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

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	Test name	SCR	Within period	End-of- trial
Haematology	Haematocrit	x	x	x
	Haemoglobin	x	x	x
	Red blood cell count (RBC)	x	x	x
	White blood cell count (WBC)	x	x	x
	Platelet count	x	x	x
Automatic WBC differential (relative and absolute)	Neutrophils	x	-	x
	Eosinophils	x	-	x
	Basophils	x	-	x
	Monocytes	x	-	x
	Lymphocytes	x	-	x
Manual WBC differential (if automatic is abnormal)	Polymorphnuclear neutrophils (segs)	x	-	x
	Band neutrophils (stabs)	x	-	x
	Eosinophils	x	-	x
	Basophils	x	-	x
	Monocytes	x	-	x
	Lymphocytes	x	-	x
Enzymes	Aspartate transaminase (AST/GOT)	x	x	x
	Alanine transaminase (ALT/GPT)	x	x	x
	Alkaline phosphatase (AP)	x	x	x
	Gamma-glutamyl transferase (GGT)	x	x	x
	Lactate dehydrogenase (LDH)	x	x	x
Hormones	Thyroid stimulating hormone (TSH)	x	-	-
Substrates	Plasma glucose	x	-	x
	Serum creatinine	x	-	x
	eGFR (CKD-EPI for creatinine)	x	-	x
	Total bilirubin	x	x	x
	Direct bilirubin	x	x	x
	Total protein	x	-	x
	C-Reactive Protein (CRP)	x	-	x
Electrolytes	Sodium	x	-	x
	Potassium	x	-	x
	Calcium	x	-	x
Urinalysis (Stix)	Urine nitrite	x	-	x
	Urine protein	x	-	x
	Urine glucose	x	-	x
	Urine ketone	x	-	x
	Urobilinogen	x	-	x
	Urine bilirubin	x	-	x
	Urine erythrocytes	x	-	x
	Urine leukocytes	x	-	x
	Urine pH	x	-	x
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	x	-	x

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which 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 at the times indicated in the Flow Chart.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test (Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed at the start of each 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.

[redacted]

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the time points given in the Flow Chart.

All ECGs will be recorded for 10-sec duration after the subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid impact of sampling on the ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode

dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

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

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

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

5.2.5.2 Medical examinations

At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, 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.

[redacted]

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters

in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded.

Exact time points of plasma sampling will be derived from the study management system ClinBase™ and documented in the CRFs by the medical personnel or sent as electronic files to the trial data manager. The actual sampling times will be used for determination of pharmacokinetic parameters.

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be used to assess the relative bioavailability of BI 425809 in plasma with and without co-administration of rifampicin:

- AUC_{0-168} (area under the concentration-time curve of BI 425809 in plasma over the time interval from 0 to 168 h)
- C_{max} (maximum measured concentration of BI 425809 in plasma)

5.5.1.2 Secondary endpoint

Additionally, the following secondary endpoint will be evaluated for BI 425809 in plasma:

- $AUC_{0-\infty}$ (area under the concentration-time curve of BI 425809 in plasma over the time interval from 0 extrapolated to infinity)

And further, the following secondary endpoint will be evaluated for BI 761036 in plasma:

- $t_{1/2}$ (terminal half-life of BI 761036 in plasma)

[redacted]

[redacted]

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 425809 plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart.

For quantification of metabolites BI 761036, [redacted] plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA-anticoagulant blood drawing tube at the times indicated in the Flow Chart.

Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

Blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and 4 to 8 °C. Two plasma aliquots will be obtained from each blood sample and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min with interim storage of blood samples on ice. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

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

After completion of the trial the plasma samples may be used for further methodological investigations**,** e.g. for stability testing, 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 upon the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 425809 and metabolites BI 761036, [redacted] plasma concentration

BI 425809 and metabolites BI 761036, [redacted] concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis. [redacted]

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs and laboratory tests will be ± 60 min if not specified otherwise in the Flow Chart.

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

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

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 give their written informed consent in accordance with GCP and local legislation prior to enrolment in the study.

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

Pharmacogenomic genotyping will be performed in those volunteers whose genotypes are not known (for details see Section 5.3).

