# Clinical Trial Protocol

| | |
|---|---|
| | **Document Number: c13704479-01** |
| **EudraCT No.:** | 2016-004828-37 |
| **BI Trial No.:** | 1289-0044 |
| **BI Investigational Product:** | BI 409306 |
| **Title:** | Effect of rifampicin on the pharmacokinetics of BI 409306 following oral administration in healthy male subjects<br>(an open-label, two-period, fixed sequence trial) |
| **Clinical Phase:** | I |
| **Trial Clinical Monitor:** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] |
| **Principal Investigator:** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] |
| **Status:** | Final Protocol |
| **Version and Date:** | Version: 1.0 Date: 30 Jan 2017 |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

| | | | |
|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br>Not applicable | | | |
| **Name of active ingredient:**<br>BI 409306 | | | |
| **Protocol date:**<br>30 Jan 2017 | **Trial number:**<br>1289-0044 | | **Revision date:**<br>Not applicable |

| | |
|---|---|
| **Title of trial:** | Effect of rifampicin on the pharmacokinetics of BI 409306 following oral administration in healthy male subjects<br>(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 409306 in healthy male subjects |
| **Methodology:** | Open-label, two-period, fixed sequence |
| **No. of subjects:** | |
| **total entered:** | 16 |
| **each treatment:** | 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:** | BI 409306 film-coated tablets |
| **dose:** | 50 mg as single dose in treatments R and T |
| **mode of admin.:** | Oral with 240 mL of water under fasted conditions |
| **Trial product 2:** | Eremfat® 600 mg film-coated tablet (1 tablet containing 600 mg rifampicin) |
| **dose:** | 600 mg once daily (QD) for 7 days in treatment T |
| **mode of admin.:** | Oral with 240 mL of water |

| | | | |
|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br>Not applicable | | | |
| **Name of active ingredient:**<br>BI 409306 | | | |
| **Protocol date:**<br>30 Jan 2017 | **Trial number:**<br>1289-0044 | | **Revision date:**<br>Not applicable |

| | |
|---|---|
| **Duration of treatment:** | Period 1: 50 mg BI 409306 as single dose (Reference - R)<br><br>Period 2: 600 mg of rifampicin as single dose for 7 days (Day -7 to -1)<br>50 mg BI 409306 as single dose (Day 1) (Test -T)<br><br>Period 2 directly follows Period 1 without washout period due to the short half-life of BI 409306. |
| **Criteria for pharmacokinetics:** | Primary endpoints: $AUC_{0-tz}$ and $C_{max}$ of BI 409306<br>Secondary endpoints: $AUC_{0-\infty}$ of BI 409306 |
| **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. Additionally their corresponding two-sided 90% confidence intervals will be provided.<br>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.<br>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 | $PK_{blood}$ BI 409306 | $PK_{blood}$ rifampicin | 12-lead ECG | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [6] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SCR | 1 | -21 to -1 | n.a. | n.a. | Screening (SCR)[1] | x | | | x | x | |
| 1 | 2 | 1 | -02:00 | 06:00 | Admission to trial site<br>Assignment of subject numbers[2] | x[2,5] | x[2] | x[2] | | x[2] | x[2] |
| | | | 0:00 | 08:00 | Drug administration BI 409306 | | | | | | |
| | | | 0:20 | 08:20 | | | x | | | | |
| | | | 0:30 | 08:30 | | | x | | | | |
| | | | 0:45 | 08:45 | | | x | | | | |
| | | | 1:00 | 09:00 | | | x | | | 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 | | | | |
| | | | 4:00 | 12:00 | 240 mL fluid intake, thereafter lunch[3] | | x | | | | |
| | | | 6:00 | 14:00 | | | x | | | | |
| | | | 8:00 | 16:00 | Snack[3] (voluntary) | | x | | | | |
| | | | 10:00 | 18:00 | | | x | | | | |
| | | | 11:00 | 19:00 | Dinner | | | | | | |
| | | | 12:00 | 20:00 | | | x | | | | x |
| | | 2 | 24:00 | 08:00 | Discharge from trial site<br>Breakfast [3](voluntary) | | x | | | | x |
| 2 | 3[7] | -7 | -158:30 | 17:30 | Admission to trial site[2] | | | | | | x[2] |
| | | | -158:00 | 18:00 | Rifampicin administration | | | | | | |
| | | | -157:00 | 19:00 | Dinner | | | | | | |
| | | | -156:00 | 20:00 | Discharge from trial site | | | | | | x |
| | | -6 | -134:00 | 18:00 | Ambulatory visit. Rifampicin administration | | | | | | x |
| | | -5 | -110:00 | 18:00 | Ambulatory visit. Rifampicin administration | | | | | | x |
| | | -4 | -86:00 | 18:00 | Ambulatory visit. Rifampicin administration | x[2,8] | | | | | x |
| | | -3 | -62:00 | 18:00 | Ambulatory visit. Rifampicin administration | | | | | | x |
| | | -2 | -38:00 | 18:00 | Ambulatory visit. Rifampicin administration | | | | | | x |
| | | -1 | -15:00 | 17:00 | Admission to trial site | x[2,9] | | | | | x |
| | | | -14:00 | 18:00 | Rifampicin administration | | | | | | |
| | | | -13:30 | 18:30 | Dinner | | | | | | |
| | | | -12:00 | 20:00 | | | | x | | | |

FLOW CHART (cont.)

| 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 $_{blood}$ BI 409306 | PK $_{blood}$ rifampicin | 12-lead ECG | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [6] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 3 | 1 | -02:00 | 06:00 | | x[2] | x[2] | x[2] | | x[2] | x[2] |
| | | | 0:00 | 08:00 | Drug administration BI 409306 | | | | | | |
| | | | 0:20 | 08:20 | | | x | | | | |
| | | | 0:30 | 08:30 | | | x | | | | |
| | | | 0:45 | 08:45 | | | x | | | | |
| | | | 1:00 | 09:00 | | | x | | | 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 | | | | |
| | | | 4:00 | 12:00 | 240 mL fluid intake, thereafter lunch[3] | | x | | | | |
| | | | 6:00 | 14:00 | | | x | | | | |
| | | | 8:00 | 16:00 | Snack[3] (voluntary) | | x | | | | |
| | | | 10:00 | 18:00 | | | x | | | | |
| | | | 11:00 | 19:00 | Dinner | | | | | | |
| | | | 12:00 | 20:00 | | | x | | | | x |
| | | 2 | 24:00 | 08:00 | Discharge from trial site<br>Breakfast[3] (voluntary) | | x | | | | x |
| EOT | 4 | 7 to 14 | | | 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, the intake of meals 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. Start of Visit 3 (day-7) follows directly after day 2 of Visit 2
8. AST, ALT, AP, GGT, LDH, total and direct bilirubin only. This safety lab does not require fasting.
9. Urine drug screening and alcohol breath test only