6.2.2 Treatment periods

Each subject is expected to participate in two treatment periods (Days 1 to 43 in period 1, day –6 to 8 in period 2). The administration of BI 425809 in period 1 and 2 will be separated by at least 49 days.

On Day 1 of each treatment period study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following 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, the study will be performed 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 5.5.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on time points for 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 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial visit.

All abnormal values (including laboratory parameters) that are judged 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 subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

The end of the trial as a whole is defined by the 'last regular visit completed by last subject' 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.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the relative bioavailability of a single dose (25 mg) of BI 425809 when given alone (Reference, B) compared with co-administration (Test, A) on the seventh day of a 10-day treatment with rifampicin.

The study will be conducted as an open-label, two-period, fixed sequence trial. This design allows each subject to serve as its own control. The comparison between treatments is based on a comparison within subjects rather than between subjects. This means that the inter-subject variability is removed from the comparison between treatments and the trial will be evaluated statistically by use of an appropriate linear model.

The characterization of the pharmacokinetics of the main metabolites BI 761036 (M232), [redacted] as well as the assessment of safety and tolerability will be additional objectives of this trial, and will be evaluated by descriptive statistics. Inferential statistics is not planned.

7.1.2 Endpoints

Relative bioavailability is to be determined on the basis of the primary pharmacokinetic endpoints (see Section 5.5.1) and the secondary pharmacokinetic endpoint $AUC_{0-\infty}$ of BI 425809 in plasma.

Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1.

7.1.3 Model

The statistical model used for the analysis of primary and secondary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘subject’ and ‘treatment’. The effect ‘subject’ will be considered as random, whereas the effect ‘treatment’ will be considered as fixed. The model is described by the following equation:

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

y_{km} = logarithm of response (endpoint, see Section 5.5.1) measured on subject m receiving treatment k,

μ = the overall mean,

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

s_m = the effect associated with the mth subject, m = 1, 2, ..., n

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of combined treatment of rifampicin and BI 425809 compared to single treatment with BI 425809 will be estimated by the ratios of the geometric means (test/reference) for the primary PK endpoints and the secondary PK endpoint $AUC_{0-\infty}$ of BI 425809 in plasma.

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 was not specified, that is, no hypothesis will be tested.

7.3 PLANNED ANALYSES

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations will be identified no later than in the report planning meeting (RPM) and provided in the trial statistical analysis plan (TSAP).

The following analysis sets will be defined for this trial:

- Entered set (ES):

  This subject set includes all entered subjects, whether treated or not.

- Treated set (TS):

  This subject set includes all subjects from the ES who were documented to have received one dose of study drug. This is the full analysis set population in the sense of ICH-E9.

- PK analysis set (PKS):

  This subject set includes all subjects from the TS who provide at least one primary or secondary PK endpoint value that is judged as PK evaluable and is not affected by protocol violations relevant to the statistical evaluation of PK endpoints. Thus, a subject will be included in the PKS, even if he contributes only one PK endpoint value for one period to the statistical assessment.

Whether a PK endpoint is evaluable or a protocol violation is relevant will be decided no later than at the RPM.

Relevant protocol violations may be:

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

- Incorrect dose of trial medication taken
- Use of restricted medications

Pharmacokinetic endpoint values of a subject will be included in the analysis if they are not flagged for exclusion, e.g. due to PK non-evaluability or a protocol violation relevant to the evaluation of PK endpoints.

A PK endpoint value will be considered as non-evaluable, if for example:

- The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be taken either from the median t_{max} for the reference product or from median t_{max} for the test product, depending on whether the subject had experienced emesis after taken the test or the reference product. Median t_{max} is to be determined excluding the subjects experiencing emesis.
- The subject has a protocol deviation relevant to the evaluation of relative bioavailability
- Use of restricted medications

Violations may lead to exclusion of single measurements or parameters for a subject or even to exclusion of all data of the subject.

Excluded subjects will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessments.

7.3.1 Primary analyses

The primary and secondary PK parameters AUC_{0-168} , C_{max} and $AUC_{0-\infty}$ (of BI 425809 in plasma) will be log-transformed (natural logarithm) prior to fitting the ANOVA model. The difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding least square means (point estimate) and 2-sided 90% confidence intervals based on the t-distribution will be computed.

These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and 90% confidence interval estimates for the intra-subject ratio of the geometric means for treatments test and reference.

The primary analysis will be based on the pharmacokinetic analysis set (see Section 7.3).

7.3.2 Secondary analyses

For the primary and secondary PK parameters the primary analysis will be repeated using both, ‘subject’ and ‘treatment’, as fixed effects in the ANOVA model.

The following descriptive statistics will be calculated for plasma concentrations as well as for the primary and secondary PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be

identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report. Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic mean, geometric mean and the planned blood sampling times will be used.

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety analysis. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

The analyses will be done by ‘planned treatment sequence’.

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

Measurements (such as 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 'screening', those between first trial medication intake until next intake or the end of trial visit will be assigned to the preceding treatment, and those after the end of trial examination will be assigned to ‘post-study’. Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until end of the residual effect period (see Section 5.2.2.2) will be assigned to the treatment period. Events after the residual effect period but prior to next intake or end of trial examination will be summarized as ‘post-treatment’, those after the end of trial examination will be assigned to ‘post-study’. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Additionally, further treatment intervals (analysing treatments) may be defined 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 post-study intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Additionally, differences from baseline (Day 1 of the first period) will be evaluated.

Vital signs or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Relevant ECG findings will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for BI 425809 and BI 761036 will be calculated according to the relevant SOP of the Sponsor [001-MCS-36-472].

Subjects who are not included in the PKS (refer to Section 7.3.1) will be reported with their individual plasma concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

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).

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

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

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

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma drug concentration - time profiles

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

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

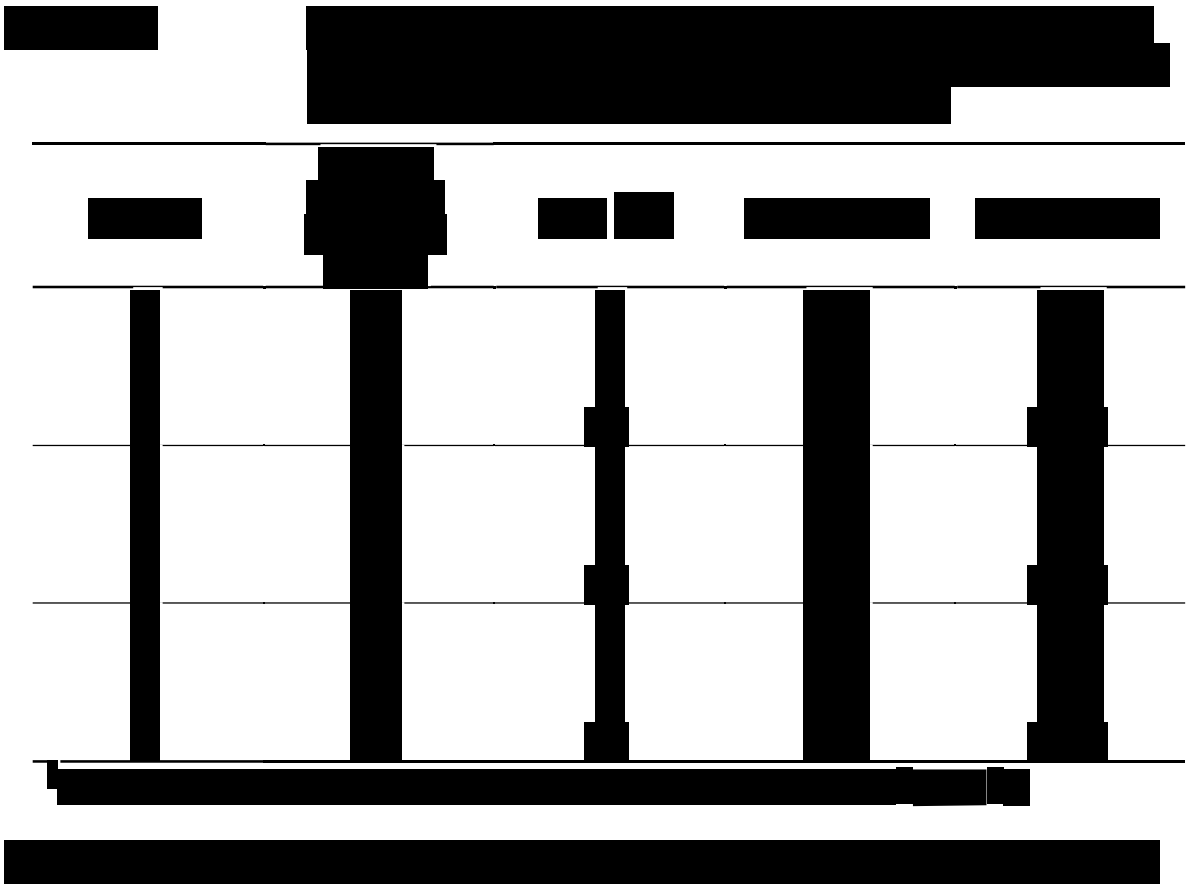
Handling of missing PK data will be performed according to the relevant SOP of the Sponsor [001-MCS-36-472].