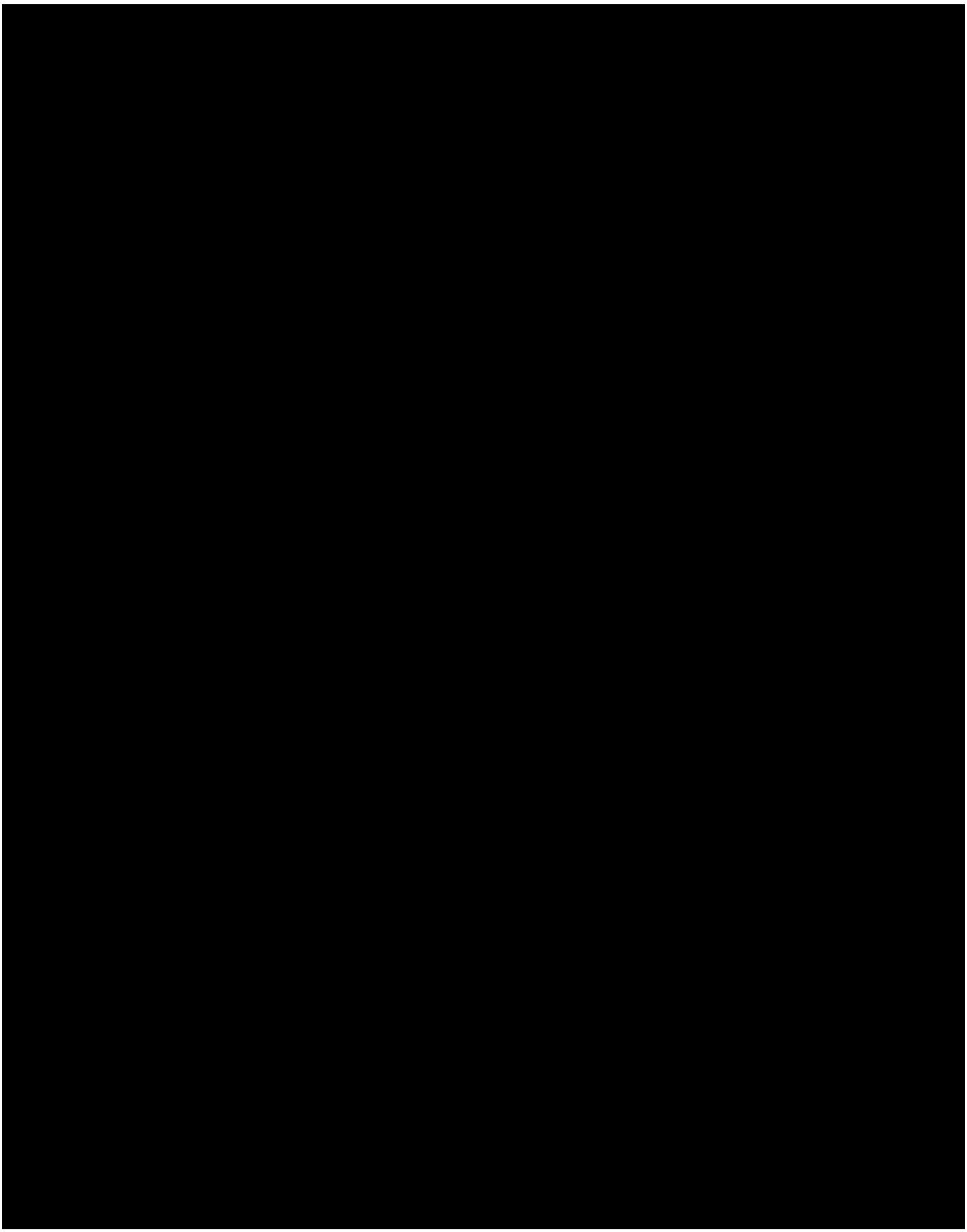
# TABLE OF CONTENTS

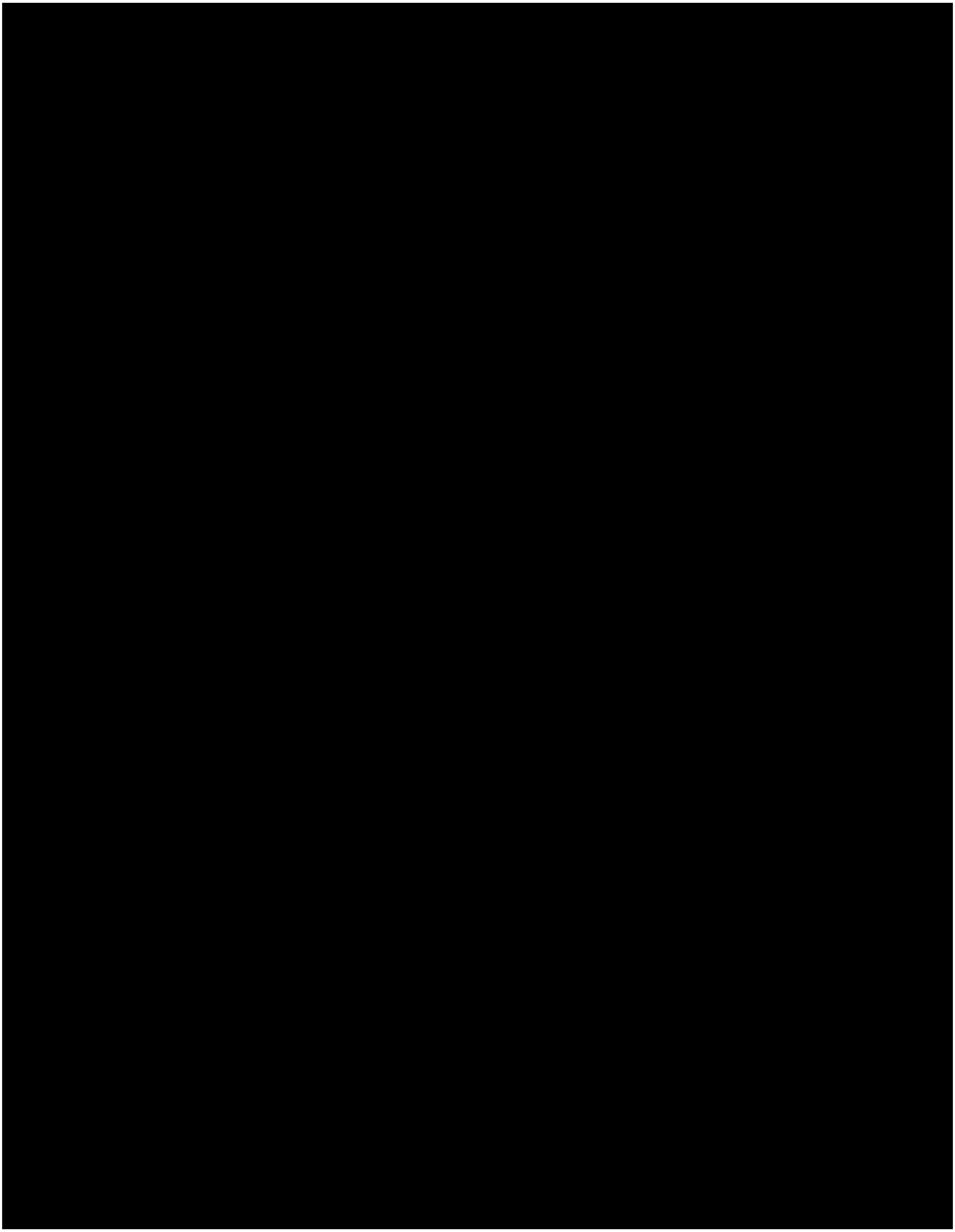
# ABBREVIATIONS

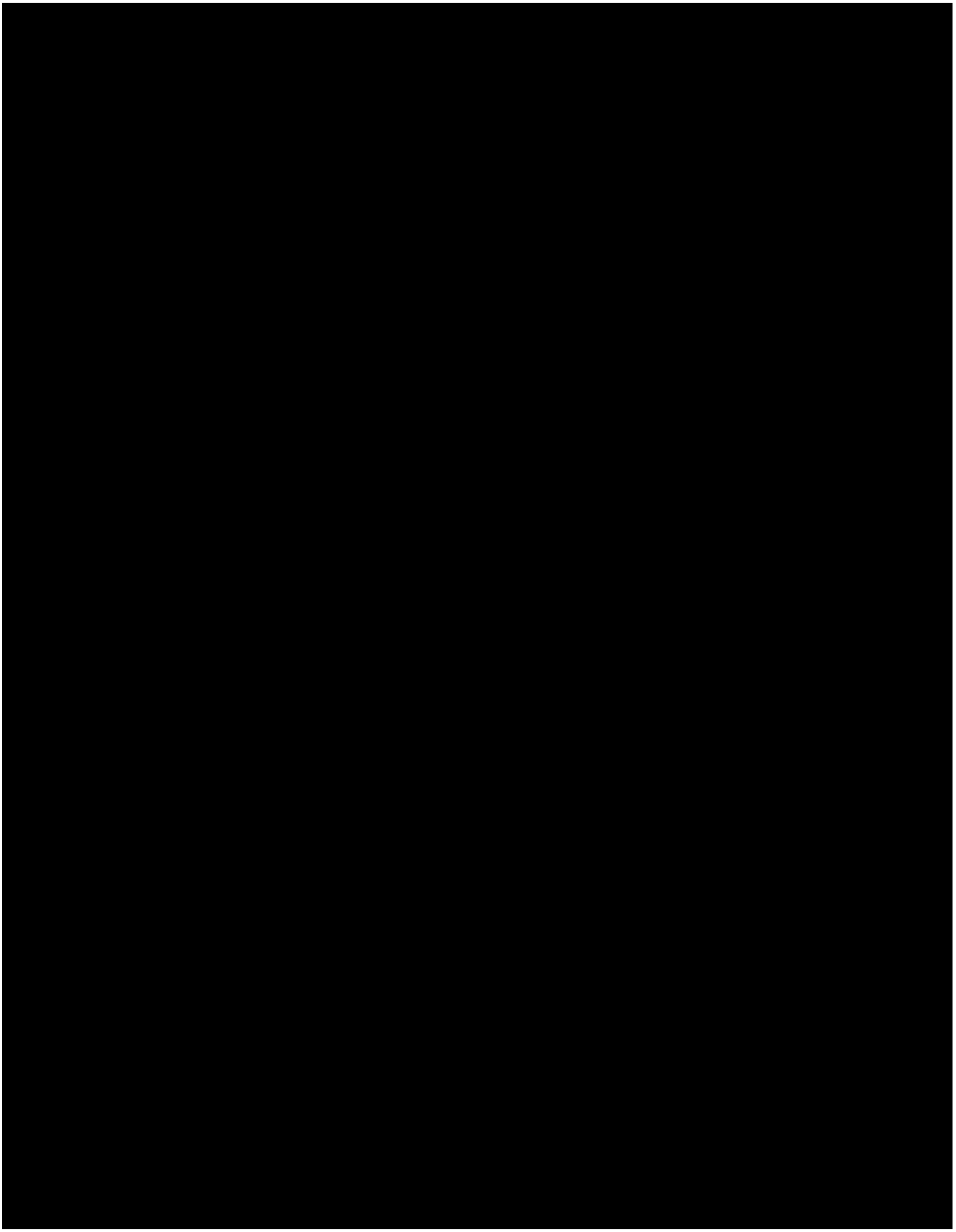
| | |
|---|---|
| AD | Alzheimer's Disease |
| ADME | Absorption, Distribution, Metabolism and Excretion |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ANOVA | Analysis of variance |
| APS | Attenuated Psychosis Syndrome |
| $AUC_{0-\infty}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| $AUC_{t1-t2}$ | 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 |
| BA | Bioavailability |
| BI | Boehringer Ingelheim |
| BLQ | Below limit of quantification |
| BMI | Body mass index (weight divided by height squared) |
| BP | Blood pressure |
| CA | Competent authority |
| CGMP | cyclic guanosine monophosphate |
| CI | Confidence interval |
| CIAS | Cognitive 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 |
| CRF | Case report form |
| CTP | Clinical trial protocol |
| CTR | Clinical trial report |
| CV | Arithmetic coefficient of variation |
| DILI | Drug induced liver injury |
| ECG | Electrocardiogram |
| EDTA | Ethylenediaminetetraacetic acid |
| EM | Extensive metabolizer |
| EOT | End of trial |
| F | Absolute bioavailability factor |
| GCP | Good Clinical Practice |
| gCV | Geometric coefficient of variation |

| | |
|---|---|
| GI | Gastro-intestinal |
| gMean | Geometric mean |
| HPC | Human Pharmacology Centre |
| HR | Heart rate |
| IB | Investigator's brochure |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| $\lambda_z$ | Terminal rate constant of the analyte in plasma |
| LC-MS/MS | Liquid chromatography with tandem mass spectrometry |
| LTP | Long term potentiation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| $MRT_{po}$ | Mean residence time of the analyte in the body after oral administration |
| NC | Not calculated |
| NMDA | N-methyl-D-aspartate |
| NOA | Not analysed |
| NOP | No peak detectable |
| NOR | No valid result |
| NOS | No sample available |
| PD | Pharmacodynamic(s) |
| PDE9 | Phosphodiesterase-9 |
| P-gp | P-glycoprotein |
| PK | Pharmacokinetic(s) |
| PKS | Pharmacokinetic set |
| PM | Poor metabolizer |
| PR | Pulse rate |
| q.d. | *Quaque die*, once daily |
| QT | Time between start of the Q-wave and the end of the T-wave in an electrocardiogram |
| R | Reference treatment |
| REP | Residual effect period |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SCR | Screening |
| SPC | Summary of product characteristics |
| SRD | Single-rising dose |
| Ss | (at) steady state |
| T | Test product or treatment |

| | |
|---|---|
| $t_{\lambda z,start(end)}$ | Lower (upper) limit on time for values to be included in the calculation of $\lambda_z$ |
| TMF | Trial master file |
| $t_{1/2}$ | Terminal half-life of the analyte in plasma |
| $t_{max}$ | Time from (last) dosing to the maximum measured concentration of the analyte in plasma |
| $t_z$ | Time of last measurable concentration of the analyte in plasma |
| TDMAP | Trial Data Management and Analysis Plan |
| TS | Treated Set |
| TSAP | Trial statistical analysis plan |
| $V_{ss}$ | Apparent volume of distribution at steady state after intravascular administration |
| $V_z$ | Apparent volume of distribution during the terminal phase after intravascular administration |
| $V_z/F$ | Apparent volume of distribution during the terminal phase after extravascular administration |







### 1.2.2 Rifampicin

Rifampicin is a broad-spectrum antibiotic that can be used to treat many infectious agents of clinical importance. Rifampicin inhibits bacterial RNA polymerase by blocking the path of the elongating RNA. Rifampicin is used mainly in the treatment of tuberculosis, but it is also a useful orally active alternative in the treatment of other infections such as those caused by methicillin-sensitive or methicillin-resistant staphylococcus [P03-08008]. The dosage of rifampicin in adults in the treatment of tuberculosis is usually between 450 and 600 mg/day.

*Pharmacokinetics*

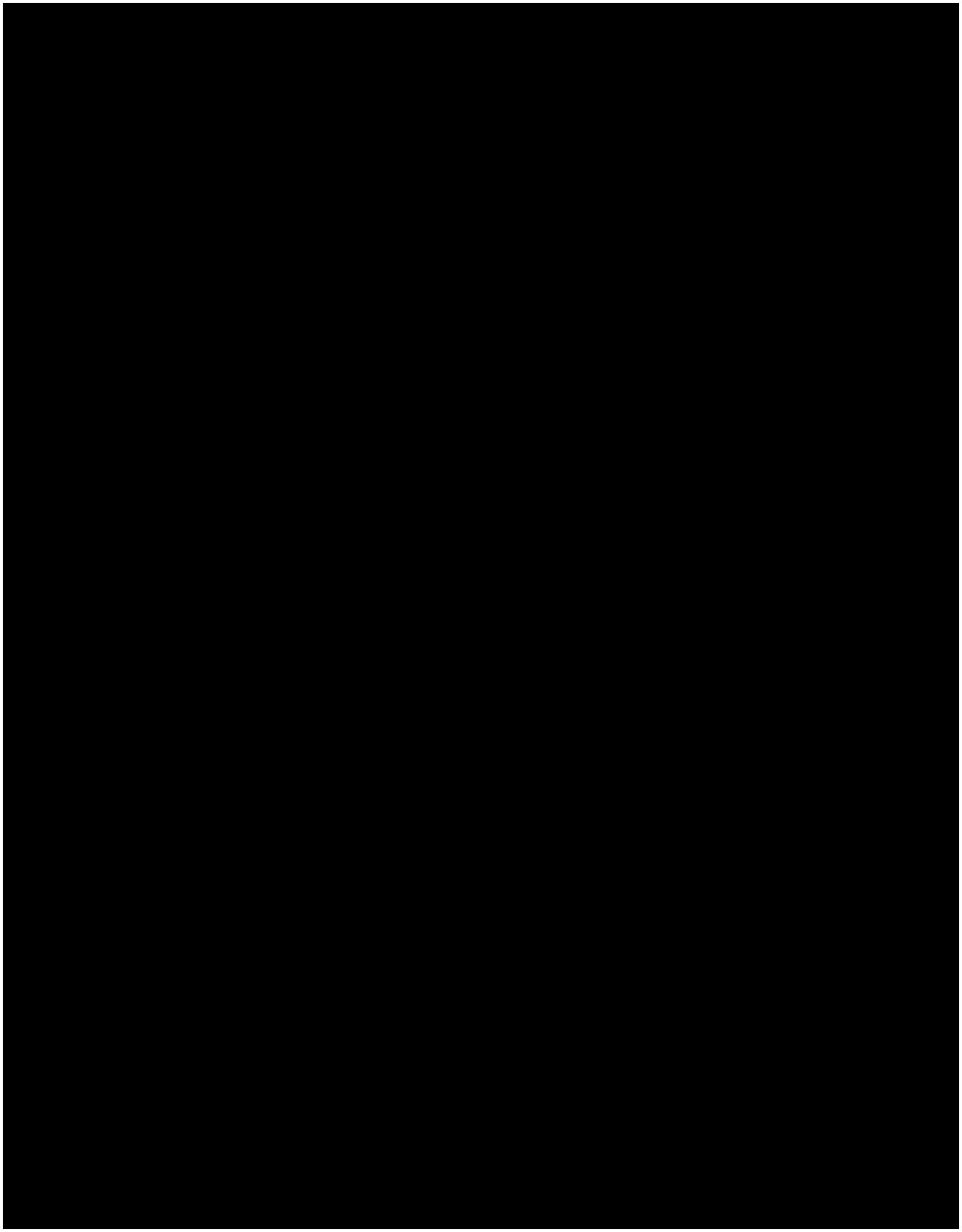
Rifampicin is readily absorbed from the gastrointestinal tract. Two hours after a single 600 mg oral dose of rifampicin in healthy adults, the mean peak serum concentration was 7 µg/mL (range: 4 to 32 µg/mL). Absorption of rifampicin was reduced by about 30% when the drug was ingested with food. Rifampicin has a large volume of distribution, and approximately 80% is plasma-protein bound. Most of the unbound fraction is ionized and, therefore, diffuses freely into tissues. Rifampicin is rapidly eliminated in the bile and is circulated enterohepatically. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.
In healthy adults, the mean biological half-life of rifampicin in serum averaged 3.4± 0.7 h after a 600 mg oral dose [R11-0197].
Rifampicin induces a number of drug-metabolising enzymes, having the greatest effects on the expression of CYP3A4 in the liver and in the small intestine. It induces several other CYP enzymes as well including CYP2C19 and 1A2. In addition, rifampicin induces some drug transporter proteins, such as intestinal and hepatic P-gp.
Full induction of drug-metabolising enzymes is reached in about 1 week after starting rifampicin treatment and the induction dissipates in roughly 2 weeks after discontinuing rifampicin [P03-08008].

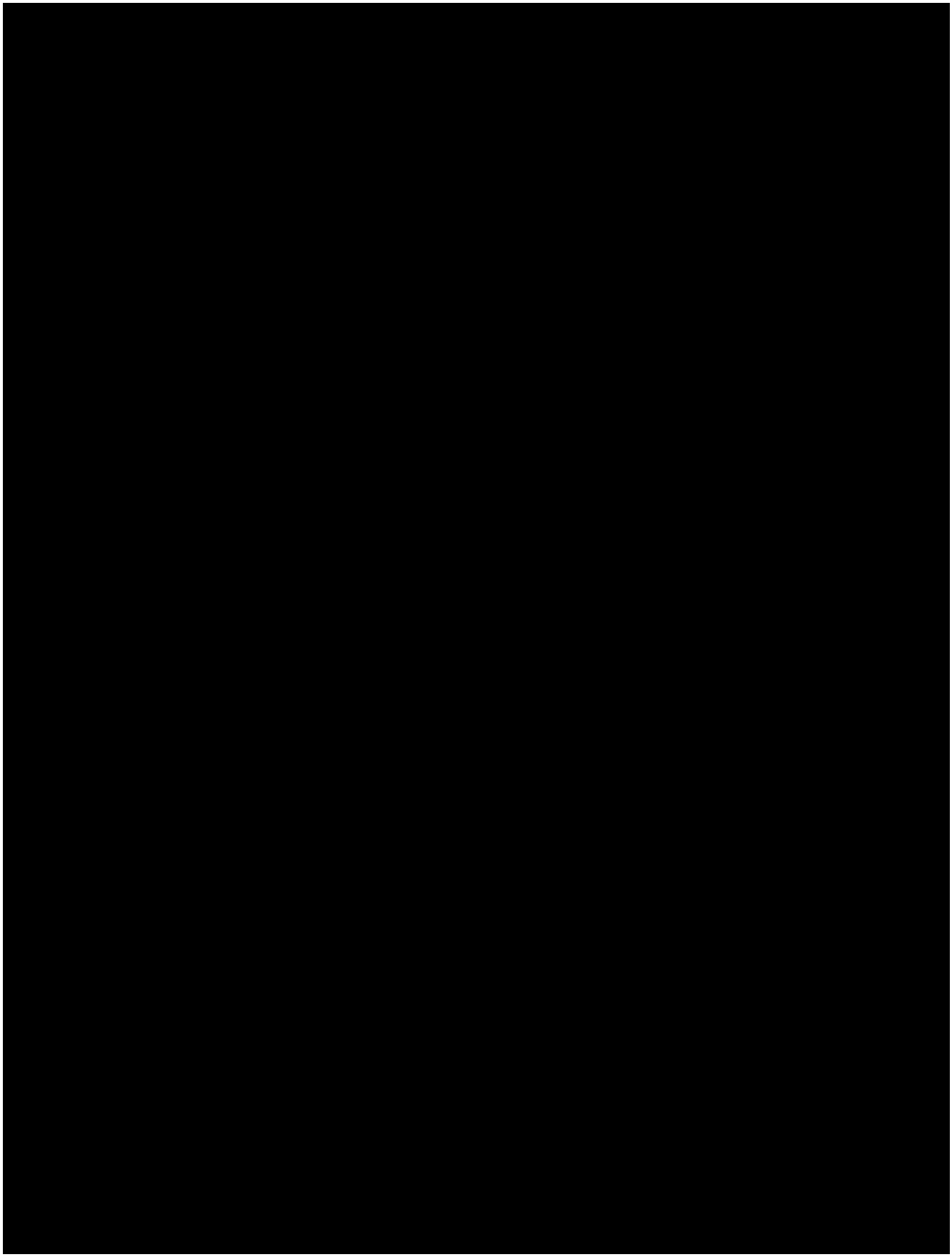
*Safety*

Very common adverse reactions to rifampicin are asymptomatic elevations of liver enzymes. In some patients hyperbilirubinaemia can occur in the early days of treatment. This results from competition between rifampicin and bilirubin for hepatic excretion. Hepatitis can be caused by rifampicin and monitoring of liver function tests is recommended.

Common adverse reactions are gastro-intestinal reactions including anorexia, nausea, vomiting, abdominal pain, meteorism, and diarrhoea as well as mild hypersensitivity reactions such as flushing, itching with or without skin rash, and urticaria. More serious hypersensitivity cutaneous reactions have been reported but are uncommon. Exfoliate dermatitis, pemphigoid reaction, erythema multiforme including Stevens-Johnson syndrome, Lyells syndrome and vasculitis have been reported rarely. Pseudomembranous colitis has been reported with rifampicin therapy in very rare cases.

For a complete listing of adverse reactions including frequency of occurrence please refer to the current version of the summary of product characteristics (SPC) [R16-5180].





# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

This clinical phase I study will be conducted as an open-label, two period, fixed-sequence trial with 2 treatments in order to compare the test treatment (T) to the reference treatment (R) in a single centre.
The trial will consist of 4 visits. Visit 1 will be the screening investigation.

Each subject will receive treatment R (reference) in Visit 2 and treatment T (test) in Visit 3. The two treatments are described below. The administrations of the single dose of BI 409306 in the first period (Visit 2) will be followed directly by the combined treatment period (Visit 3) without wash-out period. This is owed to the short half-life of BI 409306. For details refer to Section 4.1.

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

Reference treatment (BI 409306 alone):

One tablet of 50 mg BI 409306 will be given as a single dose on Day 1 of Visit 2 (treatment R).

Test treatment (rifampicin + BI 409306):

During the second period of the study (Visit 3, treatment T) one tablet of 600 mg rifampicin will be given once daily on Days -7 to Day -1. One tablet of 50 mg BI 409306 will be given as a single dose on day 1, approximately 14 h after the last rifampicin administration.

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.

[redacted]

[redacted]

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

[redacted]

## 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.

[redacted]

[redacted]

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 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease 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. Current smoker or ex-smoker who quit smoking less than 30 days prior to screening.
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 30 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

### 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.

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 product

The characteristics of trial product 1 are given below:

| | |
|---|---|
| Substance: | BI 409306 |
| Pharmaceutical formulation: | film-coated tablet |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | 50 mg |
| Posology: | 1-0-0 on day 1 of period 1 and 2 |
| Route of administration: | p.o. |
| Duration of use: | single dose in treatment T and R |

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 on day -7 to day -1 of period 2 |
| Route of administration: | p.o. |
| Duration of use: | 7 days (in treatment T 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 CYP2C19 induction. [redacted]

### 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 |
|---|---|---|---|---|---|
| R (Reference) | BI 409306 | Tablet | 50 mg | 1 tablet (50 mg) as single dose on day 1 of Visit 2 | 50 mg |
| T (Test) | BI 409306 | Tablet | 50 mg | 1 tablet (50 mg) as single dose on day 1 of Visit 3 | 50 mg |
| | Rifampicin | Tablet | 600 mg | 1 tablet (600 mg) once daily over 7 days (i.e. from day -7 to day -1 of Visit 3) | 4200 mg |

The medication will be administered 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 and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. BI 409306 administration will be performed in the morning of day 1(of period 1 and period 2) following an overnight fast starting no later than 10 h before scheduled dosing.
For rifampicin, subjects are advised to fast for at least 2 hours before and at least 30 minutes after drug administrations.
[redacted].

For restrictions with regard to diet see Section 4.2.2.2.

### 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

BI 409306 drug supply 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 German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers. The clinical trial supply containers for BI 409306 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.

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.

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 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 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.

## 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 and diclofenac must be avoided as symptomatic therapy of AEs due to its potential liver toxicity. Acetylsalicylic acid and dexamethasone is not allowed due to potential for CYP2C19 induction. Ibuprofen may be used as analgetic drug if need be.

Cimetidine, allicin, indomethacin, ketoconazole (non-topical), voriconazole (non-topical), fluconazole (non-topical), esomeprazole, lansoprazole, pantoprazole, or omeprazole are not allowed due to potential for CYP2C19 inhibition.

Ciprofloxacin, enoxacin, rofecoxib, and zafirlukast are not allowed due to potential for CYP1A2 inhibition.

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. Standardized meals will be served at the time points described in the Flow Chart.

On day 1 of period 1 and 2 the following applies:
No food is allowed for at least 4 h after intake of BI 409306 administration.
From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water 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.

For rifampicin, subjects are advised to fast for at least 2 hours before and at least 30 minutes after drug administrations (day-7 to –day -1). The restriction refers to food, water intake is allowed.

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 in this trial.

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 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)

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.

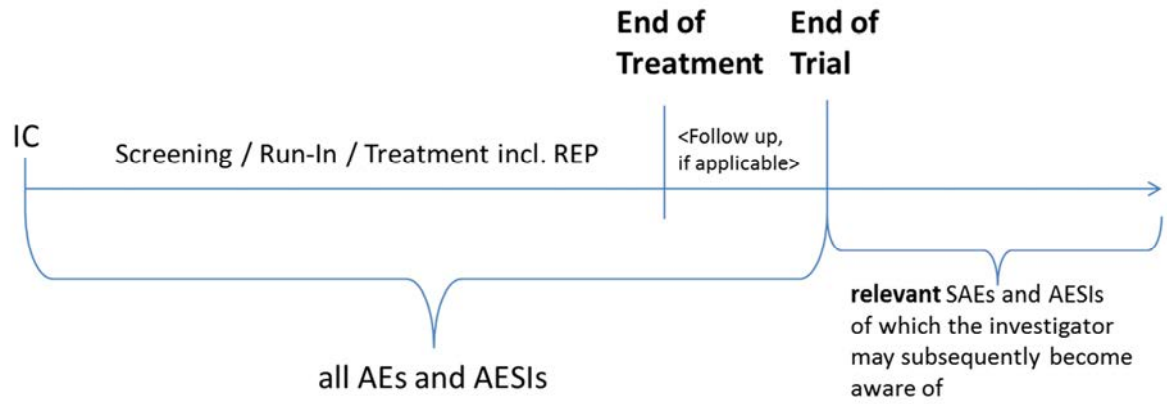
A careful written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.

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.




[redacted] The REP for rifampicin is defined as 6 days after the last administration of rifampicin.
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.

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 taken in the evening prior to rifampicin administration.

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

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

Table 5.2.3: 1 Routine laboratory tests

| Functional lab group | 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 | 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 |

* on day -4 of visit 3: safety lab without haematology and CRP.

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<br>Barbiturates<br>Benzodiazepine<br>Cannabis<br>Cocaine<br>Methadone<br>Methamphetamines/MDMA/XTC<br>Opiates<br>Phencyclidine<br>Tricyclic antidepressants |
| Infectious serology (blood) | Hepatitis B surface antigen (qualitative)<br>Hepatitis B core antibody (qualitative)<br>Hepatitis C antibodies (qualitative)<br>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 in 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.

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted]. These tests will be performed at the trial site using e.g. AccuSign DOA 10 test.

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 ECGC, 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 determined for BI 409306

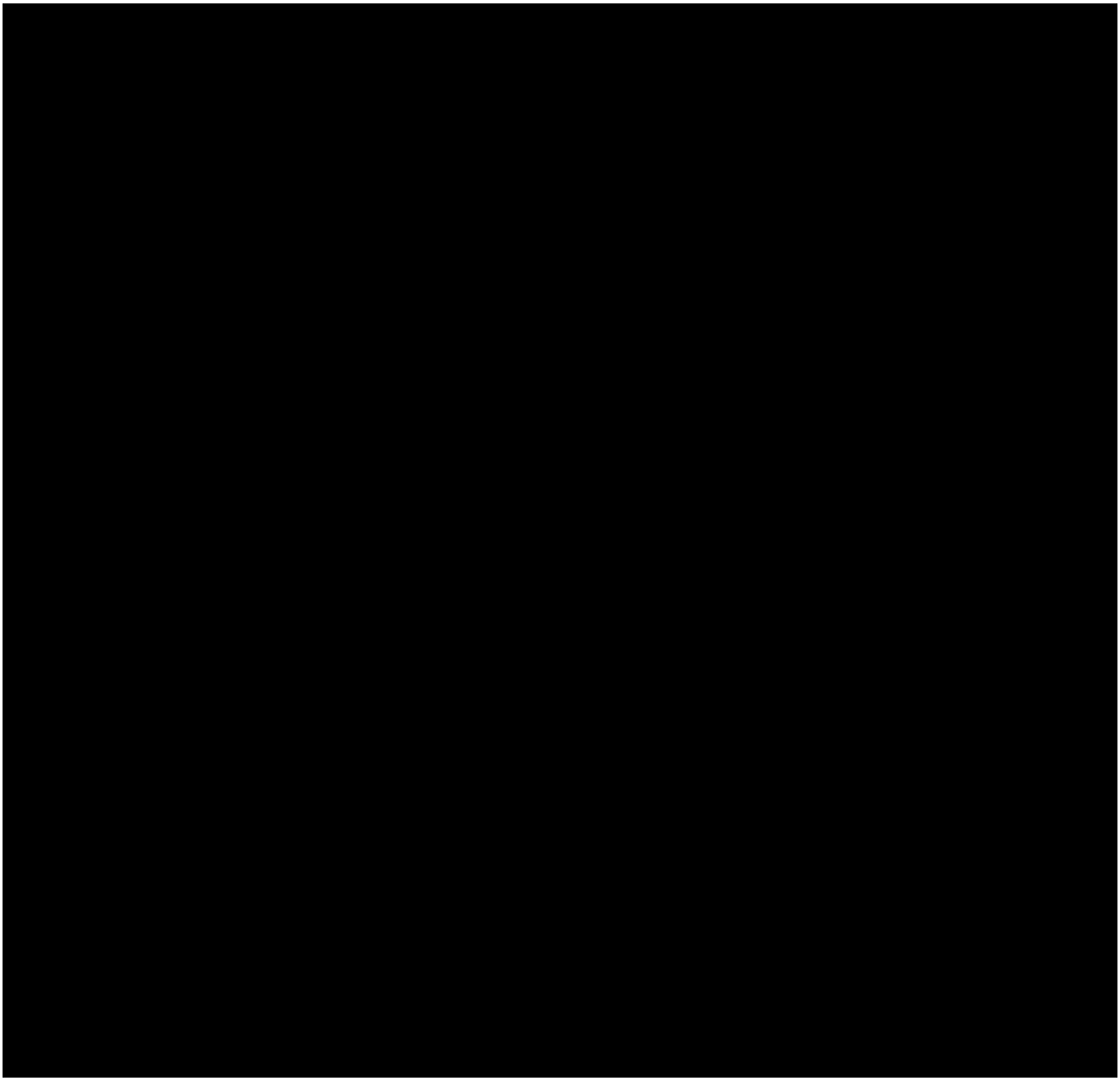
- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)

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

5.5.1.2 Secondary endpoints

The following secondary endpoints will be evaluated for BI 409306:

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



### 5.5.2 Methods of sample collection

[redacted]

The sample tube labels should list at least the following information: study number, subject number, visit, planned time and aliquot. Further information such as matrix and analyte may also be given.

After completion of the study the plasma samples may be used for methodological investigations, e.g. for stability testing, assessment of other metabolites, or further biomarker investigations. However, only data related to BI 409306, rifampicin and their metabolites 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 final study report has been signed.

5.5.2.2 Plasma sampling for analysis of rifampicin concentrations

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

The EDTA-anticoagulated 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 and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL plasma whereas the second aliquot should contain the remaining plasma (0.5 mL or less). Within a maximum time of 2 hours after sampling at room temperature, the samples should be stored in a freezer. Until shipment on dry ice to the analytical laboratory, plasma samples will be stored frozen in an upright position at about –20°C or below. The second aliquot will be shipped 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.

The sample tube labels should list at least the following information: study number, subject number, visit, planned time and aliquot. Further information such as matrix and analyte may also be given.

Backup samples (aliquot 3) from BI 409306 PK might be used for measurement of rifampicin concentrations if need be.

### 5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

[redacted]

[redacted]
Boehringer Ingelheim Pharma GmbH & Co. KG
Drug Metabolism and Pharmacokinetics Germany, G144
Birkendorfer Straße 65, 88397 Biberach/ Riß, Germany

Analysis of CD 13896 and CD 14084 in PK plasma study samples (aliquot 2) will be performed using validated liquid chromatography tandem mass spectrometry assays (LC-MS/MS) in the laboratory of:

[redacted]
Boehringer Ingelheim Pharma GmbH & Co. KG
Drug Metabolism and Pharmacokinetics Germany, G144
Birkendorfer Straße 65, 88397 Biberach/ Riß, Germany

[redacted]

[redacted].
Covance Laboratories Limited
Otley Road, Harrogate HG3 1PY
United Kingdom
Email : [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 -4, Day -1, and 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.

The time window for rifampicin administration from Day -7 to Day -2 is ± 60 min.

If scheduled in the Flow Chart at the same time as a meal, blood sampling and vital signs 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 and 2) in period 1, days -7 to day 2 in period 2.

[redacted]

On Day 1 of period 1 and Day – 1 of period 2 study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following BI 409306 drug

administration. On Day -7 of period 2 study participants will be admitted to the trial site and kept under close medical surveillance for at least 2 h following rifampicin 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 50 mg of BI 409306 tablets with prior 7-day intake of 600 mg rifampicin tablets (Test, T) compared to 50 mg of BI 409306 tablets without prior administration of rifampicin (Reference, R) following oral administration in healthy male subjects. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of an appropriate linear model.
The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between the treatments. The secondary objectives will be assessed by descriptive statistics.
The assessment of safety and tolerability will be an additional objective of this trial, and will be evaluated by descriptive statistics.

### 7.1.2 Endpoints

Relative bioavailability is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (see Section 5.5.1).
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 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: ‘subjects’ and ‘treatment’. The effect ‘subjects’ will be considered as random, whereas the treatment effect 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 (endpoint, see Section 7.1.3) measured on subject m receiving treatment k,

$\mu$ = the overall mean,

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

$\tau_k$ = the $k^{th}$ treatment effect, k = 1, 2,

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

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 409306 50 mg tablet after pre-administration of rifampicin 600 mg tablet for 7 days compared to BI 409306 50 mg tablet without pre-administration will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary PK endpoints. 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.
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

### 7.3.1 Primary analyses

The primary and secondary pharmacokinetic endpoints listed in Section 5.5.1 will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472].

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

Relevant protocol violations may be

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

Plasma 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 pre-dose concentration is >5% of the $C_{max}$ value of that subject
- missing samples/concentration data at important phases of PK disposition curve.

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one primary or secondary PK parameter that was not excluded according to the description above. Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment.

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.

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Only concentrations within the validated concentration range and actual sampling times will be used for the calculation of PK 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).

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.

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.

Point estimates of bioavailability, the intra-subject ratios of the geometric means (test/reference) for the primary and secondary endpoints (see 5.5.1.1, 5.5.1.2), and their two-sided 90% confidence intervals (CIs) will be provided.

To this end, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model (cf. Section 7.1.3). 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), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

### 7.3.2 Secondary analyses

As sensitivity analysis, the ANOVA performed as primary analysis will be repeated with subject as fixed effect instead of random effect. The results will be presented in the same manner as for primary analyses.

The following descriptive statistics will be calculated for primary and secondary PK parameters and for further endpoints: 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 3 significant digits in the clinical trial report.

### 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 evaluation. Safety analyses will be descriptive in nature and will be based on BI standards.

The analyses will be done by ‘treatment at onset’.

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. 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 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 ‘follow-up’. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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

Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline (day 1 of period 1) will be evaluated.

For vital signs, the differences from baseline will be evaluated.

Relevant ECG findings will be reported as AEs.

### 7.3.4 Interim analyses

No interim analysis is planned.

### 7.3.5 Pharmacokinetic analyses

For the analysis of pharmacokinetic parameters please refer to Section 7.3.1.

## 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

Randomization is not applicable in this open-label and single group clinical study. All subjects will receive the same treatment. A list of consecutive subject numbers for non-PM subjects will be provided (see Section 4.1.2 for details of allocation of subject numbers to subjects).

## 7.6 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 16 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial.

[redacted]

These calculations were performed as described by Kupper and Hafner [R12-0972] with R Version 3.0.2 and the package PowerTOST.

# 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 (TDMAP) available in the TMF.

## 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 (HPC) – 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

P03-08008 Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinet 2003. 42(9):819-850.

R10-5092 Cooke SF, Bliss TVP. Plasticity in the human central nervous system. Brain

R10-5102 Reymann KG, Frey JU. The late maintenance of hippocampal LTP: requirements, phases, 'synaptic tagging', 'late-associativity' and implications. Neuropharmacology 52, 24 - 40 (2007)

R11-0197 Rifadin (rifampin capsules USP) and Rifadin iv (rifampin for injection USP) (sanofi-aventis U.S.), Rx only (prescribing information, revised: November 2010). 2010.

R12-0972 Kupper LL, Hafner KB. How appropriate are popular sample size formulas? Am Stat 1989. 43(2):101-105.

R13-4518 Hu NW, Ondrejcak T, Rowan MJ. Glutamate receptors in preclinical research on Alzheimer's disease: update on recent advances. Pharmacol Biochem Behav 100, 855 - 862 (2012)

R13-4521 Lin CH, Lane HY, Tsai GE. Glutamate signaling in the pathophysiology and therapy of schizophrenia. Pharmacol Biochem Behav 100, 665 - 677 (2012)

R15-1457 Mathalon DH, Perkins D, Walker E, Addington J, Bearden C, Cadenhead K, Cornblatt B, McGlashan T, Seidman L, Tsuang M, Woods S, Cannon T, NAPLS, Consortium. Impaired synaptic plasticity, synaptic over-pruning, inflammation, and stress: a pathogenic model of the transition to psychosis in clinical high risk youth. 69th Ann Sci Convention and Mtg of the Society of Biological Psychiatry (SOBP), New York, 8 - 10 May 2014. Biol Psychiatry, 2014;75(9)(Suppl)

R15-3327 Perez VB, Woods SW, Roach BJ, Ford JM, McGlashan TH, Srihari VH, et al. Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: forecasting psychosis risk with mismatch negativity. Biol Psychiatry 2014. 75(6):459-469

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

R16-5274 Zhou HH, Anthony LB, Wood AJJ, Wilkinson GR. Induction of polymorphic 4'-hydroxylation of S-mephenytoin by rifampicin. Br J Clin Pharmacol 1990. 30:471-475

R16-5275 Zhou HH. CYP2C19 genotype determines enzyme activity and inducibility of S-mephenytoin hydroxylase. Clin Chim Acta 2001. 313:203-208

R16-5276 Feng HJ, Huang SL, Wang W, Zhou HH. The induction effect of rifampicin on activity of mephenytoin 4-hydroxylase related to M1 mutation of CYP2C19 and gene dose. Br J Clin Pharmacol 1998. 45:27-29

R17-0138 Dymond AW, So K, Martin P, Huang Y, Severin P, Mathews D et al. Effects of cytochrome P450 (CYP3A4 and CYP2C19) inhibition and induction on the exposure of selumetinib, a MEK1/2 inhibitor, in healthy subjects: results from two clinical trials. Eur J Clin Pharmacol 2017. 73:175-184

## 9.2 UNPUBLISHED REFERENCES

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

001-MCS-40-302 Reference document No. 24 (RD-24). Investigational Medicinal Product (IMP) and Auxiliary Medicinal Product (AMP) Manual. Current version.

[redacted] [redacted] c02098989-02 [redacted] Safety, tolerability and pharmacokinetics of single oral doses of BI 409306 (tablet) in healthy Chinese and Japanese male volunteers and multiple oral doses of BI 409306 (tablet) in healthy Japanese male volunteers (randomized, double-blind, placebo-controlled within dose groups), 1289.4, 13 March 2014

c09564954-01 [redacted]: A study to investigate the pharmacokinetic drug-drug interaction following oral administration of BI 409306 and donepezil in healthy male and female subjects. Clinical Trial Report 29-Nov-2016.

U12-1034-01 [redacted]. A randomized, double-blind, placebo-controlled (within dose groups) Phase I study to assess the safety, tolerability and pharmacokinetics of single rising doses 0.5 mg to 500 mg of BI 409306 administered orally in healthy male volunteers, Clinical Trial Report 1289.1, 19 Jan 2012

# 10. APPENDICES

Not applicable.

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

| | | |
|---|---|---|
| **Number of global amendment** | | |
| **Date of CTP revision** | | |
| **EudraCT number** | | |
| **BI Trial number** | | |
| **BI Investigational Product(s)** | | |
| **Title of protocol** | | |
| | | |
| **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** | | |
| **Description of change** | | |
| **Rationale for change** | | |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c13704479** **Technical Version Number:1.0**

**Document Name:** clinical-trial-protocol

**Title:** Effect of rifampicin on the pharmacokinetics of BI 409306 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 Clinical Monitor | [redacted] | 30 Jan 2017 16:35 CET |
| Approval-Therapeutic Area [redacted] | | 31 Jan 2017 08:22 CET |
| Verification-Paper Signature Completion | | 31 Jan 2017 09:40 CET |
| Author-Trial Clinical Pharmacokineticist | | 02 Feb 2017 11:18 CET |
| Author-Trial Statistician | | 03 Feb 2017 09:18 CET |
| Approval-Team Member Medicine | | 06 Feb 2017 14:26 CET |

**(Continued) Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|