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

As this is a single sequence trial, no randomisation is necessary (see also Section 4.1.2).

[redacted]



8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

As a general rule, no trial results should be published prior to finalisation of the CTR.

Insurance Coverage: The terms and conditions of the insurance coverage must be given to each subject and are made available to the investigator via documentation in the ISF.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND 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 are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, 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.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan available in the trial master file.

8.3 RECORDS

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

ClinBase™
In the Human Pharmacology Centre – Boehringer Ingelheim's Phase I unit – the validated ClinBase™ system is operated for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as data base. Instead of being entered into CRFs, selected data are directly entered into the system.

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

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

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using subject identification code numbers.

Treatment data may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated 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, i.e. the CA.

8.6 COMPLETION OF TRIAL

The EC / competent authority in each participating EU member state needs to be notified about the end of the trial (last subject / subject out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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P04-00210 Galteau MM, Shamsa F. Urinary 6beta-hydroxycortisol: a validated test for evaluating drug induction or drug inhibition mediated through CYP3A in humans and in animals. Eur J Clin Pharmacol 2003. 59(10):713-733.

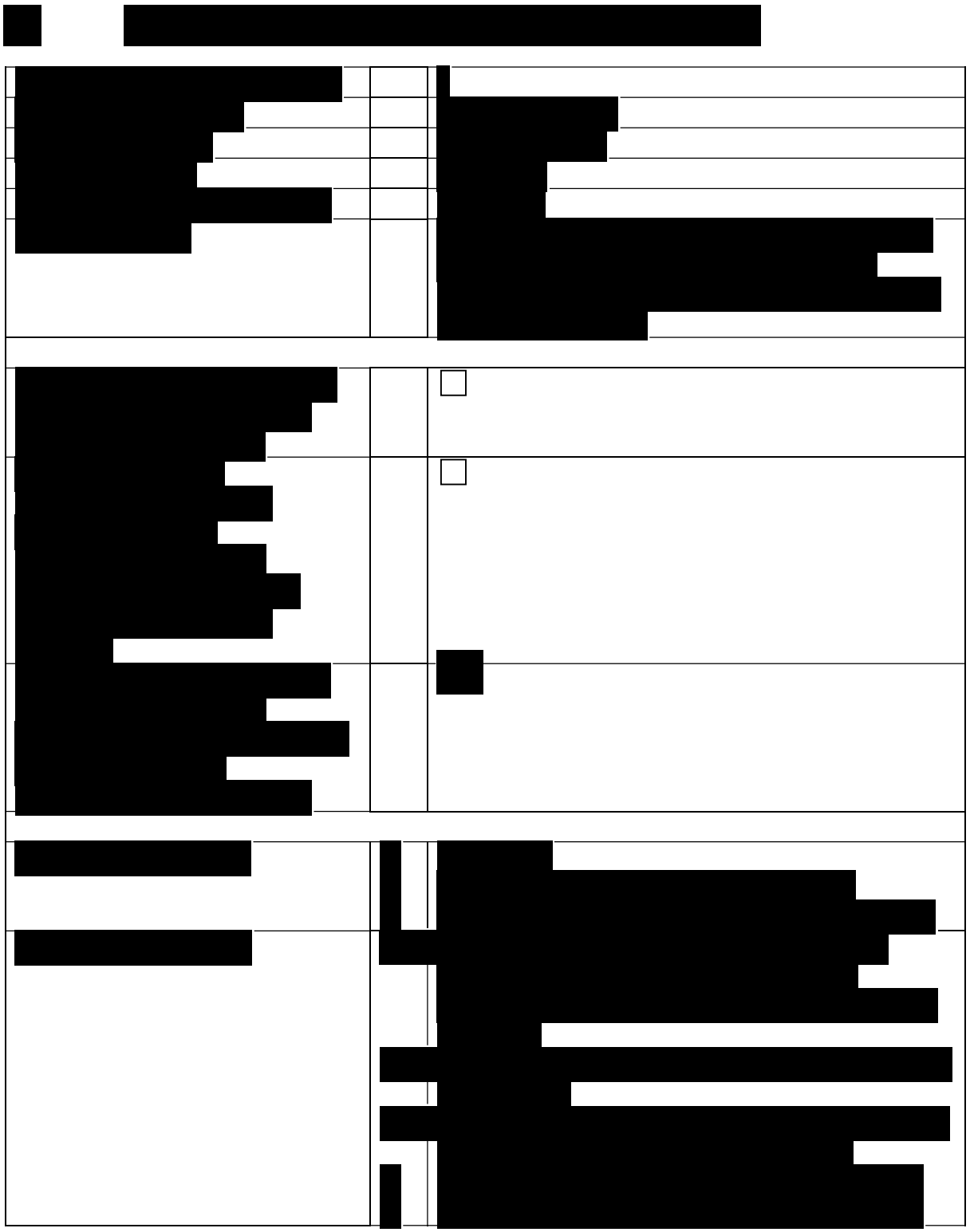
R07-0082 Rifa Dragees (Gruenenthal), verschreibungspflichtig (Fachinformation, Stand der Information: Januar 2004). 2004.

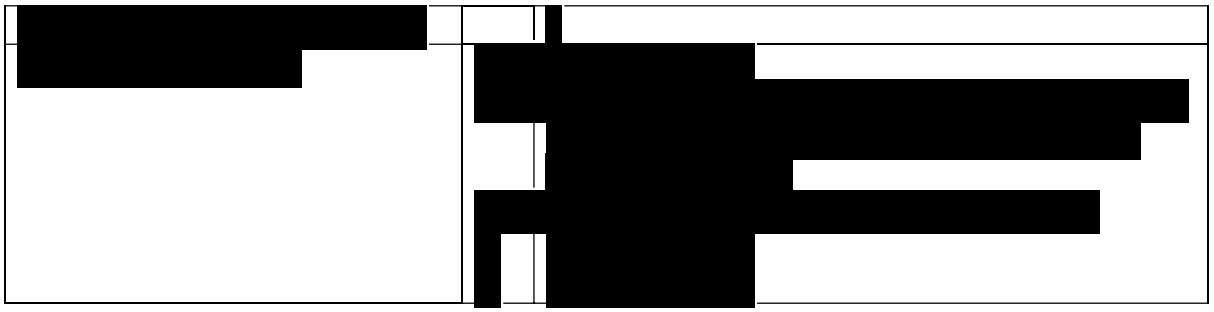
R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group 2010.

R16-5180 Eremfat 600 mg Filmtabletten (Riemser), verschreibungspflichtig (Fachinformation (Zusammenfassung der Merkmale des Arzneimittels/SPC), Stand der Information: 12.2015). 2015.

10. APPENDICES

Not applicable.





APPROVAL / SIGNATURE PAGE

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Title: Effects of rifampicin on the pharmacokinetics of BI 425809 following oral administration in healthy male subjects (an open-label, two-period,fixed-sequence trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	05 Apr 2017 10:58 CEST
Author-Trial Clinical Monitor	[redacted]	05 Apr 2017 11:00 CEST
Verification-Paper Signature Completion		05 Apr 2017 11:04 CEST
Approval-Therapeutic Area [redacted]		05 Apr 2017 11:27 CEST
Author-Trial Clinical Pharmacokineticist		05 Apr 2017 11:55 CEST
Approval-Team Member Medicine		05 Apr 2017 19:04 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed