Clinical Trial Protocol

	Document Number: c09109536-07
EudraCT No.:	2018-001335-44
BI Trial No.:	1289-0038
BI Investigational Product:	BI 409306
Title:	Thorough QT study to evaluate the effects of BI 409306 as single doses on cardiac safety parameters in healthy male and female subjects. A randomized, placebo controlled, double-blind, five-period crossover study with (open-label) moxifloxacin as positive control.
Lay Title:	This study in healthy men and women tests whether BI 409306 has an effect on the ECG (thorough QT study)
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 3))
Version and Date:	Version: 4.0 Date: 23 April 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 409306			
Protocol date: 08 February 2019	**Trial number:** 1289-0038		**Revision date:** 23 April 2019

Title of trial:	Thorough QT study to evaluate the effects of BI 409306 as single doses on cardiac safety parameters in healthy male and female subjects. A randomized, placebo controlled, double-blind, five-period crossover study with (open-label) moxifloxacin as positive control
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objective(s):	To evaluate the effect of a single therapeutic and a single supra-therapeutic dose of BI 409306 on the QT/QTc interval and other ECG parameters
Methodology:	Double-blind (moxifloxacin: open-label), randomised, placebo controlled, crossover with five treatment periods: 50 mg BI 409306, 250 mg BI 409306, 400 mg moxifloxacin (positive control) and placebo (2 periods). There will be a washout period of at least 6 days between treatments. Cardiac safety assessment will be performed based on triplicate 10-second ECGs as extracted at selected time points from 24 hours post-dose Holter recording as well as overall Holter assessment in each treatment period. For each treatment period, three triplicate baseline 10-second ECGs will be extracted at pre-defined time points from pre-dose Holter recording.
No. of subjects:	
total entered:	45
each treatment:	45 (at least 10 subjects of each gender)
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male/female subjects, age of 18 to 50 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product 1:	BI 409306 film-coated tablets (treatments 1 and 2)
Dose:	50 mg and 250 mg
Mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h

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Reference product 1:	Moxifloxacin (Avalox®) film-coated tablets (treatment 3)
Dose:	400 mg
Mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Reference product 2:	Placebo matching to BI 409306 50 mg tablets (treatment 4)
Dose:	Not applicable
Mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment:	One day (single dose) for each treatment
Criteria for pharmacokinetics:	
Criteria for safety:	Primary endpoints: The maximum mean difference between BI 409306 and placebo in the QTcF changes from baseline between 20 min to 24 hours after drug administration, for each dose of BI 409306. Secondary endpoints: • The maximum mean difference between moxifloxacin and placebo in the QTcF changes from baseline for the time points 2, 3, and 4 hours after dosing (for assessment of assay sensitivity). • The maximum mean difference between BI 409306 and placebo in heart rate (HR) changes from baseline between 20 min to 24 hours after drug administration, for each dose of BI 409306. • The minimum mean difference between BI 409306 and placebo in HR changes from baseline between 20 min to 24 hours after drug administration, for each dose of BI 409306.

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Statistical methods:

For the analysis of QTcF changes from baseline (ΔQTcF) at each time point between 20 min to 24 hours post drug administration, a linear mixed-effects model for repeated measurements will be used. The comparison between each dose of BI 409306 and placebo will be performed pairwise, i.e. data not relevant for the comparison of interest will be excluded. The model includes the covariates 'period baseline' and 'subject baseline' (defined as the arithmetic mean of the respective period baselines), the fixed categorical effects 'treatment', 'period', and 'time', the interaction terms 'period baseline-by-time', 'subject baseline-by-time', 'treatment-by-time', and 'period-by-time'. For comparisons between BI 409306 and placebo, two-sided 90% confidence intervals (CI) for the mean differences per time point and corresponding point estimators will be computed.

For assessment of assay sensitivity, the same model will be used to compare QTcF changes from baseline between moxifloxacin and placebo including all time points between 20 min to 24 hours post drug administration.

Changes from baseline in heart rate for BI 409306 as compared to placebo will be analysed in the same way as described for QTcF.

FLOW CHART (A)

Period	Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [13]		Holter ECG [7]	12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-25 to -5			Screening (SCR)[1]	x[A]			x[8]		x	
1/2/3/4/5 (5 periods with a wash-out of at least 6 days)	2/3/4/5/6	-7 to -3			Ambulatory visit for run-in ECGs (including in-house stay over at least 8 hours), in Visit 2 only[10,14]			▲ | ▼ 10,14				x[14]
		-1	-12:00	20:00	Admission to trial site[12]	x[5]						x
		1	-2:00	06:00	Allocation to treatment[2] (Visit 2 only)	x[2,B]	x[2]	▲[2]	x[2,8]	x[2]	x[2]	x[2]
			-0:50	07:10				├				
			-0:35	07:25				├				
			-0:20	07:40				├				
			0:00	08:00	Drug administration			*		▲		
			0:20	08:20			x	├		|		
			0:40	08:40			x	├		|		
			1:00	09:00			x	├	x[8]	|	x	x
			1:30	09:30			x	├		|		
			2:00	10:00	240 mL fluid intake	x[B]	x	├	x[8]	|		
			2:30	10:30			x	├		|		
			3:00	11:00			x	├		|		
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	├		▼	x	x
			8:00	16:00	Snack (voluntary)[3]		x	├				
			10:00	18:00	Dinner[3]			├				
			12:00	20:00			x	├			x	x
		2	24:00	08:00		x[C]	x	▼[11]				
			24:15	08:15	Breakfast (voluntary)[3], discharge from trial site				x[8]		x	x
EOT	7	5 to 12			End-of-trial (EOT) examination[4]	x[D]			x[8]		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, 12-lead single ECG, safety laboratory (including drug screening and pregnancy test in women), 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, pregnancy test in women, recording of AEs and concomitant therapies
5. Only urine drug screening, alcohol breath test, and pregnancy test in women will be done at this time point.
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. Holter ECG (◄—|—|—►). The arrows refer to start (►) and end (◄) of Holter ECG recording.
   The sign ├ indicates that trigger points will be set at the Holter device for extraction of triplicate 12-lead 10 second ECGs. The time is an approximate. For acceptable time deviations please refer to Section 6.1.
   The sign * indicates that a trigger point will be set at the Holter device at the time point of drug administration.
8. Single 12-lead ECG for clinical evaluation by the investigator only
9. No BI 409306 PK samples after open-label moxifloxacin administration

10. 12-lead Holter ECG is performed at Visit 2 and will be used for extraction of 7 drug-free 10-second run-in ECGs (over at least 8 hours as shown in Flow Chart (B)) and for analyses of arrhythmic events (at least 24 h recording as shown in Flow Chart (B)). The start of Holter ECG recording on Day -7 to -4 can be no earlier than 1 day after screening.
11. 12-lead Holter ECG recording on Day 1 and 2; recording to be stopped no earlier than 24 h after drug administration
12. Admission to the trial site should not be later than 10 hours prior to drug administration
13. Letters A, B, C and D describe different sets of safety laboratory examinations (see Table 5.2.3: 1)
14. in Visit 2 only

FLOW CHART (B) FOR AMBULATORY VISIT (RUN-IN), IN VISIT 2 ONLY

Period	Visit	Day	Planned time (relative to drug administration [h:min][5]	Approximate clock time of actual day [h:min]	Event and comment	Holter ECG[3]	Bed rest	Questioning for AEs and concomitant therapy
1	2	-7 to -4	-170:00	06:00	Admission to trial site, start of Holter recording	▲[1]		x[1]
			-168:50	07:10		|		
			-168:35	07:25		|		
			-168:20	07:40		|		
			-168:00	08:00	240 mL fluid intake	*	▲	
			-167:40	08:20		|	|	
			-167:20	08:40		|	|	
			-167:00	09:00		|	|	
			-166:30	09:30		|	|	
			-166:00	10:00	240 mL fluid intake	|	|	
			-165:30	10:30		|	|	
			-165:00	11:00		|	|	
			-164:00	12:00	240 mL fluid intake, thereafter lunch[2]	|	▼	
			-163:00	13:00		|		
			-162:00	14:00		|		
			-161:00	15:00		|		
			-160:00	16:00	Snack (voluntary)[2], discharge	|		
		-6 to -3	-144:00	08:00	Ambulatory visit (stop Holter recording)	▼[4]		x

1. The time is approximate; the procedure is to be performed and completed within 3 h prior to planned time -168:00.
2. If several actions are indicated at the same time point, the intake of meals will be the last action.
3. Holter ECG (◄—|—|—►). The arrows refer to start (►) and end (◄) of Holter ECG recording.

4. 12-lead Holter ECG recording to be stopped no earlier than -144:00 planned time.
5. Planned times for Holter ECG are placeholders, applicable for the time window Day -7 to -3.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AE/CT	Adverse event / Concomitant therapy
AESI	Adverse events of special interest
APS	Attenuated psychosis syndrome
AUC_{0-24h}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 – 24 h
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
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
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ at steady state
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
BI	Boehringer Ingelheim
bid	*Bis in die*, twice daily
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
bpm	Beats per minute (beats/min)
BRPM	Blinded report planning meeting
CA	Competent authority
cAMP	Cyclic adenosine monophosphate
CDISC	Clinical Data Interchange Standards Consortium
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical trial supplies unit
CV	Cardiovascular

CYP	Cytochrom P450
ΔQTc	Change from baseline in QTc
DDI	Drug drug interaction
DILI	Drug induced liver injury
DMET	Drug metabolism enzymes and transporters
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECGS	Electrocardiogram set
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EM	Extensive metabolizer
EOT	End of trial
FDA	Food and Drug Administration
FEP	First episode of psychosis
FIM	First in human
GCP	Good clinical practice
GLP	Good laboratory practice
gMean	Geometric mean
HEK293	Human embryonic kidney cells 293
hERG	human Ether-à-go-go-Related Gene
HPC	Human Pharmacology Centre
HR	Heart rate
IB	Investigator's brochure
IC_{50}	half maximal inhibitory concentration
IEC	Independent Ethics Committee
iPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LTP	Long term potentiation
MATE1	Multidrug and toxin extrusion 1
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects Model for Repeated Measurements
MRD	Multiple-rising dose

MRT_{po}	Mean residence time of the analyte in the body after oral administration
msec	Milliseconds
NMDA	N-methyl-D-aspartate
OAT	Organic anion transporter
PDE	Phosphodiesterase
PDE9	Phosphodiesterase-9
PK	Pharmacokinetic(s)
PM	Poor metabolizer
popPK	Population pharmacokinetic
PR	Pulse rate
PR interval	ECG interval from the onset of P wave to the beginning of the QRS complex
PTM	Planned time
qd	*Quaque die*, once daily
QRS duration	Combination of the Q, R, and S waves
QT interval	ECG interval from the beginning of the QRS complex to the end of the T wave
QTc	Generic term for QTcF, QTcI and QTcN intervals
QTcF	QT interval corrected using Fridericia's formula
REP	Residual effect period
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SAE	Serious adverse event
SCR	Screening
sd	Single dose
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
$t_{1/2}$	Terminal half-life of the analyte in plasma

TDMAP	Trial Data Management and Analysis Plan
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TMF	Trial master file
tQT	Thorough QT
TS	Treated set
TSAP	Trial statistical analysis plan
t_z	Time of last measurable concentration of the analyte in plasma
UGT	UDP glucuronosyltransferase
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

BI 409306 is a Phosphodiesterase-9 (PDE9) inhibitor that is being developed for relapse prevention in patients with schizophrenia (REX indication), and for the prevention of first episode of psychosis (FEP indication) in subjects with Attenuated Psychosis Syndrome (APS).

1.1 MEDICAL BACKGROUND

Schizophrenia is a chronic, severe, and disabling brain disorder affecting both men and women. Existing treatment options for schizophrenia (i.e. first- and second-generation antipsychotics) are primarily efficacious in treating positive symptoms and have limited, if any efficacy for the prevention of FEP or relapse in the chronic disorder. No pharmacologic therapies have been approved to delay or prevent a first episode of psychosis, and none are indicated for the symptomatic treatment of the cognitive impairment seen in patients with APS.

Schizophrenia is characterized by abnormalities in glutamatergic pathways related to N-methyl-D-aspartate (NMDA) receptor hypofunction in cortical and hippocampal brain areas [R13-4521]. These abnormalities are hypothesized to lead to negative symptoms and cognitive impairment in schizophrenia. NMDA receptor activation triggers a cascade of intracellular, post-synaptic signalling events through elevation of second messengers such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) with subsequent activation of protein kinases and manifestation of synaptic plasticity determined by long term potentiation (LTP), key processes underlying learning and memory formation [R10-5092, R10-5102].

PDE9 hydrolyses cGMP with the highest affinity of all PDEs and is highly expressed in the neocortex and hippocampus. Therefore it is likely to be a significant determinant of intracellular basal cGMP levels in these brain regions. In addition, increasing evidence suggests that glutamatergic dysfunction may play a key role in mediating risk for conversion to psychosis in individuals with attenuated psychosis syndrome [R15-3327; R15-1457]. Dysregulated NMDA receptor-dependent synaptic plasticity may be a proximal cause of disrupted functional connectivity seen in those who convert to first episode psychosis presumably via over-pruning of weak synapses during adolescence [R15-1457]. Consequently, inhibition of PDE9 should restore cGMP levels and thus NMDA receptor signalling to physiological levels and translate into memory improvement via strengthening of synaptic plasticity/LTP in patients. Moreover, PDE9 inhibition also represents a rational approach for improvement and potentially normalization of those processes dysfunctional in individuals with APS, leading to the delay or even prevention of FEP via decreasing synaptic over-pruning and strengthening the NMDA-receptor signalling and synaptic plasticity [c01694347-10].

1.2 DRUG PROFILE

1.2.1 BI 409306 nonclinical data

1.2.1.1 Efficacy

BI 409306 showed

1.2.1.2 Toxicology

In the nonclinical safety program, the *No Observed Adverse Effect Level* (NOAEL) after oral administration was as follows (Table 1.2.1.2: 1):

1.2.1.3 Preclinical Pharmacokinetics and Metabolism

1.2.1.4 hERG-assay

1.2.1.5 Cardiovascular function

For a more detailed description of the BI 409306 non-clinical profile please refer to the current Investigator's Brochure (IB) [c01694347-10].

1.2.2 BI 409306 clinical data

1.2.2.1 Ongoing studies/ studies under evaluation

BI 409306 is currently in Phase II clinical development with ongoing studies in the indications 'relapse prevention' in patients with schizophrenia (REX indication) and 'prevention of first episode of psychosis' (FEP indication) in subjects with APS.

1.2.2.2 Completed studies

In the current IB, data from fourteen Phase I studies in healthy volunteers (one of which also includes data from patients with schizophrenia and AD), one Phase I study and one Phase II study in patients with schizophrenia, and two Phase II studies in patients with AD are included. A total of 385 healthy volunteers (including 53 subjects age 65 years or older and 64 PM subjects) have been treated with BI 409306.

Moreover, 393 patients with schizophrenia, and 324 patients with AD have been treated with BI 409306. To date, a good safety and tolerability profile has been observed with BI 409306 [c01694347-10].

1.2.2.3 Clinical Pharmacology

1.2.2.4 Clinical Pharmacokinetics and Metabolism

Table 1.2.2.4: 1 gives an overview about exposure levels reached after single dose or multiple dose administration of BI 409306 in selected studies.

Table 1.2.2.4: 1 Overview about BI 409306 exposure levels in selected clinical studies in the BI 409306 clinical development program

Source: Tables 15.6.3: 1 of the respective clinical trial reports [U12-1034-01; U13-1182-01; c02098989-02; c03808525-02; c13128239-01]; FIM, first-in-human; sd, single dose; qd, once daily; CV, cardiovascular; DDI, drug-drug-interaction; ss, steady state;

1.2.2.5 Clinical Safety

For a more detailed description of the clinical profile of BI 409306 please refer to the current Investigator's Brochure [c01694347-10].

1.2.3 Moxifloxacin drug profile

Moxifloxacin is a fourth-generation fluoroquinolone antibacterial agent. It is marketed worldwide for treatment of a number of infections including respiratory tract infections, cellulitis, anthrax, intraabdominal infections, endocarditis, meningitis, and tuberculosis. Moxifloxacin has been used in several QT trials in healthy volunteers as a positive control due to its modest QT-prolonging properties at a dose of 400 mg. Moxifloxacin was shown to induce a mean increase in the QTc interval of between 7.5-12.5 msec with a median tmax of 2 h after a single oral dose of 400 mg [R10-0867]. Because the magnitude of the QT prolongation is small after 400 mg, there is minimal risk of moxifloxacin-induced torsade de pointes. The pattern of side effects of moxifloxacin is well established, with the most common adverse effects being headache, light-headedness, nausea, vomiting, diarrhea, gastrointestinal/abdominal pain and aspartate transaminase (AST)/alanine transaminase (ALT) increase. For details about adverse events occurring after moxifloxacin administration please refer to Section 2.3.

Following oral administration moxifloxacin is rapidly and almost completely absorbed. The absolute bioavailability amounts to approximately 91%. Following a 400 mg oral dose peak concentrations of 3.1 mg/l are reached within 0.5-4 h post administration. Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in the form of a sulpho-compound and a glucuronide. Moxifloxacin is eliminated from plasma with a mean terminal half-life of approximately 12 hours.

For a more detailed description of the clinical profile moxifloxacin please refer to [R19-0482].

1.2.4 Residual Effect Period

The Residual Effect Period (REP) of BI 409306 is 24 hours. The REP of moxifloxacin is 4 days.

The REP is the period after the last dose with measurable drug levels and/or pharmaco-dynamic effects still likely to be present.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

According to the guideline ICH E14 (CHMP/ICH/2/04 2005) “The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs” (2005) [R07-4722] and the respective Questions and Answers Document (2017) [R17-2903] concerning the evaluation of QT/QTc-interval prolongation, a randomized study with concurrent placebo control and positive control should be conducted in order to investigate the effect of a drug (here BI 409306) on the QT/QTc-interval in healthy volunteers. The conduct of such a study in healthy volunteers is preferred, as these provide a stable signal without influence of concurrent diseases or concomitant therapies. While a balanced recruitment of male and female volunteers is aimed at, a minimum of 10 subjects of each gender is mandatory. This is considered acceptable since recruitment of women is anticipated to be challenging due to exclusion of WOCBP using hormonal contraception.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to assess the effect of BI 409306 on the QT/QTc interval in healthy male and female volunteers as measured by the QTcF change from baseline compared with placebo.

Secondary objectives are to show the assay sensitivity of the trial, by reproducing the typical effect of the positive control moxifloxacin on the QT/QTc interval, and to assess the effect of BI 409306 on heart rate.

The assessment of safety and tolerability of BI 409306 particularly with regard to cardiac safety are additional objectives of this trial.

A detailed description of the study endpoints is provided in Sections 5 and 7.1.2.

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance for the further clinical development of BI 409306. The assessment of the potential of BI 409306 to induce QTc prolongation will contribute to a safe clinical use of this PDE9 inhibitor in patients with schizophrenia or APS. The subjects in this trial are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous

catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

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

Drug-related risks and safety measures

Risks related to BI 409306 administration

Thus, for this trial the assumed therapeutic dose of 50 mg and a supra-therapeutic dose of 250 mg were selected.

Risks related to moxifloxacin administration

In all clinical trials and derived from post-marketing reports with moxifloxacin 400 mg (used as an antibiotic), the following adverse reactions are reported [R19-0482]. Apart from nausea and diarrhea all adverse reactions were observed at frequencies below 3%.

- Common (≥1/100 to <1/10):
  - Superinfections (due to resistant bacteria or fungi, e.g. oral and vaginal candidiasis)
  - Headache, dizziness
  - QT prolongation (in patients with hypokalaemia)
  - Nausea, vomiting, gastrointestinal and abdominal pains, diarrhoea
  - Increase in transaminases
- Uncommon (≥1/1,000 to <1/100):
  - Anaemia, leucopenia(s), neutropenia, thrombocytopenia, thrombocythemia, blood eosinophilia, prothrombin time prolonged/INR increased
  - Allergic reaction
  - Hyperlipidemia
  - Anxiety reactions, psychomotor hyperactivity/agitation
  - Par- and dysaesthesia, taste disorders (incl. ageusia in very rare cases), confusion and disorientation, sleep disorders (predominantly insomnia), tremor, vertigo, somnolence
  - Visual disturbances, incl. diplopia and blurred vision (especially in the course of CNS reactions)
  - QT prolongation, palpitations, tachycardia, atrial fibrillation, angina pectoris

- Vasodilatation
- Dyspnea (incl. asthmatic conditions)
- Decreased appetite and food intake, constipation, dyspepsia, flatulence, gastritis, increased amylase
- Hepatic impairment (incl. LDH increase), increased bilirubin, gamma-glutamyl-transferase and blood alkaline phosphatase
- Pruritus, rash, urticaria, dry skin
- Arthralgia, myalgia
- Dehydration
- Feeling unwell (predominantly asthenia or fatigue), painful conditions (incl. pain in back, chest, pelvic and extremities), sweating

- Rare (≥1/10,000 to <1/1,000):
  - Anaphylaxis (incl. very rarely life-threatening shock), allergic oedema/angioedema (incl. laryngeal oedema, potentially life-threatening)
  - Hyperglycemia, hyperuricemia
  - Emotional lability, depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideations/thoughts, or suicide attempts), hallucination
  - Hypoaesthesia, smell disorders (incl. anosmia), abnormal dreams, disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo), seizures (incl. grand mal convulsions), disturbed attention, speech disorders, amnesia, peripheral neuropathy and polyneuropathy
  - Photophobia
  - Tinnitus, hearing impairment incl. deafness (usually reversible)
  - Ventricular tachyarrhythmias, syncope (i.e., acute and short lasting loss of consciousness)
  - Hypertension, hypotension
  - Dysphagia, stomatitis, antibiotic associated colitis (incl. pseudo-membranous colitis, in very rare cases associated with life-threatening complications)
  - Jaundice, hepatitis (predominantly cholestatic)
  - Tendonitis, muscle cramp, muscle twitching, muscle weakness
  - Renal impairment (incl. increase in blood urea nitrogen and creatinine), renal failure
  - Oedema
- Very rare (<1/10,000):
  - Prothrombin level increased/INR decreased, agranulocytosis
  - Hypoglycaemia
  - Depersonalization, psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/thoughts, or suicide attempts)
  - Hyperaesthesia
  - Transient loss of vision (especially in the course of CNS reactions), uveitis and bilateral acute iris transillumination
  - Unspecified arrhythmias, Torsade de Pointes, cardiac arrest
  - Vasculitis
  - Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases)

- Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening)
- Tendon rupture, arthritis, muscle rigidity, exacerbation of symptoms of myasthenia gravis

For a more detailed description of the profile of Moxifloxacin please refer to the 'Summary of Product Characteristics' (SmPC) for Avalox® 400 mg film-coated tablets [R19-0482].

Safety measures

To ascertain the safety and minimise the risk for healthy volunteers, several safety measures and investigations will be implemented in this trial:

- A thorough screening examination will ensure that only suitable healthy subjects will enter the study; a marked baseline prolongation of QT/QTc interval, a history of additional risk factors for torsade de pointes or arrhythmic events in Holter ECG recording during run-in will be excluded from study participation (see Section 3.3.3).

- To reduce the risk of undesirable effects, only single doses of trial medication will be given in each treatment period.
- The subjects will be closely monitored through assessment of adverse events, safety lab, ECG and vital signs as well as through continuous ECG monitoring for 4 hours post treatment in each treatment period.
- The subjects will maintain under close medical surveillance for at least 24 hours post dosing in each treatment period.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety, see also Section 5.2.2.1, subsection "Adverse events of special interest".

In summary, the information gained from this trial will provide the basis for further clinical development of the PDE9 inhibitor BI 409306, which is expected to become a valuable therapeutic option for patients with schizophrenia and APS. BI 409306 has a favorable benefit-risk-assessment based on a thorough preclinical data package as well as knowledge gained from previous clinical studies using BI 409306, which justifies further testing in humans. Considering the medical need regarding the treatment of schizophrenia and APS, the sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers to the trial medication.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, placebo controlled, double-blind, five-period, four treatment crossover trial with two placebo periods and (open-label) moxifloxacin as positive control in healthy male and female subjects. The replicate design with respect to placebo allows for estimating the treatment contrasts of each active drug to placebo more precisely than with only one single placebo period, thus enabling a reduced sample size (see [R12-0517] and Section 7.6).

The treatments will be:

- Treatment 1 ([**L**] – low):
  50 mg BI 409306 (1x 50 mg tablet + 4x placebo matching to 50 mg tablet) in the fasting state, single dose
- Treatment 2 ([**H**] – high):
  250 mg BI 409306 (5x 50 mg tablet) in the fasting state, single dose
- Treatment 3 ([**M**] – moxifloxacin):
  400 mg moxifloxacin (1 tablet) in the fasting state, single dose
- Treatment 4 ([**P1**] – 1st placebo period and [**P2**] – 2nd placebo period):
  Matching placebo (5x placebo matching to 50 mg tablet) in the fasting state, single dose

For details refer to Section 4.1.

The subjects will be randomly allocated to the 15 treatment sequences (3 subjects per sequence) planned in this trial (see Section 7.1).

There will be a washout phase of at least 6 days between the treatments.

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

3.1.1 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 (CML), Clinical Research Associates (CRAs), and participating trial sites.

BI 409306 and matching placebo trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany. Moxifloxacin (Avalox®) will be ordered by the trial site from a local pharmacy.

The trial will be conducted at the , under the supervision of the Principal Investigator.

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

The analyses of the concentrations of BI 409306 and metabolites in plasma will be performed at the contract research organisation . The pre-specified will be performed at the

The digitally recorded Holter ECGs in Visits 2-6 will be sent to a specialised contract research organisation ( ) for evaluation.

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

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

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

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

According to the guideline ICH E14 (CHMP/ICH/2/04 2005) “The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs” (2005) [R07-4722] and the respective Questions and Answers Document (2017) [R17-2903] concerning the evaluation of QT/QTc-interval prolongation, a randomised study with concurrent placebo control and a positive control will be conducted in order to investigate the effect of a drug (BI 409306) on QT/QTc-interval in healthy volunteers.

As positive control, the subjects will receive a single dose of moxifloxacin 400 mg, which is known to induce moderate QT/QTc-prolongation (see Section 2.1) and will therefore verify the ability of the study to detect relevant changes in the QT/QTc-interval.

For thorough QT trials, the crossover design is preferred due to its efficiency: since each subject serves as his/her own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This trial design therefore removes intersubject variability from the comparison between treatments [R94-1529]. Moreover, with proper randomisation of subjects to the different sequences of treatment administrations, it provides the best unbiased estimates for the differences between treatments. Additionally, the total number of subjects needed to participate in this trial is minimised compared to a parallel

group design trial. Since all assessments in tQT trials are based on the comparisons between active treatment and placebo, these treatment contrasts should be estimated with the highest statistical efficiency. To account for this, the selected crossover design for this trial will include a second placebo period instead of only one. The sample size for the resulting 4-treatment 5-period crossover design can be determined as 3/4 of the sample size of the corresponding 4-period crossover design (see also Section 7.6).

Blinding with regard to the study drug substances to be investigated versus their matching placebos is essential in such a study. ECG profiles will be performed for BI 409306 and placebo in a double-blind fashion. The positive control (moxifloxacin) will be administered open-label. This is not expected to bias results, since moxifloxacin is known to robustly induce a mean increase in the QTc interval of between 7.5 – 12.5 msec with a median t_{max} of 2 hours after a single oral dose of 400 mg [R10-0867]. The technicians and cardiologists at the ECG laboratory performing the ECG interval measurements and assessments will remain blinded in this study with regard to all treatments, including moxifloxacin and placebo (see Section 5.2.4).

3.3 SELECTION OF TRIAL POPULATION

It is planned that 45 healthy male and female subjects (at least 10 subjects of each gender) will enter the study. They will be recruited from the volunteers' pool of the trial site.

A log of all subjects enrolled into the trial (that is, 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 or female subjects according to the assessment of the investigator, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead single ECG and 12-lead Holter ECG, and clinical laboratory tests
2. Age of 18 to 50 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
5. Male subjects, or female subjects who meet any of the following criteria starting from at least 30 days before the first administration of trial medication and until 30 days after trial completion:
   - Use of adequate contraception, e.g. non-hormonal intrauterine device *plus* condom
   - Sexually abstinent

- A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
- Surgically sterilised (including hysterectomy)
- Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

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 100 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

14. Inability to refrain from smoking
15. Alcohol abuse (consumption of more than 20 g per day for females and 30 g per day for males)
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. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 msec) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. For female subjects, positive pregnancy test, pregnancy or plans to become pregnant within 30 days after study completion
24. For female subjects, lactation period
25. For female subjects, concomitant use of hormonal replacement therapy or hormonal contraceptives

27. Findings from run-in Holter ECG recording judged to be clinically relevant
28. Subjects with any condition that would preclude administration of moxifloxacin (i.e. contraindicated as per SmPC), such as but not limited to history of tendon disease/damage as a result of quinolone therapy, clinically relevant bradycardia, clinically relevant heart failure with reduced left ventricular ejection fraction or a history of symptomatic cardiac arrhythmia.

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:

1. If the subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. If the subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. If the subject is no longer able to participate for other medical reasons (such as pregnancy, surgery, AEs, or diseases)
4. If 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. If the subjects shows an elevation of AST and/or ALT ≥3-fold ULN.
6. In case of relevant individual QT prolongations in safety ECG recordings, i.e. absolute QT or QTc > 500 msec and/or QTc increase > 60 msec from baseline (i.e., pre-dose), as confirmed by a repeat ECG recording.
7. In case of a serious adverse reaction, or in case of a severe non-serious adverse reaction not listed in Table 7.6: 1 of the current Investigator's brochure.

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

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 1.2), 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.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication has to be stopped immediately, and the subject has to be removed from the trial. The subject is to be followed until she has given birth or until the end of pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the clinical trial report. For reporting of pregnancy and events refer to Section 5.2.2.2.

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.
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.

3.3.5 Replacement of subjects

In case some subjects do not complete the trial as per protocol, the Trial Clinical Monitor together with the Trial Pharmacokineticist and the Trial Statistician are to decide if and how many subjects will be replaced. A maximum of 5 subjects will be replaced. Thus, the total number of subjects entered and dosed in this trial will not exceed 50. A replacement subject

will be assigned a unique study subject number, and will be assigned to the same treatment sequence as the subject he or she replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

BI 409306 and matching placebos will be manufactured by BI Pharma GmbH & Co. KG.

Moxifloxacin (Avalox®) 400 mg tablets produced by Bayer Vital, Leverkusen, Germany, will be sourced from a local pharmacy.

4.1.1 Identity of BI investigational products

The characteristics of the test product 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 treatment 1 [L], 5-0-0 on Day 1 of treatment 2 [H]
Route of administration:	p.o.
Duration of use:	Single dose in treatments 1 [L] and 2 [H]

The characteristics of the reference products are given below:

Name:	Avalox®
Substance:	Moxifloxacin
Pharmaceutical formulation:	Film-coated tablet
Source:	Bayer Vital, Leverkusen, Germany
Unit strength:	400 mg
Posology:	1-0-0 on Day 1 of treatment 3 [M]
Route of administration:	p.o.
Duration of use:	Single dose in treatment 3 [M]

Substance:	Placebo matching to BI 409306 50 mg tablet
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	4-0-0 on Day 1 of treatment 1 [L], 5-0-0 on Day 1 of treatment 4 ([P1] and [P2])
Route of administration:	p.o.
Duration of use:	Single dose in treatments 1 [L] and 4 ([P1] and [P2])

4.1.2 Method of assigning subjects to treatment groups

According to the calculated sample size, 5 cohorts are planned. Prior to start of the study, subjects willing to participate will be recruited to cohorts according to their temporal availability. Since the study includes healthy volunteers from a homogenous population, relevant imbalances between the treatment sequences are not expected.

The list of study subject and medication numbers will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. 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.

The randomisation procedure is described in Section 7.5.

The overall number of 45 subjects is planned to be split into 5 cohorts. In case subjects need to be replaced an additional cohort may be added or replacement subjects may be added to existing cohorts allowing up to 12 subjects on treatment days. The planned cohort size allows a timely conduct of the study with reasonable duration minimizing seasonal impact on trial data while at the same time still allows adequate medical surveillance of the subjects. Within one cohort, subjects will be treated on the same calender day. No minimal time interval between dosing is defined. This is acceptable from a safety point of view (for safety margin margins refer to Section 1.2.2.4; for discussion of study-associated risk and safety measures see Section 2.3).

4.1.3 Selection of doses in the trial

The dose of 50 mg was selected in order to measure the effect of the anticipated therapeutic dose of BI 409306. The dose of 250 mg was selected in order to measure the effect of a tolerable supra-therapeutic dose of BI 409306 on cardiac safety (see Section 1.2).

4.1.4 Drug assignment and administration of doses for each subject

This trial is a five-period crossover study. All subjects will receive the 4 treatments (two placebo periods) in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule, oral administration

Treatment	Substance	Formulation	Unit strength	Number of units	Total dose
1 [L]	BI 409306	Tablet	50 mg	1	50 mg
	Placebo to BI 409306 50 mg	Tablet	---	4	
2 [H]	BI 409306	Tablet	50 mg	5	250 mg
3 [M]	Moxifloxacin	Tablet	400 mg	1	400 mg
4 ([P1] and [P2])	Placebo to BI 409306 50 mg	Tablet	---	5	---

The medication will be administered as a single oral dose together with about 240 mL of water to a subject in a 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 will be performed following an overnight fast which is to start no later than 10 h before scheduled dosing.

Subjects will be kept under close medical surveillance until at least 24 h following BI 406309, moxifloxacin and placebo administration. Holter ECG will be recorded from up to 3 hours prior to drug administration until at least 24 hours after drug administration. During the first 2 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) except for medical examinations, single ECG recordings and triplicate ECG extraction time points and preceding resting time. For restrictions with regard to diet see Section 4.2.2.2.

The treatments will be separated by a wash-out phase of at least 6 days.

4.1.5 Blinding and procedures for unblinding

The two doses of BI 409306 and matching placebos will be administered double-blind with regard to the subjects and the investigators (as well as the research staff at the trial site) in order to eliminate observer or performance bias; moxifloxacin will be administered open-label. This means avoiding systematic differences in assessments regarding the subject's treatment (active or placebo). Persons directly involved in the clinical conduct or statistical analysis of the trial will not have access to the treatment allocation prior to database lock.

At the sponsor, access to the randomisation schedule is restricted to the Clinical Trial Support group, who generates the randomisation code and labels, to the Pharmaceutics Department, where the packaging takes place, to the independent programmer as described below, and to the trial bioanalyst.

Prior to trial initiation, the randomisation codes will be provided to an independent programmer, who will generate a list indicating the moxifloxacin treatment period for each subject in the form of e.g. X-X-M-X-X or M-X-X-X-X. This list will be provided to the

clinical site to enable study set up. The independent programmer will confirm that the original randomisation codes will be treated confidentially.

Prior to unblinding of the trial database, the randomisation codes will be provided to bioanalytical staff to allow them to exclude from the bioanalytical analyses PK samples taken from placebo-treated subjects. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.

The trial will only be unblinded after locking of the database.

Within the central ECG lab, the staff involved with interval measurements and morphological analyses will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician.

4.1.5.1 Procedures for emergency unblinding

For this blinded trial, the investigator will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomisation scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or to assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope or appropriate CRF page along with the date and the initials of the person who broke the code. At the close-out visit all envelopes are collected.

4.1.6 Packaging, labelling, and re-supply

BI 406309 and matching placebos 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. Each container will contain 2 blisters with 7 tablets each of either BI 409306 50 mg or matching placebo. The 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
- Subject or medication number
- Visit number
- Batch number

At the trial site, drug will be dispensed by the investigator or authorised designee according to medication and visit numbers (table 4.1.6: 1):

Table 4.1.6: 1 Content of the blisters containing trial medication for treatments 1 [L], 2 [H], and 4 ([P1] and [P2])

Treatment	Blister	Number of units (tablets) to be dispensed#	Blister containing *	Unit strength	Total dose
1 [L]	Blister 1	1	BI 409306 50 mg tablet	50 mg	50 mg
	Blister 2	4	Matching placebo tablet	---	
2 [H]	Blister 1	1	BI 409306 50 mg tablet	50 mg	250 mg
	Blister 2	4	BI 409306 50 mg tablet	4x 50 mg	
4 ([P1] and [P2])	Blister 1	1	Matching placebo tablet	---	---
	Blister 2	4	Matching placebo tablet	---	---

* The information about blister content will not be provided to the clinical site
# Each blister contains 7 tablets; only 1 tablet (of blister 1) and 4 tablets (of blister 2) will be used

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.

Moxifloxacin (Avalox®) will be sourced from a local pharmacy. It will not be labelled. The original packaging (German commodity) will be used for the open-label part of the trial.

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 ensure 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 amounts of tablets 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. 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.

Ibuprofen may be used as an analgesic drug if needed.

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 drug intake.

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 fasting requirements see Section 4.1.4.

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 in the study is collected.

Smoking is not allowed starting from 30 days prior to screening until end-of-trial examination.

Alcoholic beverages are not allowed from 48 h before administration of trial medication until the end of hospitalisation period in each treatment period.

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

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 (that is, sunbathing) or exposure to solarium radiation should be avoided during the entire study.

If female subjects of child-bearing potential are included, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for adequate measures).

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

5.2.1.1 Primary safety endpoints

The primary endpoint will be the maximum mean difference between each single dose of either 50 mg or 250 mg BI 409306 and placebo in QTcF changes from baseline between 20 min to 24 hours after drug administration. QTcF is the heart rate corrected QT interval according to Fridericia (see Section 7.3.2.5).

5.2.1.2 Secondary safety endpoints

- The maximum mean difference between moxifloxacin and placebo in QTcF changes from baseline between 20 min to 24 hours after drug administration.
- The maximum mean difference between each single dose of either 50 mg or 250 mg BI 409306 and placebo in HR changes from baseline between 20 min to 24 hours after drug administration. HR will be derived from the RR interval (see Section 7.3).
- The minimum mean difference between each single dose of either 50 mg or 250 mg BI 409306 and placebo in HR changes from baseline between 20 min to 24 hours after drug administration.

5.2.1.3 Further safety endpoints

5.2.1.3.2 Further criteria of interest

Safety and tolerability of the investigational drugs will be assessed based on:

- AEs (including clinically relevant findings from physical examination)
- Safety laboratory tests
- 12-lead single ECGs or Holter ECG recordings
- Vital signs (blood pressure, pulse rate)

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.

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

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

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

Serious adverse event

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

- results in death
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- requires inpatient hospitalisation
- requires prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect
- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.2.2.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

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

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

Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.2.2.

The following is considered as AESI:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

Intensity (severity) of AEs

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

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

Causal relationship of AEs

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned)
- Disappearance of the event even though the study drug treatment continues or remains unchanged

5.2.2.2 Adverse event collection and reporting

AE collection

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

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

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

If subjects report a change in perception or any vision-related AE, site staff must record the subject's verbatim description in the source documents to be reported in the eCRF.

A local ophthalmology assessment will be required if any visual AE is rated as severe by the subject or at the discretion of the investigator. The ophthalmologist will act as a consultant to the investigator and may offer advice on the proper management and treatment for the reaction.

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

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs

      The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to

screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the Investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

AE reporting to sponsor and timelines

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

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

Information required

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

Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the Investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

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

5.2.3 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. Over-night fasting is not required for drug screening and pregnancy test at admission and at the discretion of the investigator or designee for re-tests.

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D
Haematology	Haematocrit	X	--	--	X
	Haemoglobin	X	--	--	X
	Red Blood Cell Count/Erythrocytes	X	--	--	X
	White Blood Cells/Leucocytes	X	--	--	X
	Platelet Count/Thrombocytes (quant)	X	--	--	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	--	--	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	--	--	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.				
Coagulation	Activated Partial Thromboplastin Time	X	--	--	X
	Prothrombin time	X	--	--	X
	Prothrombin time – INR (International Normalization Ratio)	X	--	--	X
Enzymes	AST (Aspartate transaminase) /GOT, SGOT	X	--	X	X
	ALT (Alanine transaminase) /GPT, SGPT	X	--	X	X
	Alkaline Phosphatase	X	--	--	X
	Gamma-Glutamyl-Transferase	X	--	X	X
	Amylase	X	--	--	X
	Lipase	X	--	--	X
Hormones	Thyroid Stimulating Hormone	X	--	--	--
Substrates	Glucose (Plasma)	X	--	--	X
	Creatinine	X	--	--	X
	Bilirubin, Total	X	--	--	X
	Bilirubin, Direct	X	--	--	X
	Protein, Total	X	--	--	X
	C-Reactive Protein (Quant)	X	--	--	X
	Cholesterol, total	X	--	--	X
	Triglyceride	X	--	--	X
Electrolytes	Sodium	X	X	--	X
	Potassium	X	X	--	X
	Calcium	X	X	--	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

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

A: Parameters to be determined at Visit 1 (screening examination)
B: Parameters to be determined prior to dosing and at 2:00 PTM on Day 1 of Visits 2 to 6
C: Parameters to be determined on prior to discharge on Day 2 of Visits 2 to 6
D: Parameters to be determined at Visit 7 (end-of-trial examination)

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 pregnancy test and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each treatment period (on Days -1 or 1), and as part of the end-of-trial examination. Drug screening will be performed at screening and prior to each treatment period (on Days -1 or 1).

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 (qual) Hepatitis B core antibody (qual) Hepatitis C antibodies (qual) HIV-1 and HIV-2 antibody (qual)
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with alcoholic restrictions, a breath alcohol test (Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed prior to each treatment period (on Days -1

or 1), 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 with the exception of the drug screening and pregnancy tests. These tests will be performed at the trial site using M-10/14-PDT test and HCG-K20 test, respectively, or comparable test kits.

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead continuous (Holter) ECG recording at the clinical site

To determine potential effects of BI 406309 on cardiac safety parameters, 12-lead continuous 24-hour Holter ECG recordings will be used to extract 10-second triplicate ECGs for cardiac interval and heart rate analysis (see Section 5.2.4.2) as well as to analyse heart rhythm and conduction (see Section 5.2.4.3).

The 12-lead continuous 24-hour Holter ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be recorded using Holter devices (e.g. CardioMem® CM 3000, GETEMED AG, Berlin, Germany) provided by the core lab. Recordings will be started within 3 h prior to drug administration and will last at least until 24 h post drug administration in each treatment period. Prior to each Holter recording, the device will be initialized with subject ID and visit number. The exact starting time of the Holter recordings will be documented on a provided housekeeping list. Moreover, at dosing a trigger button will be pressed on the Holter recorder to electronically mark the time point of drug administration on the Holter recordings.

A lead system with modified Einthoven/Goldberger leads (the so called Mason/Likar lead system) and precordial leads according to Wilson will be applied. Electrode placement will be performed by trained personnel according to established anatomical landmarks to ensure individual placement of electrodes will be identical throughout all 5 treatment periods.

Before and at the planned time points at which resting ECGs are to be extracted from 24-hour Holter ECG recordings, the subjects should be kept in a relaxed and quiet environment. Thus, at least 5 minutes prior to the triplicate ECG extraction time points (see Flow Chart), the subjects will take a supine position to ensure a stable heart rate at rest and high ECG quality during the recordings. These resting periods and ECG recordings will always precede all other study procedures planned for the same time point to avoid compromising ECG quality.

To guide the extraction of the ECGs by the core lab, the study staff will be instructed to press a trigger button twice on the recorder after the intended 3-minute extraction period (which was preceded by a 5-minute resting period) to electronically mark the end of the 3-minute extraction period. Triplicate 10-second ECGs will be extracted by the core lab (see Section 5.2.4.2) during the 3-minute time window preceding the electronic marks.

The Holter ECG recordings from each treatment period will be transmitted to the central ECG laboratory using a provided secure transfer program. The ECG data will be checked by the core lab for any timing inconsistencies prior to the evaluation of the ECGs.

5.2.4.2 12-lead triplicate ECG evaluation at the central ECG laboratory

At the core lab, the evaluation of the triplicate 10-second ECGs extracted per ECG time point from the 24-hour Holter ECG recordings on Days 1 and 2 of Visits 2-6 comprises the determination of cardiac axis (measured automatically) as well as the intervals RR, PR, QRS and QT measured semi-automatically. All semi-automatic interval measurements in an individual subject will be performed on the same lead. The intervals will be measured from 4 cardiac cycles (beats) in Lead II. If Lead II shows a flat T wave or is not measurable for any reason, Lead V5 will be used, or if that lead is not measurable, then Lead I will be used. The lead actually used will be reported in the CTR. HR and the QT interval corrected for HR (QTc, e.g. QTcF) will be determined by BI (see TSAP for details). For the run-in ECGs on Day -7 of Visit 2 only QT and RR will be determined semi-automatically.

Morphological analyses of the extracted triplicate ECGs will be performed by a board-certified cardiologist or equivalent for 1 randomly selected ECG per extraction time point (exception: No morphological analysis for run-in ECGs). The cardiologists' assessments will include an overall assessment (classifications are: 'normal', 'abnormal, clinically relevant', 'abnormal, clinically not relevant', 'not evaluable') as well as qualitative ECG findings with respect to e.g. rhythm, conduction and morphological abnormalities, presence of myocardial infarction, ST segment deviations, T wave morphology and presence of U-wave. Basis of the terminology used for the evaluation is the most current published version of CDISC controlled terms at the time of the final ECG transfer. Abnormalities detected during centralised ECG evaluation will be entered as AEs if assessed as clinically relevant based on the investigator's judgement.

For blinding arrangements see Section 4.1.5. Within the ECG laboratory, the staff involved with ECG interval measurements and morphological analyses will be blinded with regard to treatment, date and time as well as time points of the ECG measurements. No more than two blinded readers will evaluate all ECGs of the study. The interval measurements for a given subject will be performed in random and blinded sequence by a single reader. For quality assurance and control of the measurements, all ECGs of an individual subject will be subsequently reviewed by the ECG technician supervisor or his/her designee to assess the overall variance of the measured intervals and to detect accidental switching of leads and/or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

Evaluation of extracted triplicate ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R17-2903] as well as the FDA requirements for annotated digital ECGs [R09-4830].

5.2.4.3 12-lead Holter ECG evaluation at the central ECG laboratory

In addition to the interval measurements on extracted triplicate ECGs, also Holter arrhythmia analysis (as defined in the TSAP) will be performed for the complete recording period of 24 h post dosing in each of the 5 treatment periods (at Visits 2 to 6). Holter arrhythmia analysis will also be performed for the run-in Holter (as defined in the TSAP). These analyses will be performed by the same board-certified cardiologist or equivalent who is reviewing the extracted 10-sec ECGs. Run-in Holter ECG recording will be evaluated by the core lab and the results will be relevant for subject In/Exclusion (see Section 3.3.3).

All ECG recordings will be stored at the central ECG laboratory for later additional analyses if needed. Recording and transmission procedures will be explained in detail in a study specific "ECG manual" which will be given to the site and stored in the ISF.

5.2.4.4 Safety 12-lead single standard ECG and run-in (Holter) ECG

- For immediate cardiac safety assessment, a single standard 12-lead ECG will be recorded
  - at the screening examination (Visit 1)
  - prior to drug administration, at PTM 1:00 and at PTM 2:00 in each treatment period (Visits 2 to 6),
  - once on Day 2 in each treatment period (Visits 2 to 6) prior to discharge from the site
  - at the end-of-trial examination (Visit 7)

  These 12-lead single ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded for 10 seconds each using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) provided by the site. Electrode placement will be performed adjacent to the Holter ECG electrodes according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). For each time point, a printout should be obtained and filed at the investigational site. All locally printed ECGs will be evaluated by the investigator or a designee. These ECGs will not be sent to the central ECG laboratory responsible for evaluation of the Holter recordings (refer to Sections 5.2.4.2 and 5.2.4.3). ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation). The repeat ECGs are assigned to the respective scheduled time point. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

- To exclude clinically relevant cardiac arrhythmia and to generate drug-free RR/QT data for the derivation of QTcI, a 12-lead run-in Holter ECG recording over at least 24 h (for arrhythmia analysis; at least 22 h of recorded ECG data need to be evaluable) and at least 8 h (for drug-free RR/QT data) will be performed as described in Section 5.2.4.1
    - at Visit 2 only

  and evaluated by the core lab.

The purpose of the ECGs at screening (single standard 12-lead ECG) and the run-in 12-lead Holter ECG recording is to obtain information about the subjects' baseline condition that may not have been elicited in obtaining the medical history. Therefore, abnormal clinically relevant findings from ECG as judged by the investigator will be recorded in the medical history. The investigator will decide about subject inclusion in case of findings in the screening and run-in ECGs, thoroughly taking into account the exclusion criteria. Moreover, the 12-lead run-in Holter ECG will be used to extract multiple drug-free 10-second ECGs for proper QTcI derivation.

5.2.4.5 Continuous 3-lead ECG monitoring

In each treatment period, cardiac rhythm (including heart rate) will be monitored by means of continuous 3-lead ECG recording using the CARESCAPE Monitor B450 (GE Healthcare, Freiburg, Germany) for at least 10 min before drug administration (for baseline assessment) until 4 h after dosing. This continuous ECG monitoring supports the early detection of adverse events such as clinically relevant bradycardia, tachycardia, or arrhythmia at the trial site. Beyond this clinical evaluation at the trial site, no further data collection or analyses are performed based on continuous 3-lead ECG monitoring at the site. ECG data from continuous 3-lead ECG recording will not be transferred to the clinical trial database.

5.2.4.6 Adverse events assessment from ECG

Abnormal findings from safety 12-lead single ECGs, Holter recordings or 3-lead continuous ECG monitoring, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or recorded in the subject's medical history (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 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) 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.

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 and

pharmacodynamic 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.

5.6 BIOMARKERS

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented.

Time windows are permitted as follows:

- 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-hour period prior to the trial drug administration.
- The acceptable deviation from the scheduled time for vital signs and single safety 12-lead ECGs will be ± 30 min on Day 1 and 2 of each treatment period except for procedures which are to be completed within 3 h prior to drug administration as outlined in the Flow Chart.
- The timing of ECG extractions from 24-hour Holter recordings (see Flow Chart) is of particular importance in this study. Thus, triplicate ECG extraction from Holter ECG recordings will always precede PK sampling and measurements of vital signs if scheduled for the same time point. The acceptable time windows for ECG triggering in Holter ECG recordings to mark the end of the extraction periods (see Section 5.2.4) are ± 5 minutes up to 2 hours after dosing (or after planned time -168:00 in case of run-in Holter ECG) and ± 10 minutes from more than 2 hours to 24 hours after dosing (or after planned time -168:00 in case of run-in Holter ECG).
- 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. Acceptable deviations from nominal times are ± 5 minutes for up to 2 hours after dosing and ± 10 min from more than 2 hours to 24 hours after dosing.
- If scheduled in the Flow Chart at the same time as a meal, blood sampling or vital signs assessment, the end of the extraction periods from Holter ECG recordings have to be triggered 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, including ECG time intervals.
- For a particular subject, the clock time of dosing should be similar in all 5 treatment periods (± 60 minutes).

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 Blinded 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, and pregnancy test in females), 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 Run-in Holter ECGs in Visit 2 only

Each subject who successfully passed the screening period is expected to participate in an ambulatory visit (Visit 2 only) for run-in ECG Holter recording prior to randomisation. This will be used for generation of drug-free Holter ECG data to assess the cardiac rhythm over at least 24 hours

During this ambulatory visit, subjects will enter the trial site in the morning and stay in the trial site for at least 8 hours to allow triggering for ECG extraction. Subjects will then be allowed to leave the trial site. They will return the next morning and the Holter ECG recording will then be stopped after at least 24 h recording (for arrhythmia analysis at least 22 h of recorded ECG data need to be evaluable).

6.2.3 Treatment periods

Each subject is expected to participate in 5 treatment periods (that are each comprised of Days -1, 1 and 2). The treatment periods will be separated by at least 6 days wash-out between drug administrations.

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 in all treatment periods. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.5.2. After administration of moxifloxacin no blood samples for pharmacokinetic analysis will be taken.

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.

6.2.4 End-of-trial period

For AE/CT assessment, laboratory tests (including pregnancy test in females), 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

The study will be performed as a randomised, double-blind, 5-period crossover of single dose treatments including BI 409306 50 mg and 250 mg, as well as open-label moxifloxacin. The placebo (matching to BI 409306) will be given twice in two separate periods. This choice of BI 409306 doses allows subjects to reach BI 409306 exposure levels at and above the anticipated daily exposure of BI 409306 in the target population. The replicate design with respect to placebo allows for estimating the treatment contrasts of each active drug to placebo more precisely than with only a single placebo period, thus enabling a reduced sample size (see [R12-0517] and Section 7.6).

The treatment sequences are based on a Prescott triple Latin square design for five treatments and 5 periods, which is a balanced, efficient design [R14-5088]. Fifteen sequences will be formed according to the following scheme:

Table 7.1: 1 Prescott triple Latin square crossover design for 5 treatments and 5 periods

	Treatment Period				
Sequence	1	2	3	4	5
1	A	B	D	E	C
2	B	C	E	A	D
3	C	D	A	B	E
4	D	E	B	C	A
5	E	A	C	D	B
6	A	C	E	D	B
7	B	D	A	E	C
8	C	E	B	A	D
9	D	A	C	B	E
10	E	B	D	C	A
11	A	E	D	B	C
12	B	A	E	C	D
13	C	B	A	D	E
14	D	C	B	E	A
15	E	D	C	A	B

The allocation of the codes (A, B, C, D, E) to the 4 treatments L, H, M, P ([P1] and [P2]), (see Section 3.1) will be done prior to the randomisation in a way that the knowledge of the open-label treatment M does not unblind the other 3 treatments.

Throughout the study protocol, the term “baseline” (if not specified further) refers to the 3 pre-dose triplicate ECG measurements at Visits 2-6 (i.e. a separate baseline for each period

will be derived from the 9 ECG recordings that comprise 4 cardiac cycles each). Each ECG measurement per time point on treatment is derived from the 3 single ECGs with 4 cardiac cycles each. For further details on the derivation rules refer to Section 7.3. All ECGs used for the evaluation of QT/QTc (and additional ECG time intervals) are extracted from 12-lead 24-hour Holter recordings.

Since it is not expected that the mean of the placebo-corrected HR change from baseline will be larger than 10 beats/min for both doses of BI 409306, QTcF will be selected as the primary correction method for the present trial.

7.1.1 Objectives

The objective of this trial is to assess the effect of BI 409306 on the QT/QTc interval. As per ICH E14, this thorough QT trial will be deemed as negative if the maximum upper limit of the two-sided 90% confidence bound for the mean difference between BI 409306 and placebo in QTcF changes from baseline after single dose administration is less than 10 msec; this applies to both doses of BI 409306 (50 mg and 250 mg).

Secondary objectives are to show the assay sensitivity of the trial, by reproducing the typical effect of the positive control moxifloxacin on the QT/QTc interval, and to assess the effect of BI 409306 on the heart rate.

The assessment of safety and tolerability of BI 409306 particularly with regard to cardiac safety are additional objectives of this trial.

7.1.2 Endpoints

The primary endpoint will be derived based on the changes from baseline in QTcF at each time point between 20 min to 24 hours after drug administration of BI 409306 and placebo. For each of the 2 doses of BI 409306, the relevant outcome is the maximum mean difference between BI 409306 and placebo in the QTcF changes from baseline (see also Section 5.2.1.1).

The secondary endpoints are based on (see also Section 5.2.1.2):

- The QTcF changes from baseline at each time point between 20 min to 24 hours after drug administration of moxifloxacin and placebo (for assessment of assay sensitivity). The relevant outcome is the maximum mean difference between moxifloxacin and placebo in the QTcF changes from baseline for the time points 2, 3, and 4 hours after dosing.
- The changes from baseline in HR at each time point between 20 min to 24 hours after drug administration of BI 409306 and placebo. For each dose of BI 409306, the relevant outcomes are the maximum and the minimum mean differences between BI 409306 and placebo in HR changes from baseline after dosing. HR will be derived from the RR interval (see Section 7.3).

Safety and tolerability will be determined on the basis of further safety endpoints specified in Section 5.2.1.3.

7.1.3 Model

For the analysis of the QTcF changes from baseline at each time point between 20 min to 24 hours after dosing, a linear mixed-effects model for repeated measurements (MMRM) will be used.

The comparison between each dose of BI 409306 and placebo will be performed pairwise, i.e. data not relevant for the comparison of interest will be excluded. Data from both placebo periods per subject will be included simultaneously in the analysis, using the same treatment code 'placebo' but differentiated by the respective period numbers. This means that the model defined below can directly be used for estimating the treatment contrast between the active drug under consideration and placebo, using the observations from both placebo periods. In the following, the 'subject baseline' is defined as the arithmetic mean of the period baselines per subject (only from the periods involved in the comparison, i.e. the period baseline of the active treatment period and those of the 2 placebo periods).

The MMRM is based on Schall and Ring [R10-5353] and includes the fixed categorical effects of 'treatment', 'period' and 'time', the 'treatment-by-time' interaction and 'period-by-time' interactions, as well as the continuous fixed covariates 'period baseline' and 'subject baseline', and the 'period baseline-by-time' interaction and 'subject baseline-by-time' interaction. Subject is included as a random effect on the intercept. For the repeated effect 'time', an unstructured covariance pattern is chosen, using the blocking factor 'subject-by-period'. Note that the 'subject baseline' is included in the model to avoid cross-level bias affecting treatment comparisons; see Kenward and Roger [R10-4391].

More precisely, the model is given by

$$Y_{ikm(j)} = \mu + \gamma B_{im} + \gamma' \bar{B}_i + \pi_m + \tau_j + \zeta_k + \gamma_k B_{im} + \gamma'_k \bar{B}_i + (\pi\zeta)_{mk} + (\tau\zeta)_{jk} + s_i + e_{ikm},$$

$$s_i \sim N(0, \sigma_s^2),\ (e_{i1m}, \ldots, e_{iKm}) \sim N_K\ (\mathbf{0}, \Psi),$$

where $i=1,\ldots,I$ indicates the subject, $k=1,\ldots,K$ the time point within period, $m=1,\ldots,M$ the period and $j=1,2$ the treatment,

$Y_{ikm(j)}$	the QTcF change from period baseline for subject *i* receiving treatment *j* in period *m* at repeated measures time point *k*,
μ	the overall intercept,
B_{im}	the baseline value for subject *i* in period *m* (period baseline),
γ	the associated covariate effect of period baseline,

$\bar{B}_i$ the subject baseline value (mean of 3 period baselines) for subject *i*,

γ' the associated covariate effect of subject baseline,

π_m the effect of period *m*,

τ_j the effect of treatment *j*,

ζ_k the effect of time *k*,

γ_k the interaction effect of period baseline and time,

γ'_k the interaction effect of subject baseline and time,

$(\pi\zeta)_{mk}$ the interaction effect of period and time,

$(\tau\zeta)_{jk}$ the interaction effect of treatment and time,

s_i the random effect of subject *i* on intercept, assumed mutually independent across subject,

e_{ikm} the random error associated with subject *i* for time *k* and period *m,* assumed independent across period and subject (indices *m, i*), and

Ψ an unstructured *K-by-K* covariance matrix.

The random subject effects s_i and the random errors e_{ikm} are assumed to be independent of one another.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary objective of this study will be assessed by testing for each dose of BI 409306 the null hypothesis that the mean difference in the QTcF changes from baseline between BI 409306 and placebo is greater than or equal to 10 msec at least for one time point after dosing, against the alternative hypothesis that the mean difference is below the threshold of 10 msec for all time points.

The conclusion that this tQT trial is negative as per ICH E14 (see Section 7.1.1) will be based on the rejection of this null hypothesis for each of the two doses of BI 409306. This testing procedure is considered to be confirmatory, as the power calculations are based on this endpoint and the non-inferiority margin of 10 msec (see Section 7.6). The one-sided tests will be performed at the 5% level, which is equivalent to the estimation of two-sided 90% confidence intervals because of the symmetry of the normal distribution.

For the assessment of assay sensitivity of the trial, the null hypothesis that the mean difference in the QTcF changes from baseline between moxifloxacin and placebo is less than or equal to 5 msec for all of the time points 2, 3, and 4 hours after dosing will be tested at the 5 % level, against the alternative hypothesis that the mean difference is above the threshold of 5 msec for at least one of the three time points. The Hochberg correction will be used for adjusting for multiplicity (see Section 7.3.2.1).

7.3 PLANNED ANALYSES

For the analysis of the ECG variables QT, RR, PR, and QRS, a 2-step averaging procedure will be performed. In the first step, the 4 cardiac cycles per 10-second ECG will be averaged.

For each 10-second ECG, heart rate will then be derived from the calculated RR value as

HR[bpm]=60000/RR[msec].

Likewise, for each ECG the heart rate corrected QT intervals QTcF and QTcI will be derived from the mean values of the 4 cardiac cycles for RR and QT, respectively (see Section 7.3.2.5).

In the second step, for obtaining one ECG variable value per subject per time point, the calculated values of the three 10-second ECGs (triplicate ECGs extracted from the Holter recordings) will be averaged.

For all quantitative ECG variables derived from the 10-second ECGs, further analyses are then performed on these aggregated data on time point level. Period baseline values are calculated as the means of the values derived for the 3 baseline time points per period.

Important protocol deviations (iPDs) will be defined in the Integrated Quality and Risk Management plan.

The following analysis sets will be defined:

- Treated Set (TS): This subject set includes all randomised subjects who have received at least one dose of any study drug.

- ECG Set (ECGS): This subject set includes all subjects in the TS who have at least one on-treatment value for at least one ECG endpoint, which is not excluded due to ECG relevant iPDs. Such iPDs may be e.g. the use of pro-arrhythmic medications. Exclusion of single ECG values due to relevant iPDs is to be decided no later than in the Blinded Report Planning Meeting (BRPM) before data base lock and will be documented in the CTR.

The ECGS will be used for all analyses of the centrally assessed ECG data,
The TS will be used for all other safety summaries and all safety listings.

7.3.1 Primary analyses

The primary analyses use the MMRM described in Section 7.1.3 for the QTcF data from BI 409306 and placebo treatments, based on the ECG set.

For the pairwise comparisons between each dose of BI 409306 and placebo, mean treatment differences in the QTcF changes from baseline at each time point will be estimated by the differences in the corresponding least-squares means. Two-sided 90% confidence intervals based on the t-distribution will also be computed for each time point. The null hypothesis will be rejected if the maximum upper confidence limit for the mean difference in the QTcF changes from baseline between BI 409306 and placebo is less than 10 msec.

7.3.2 Secondary analyses

7.3.2.1 Assessment of assay sensitivity

The effect of moxifloxacin on the QTcF changes from baseline in comparison with placebo will be assessed using the same MMRM as applied in the primary analysis.

For this analysis, only the data from the moxifloxacin and placebo periods will be used.

For describing the time course of the effect of moxifloxacin on QTcF, 90% confidence intervals for the mean differences of the QTcF changes from baseline between moxifloxacin and placebo will be provided.

For the formal test of assay sensitivity at level α=5%, the method by Hochberg [R97-1003] will be applied. To this end, the three single hypotheses that the mean difference in the QTcF change from baseline between moxifloxacin and placebo is less than or equal to 5 msec at a given time point (out of the three time points 2, 3, and 4 hours after drug administration) will be tested based on the results of the MMRM (fitted to the data for all time points). If the largest of the three p-values is less than 5% (=α), then all single hypotheses can be rejected. If the second largest p-value is less than 2.5% (=α/2), then the corresponding null hypothesis and the one regarding the test with the lowest p-value can be rejected. If the lowest p-value is less than 1.667% (=α/3), then only the null hypothesis corresponding to this p-value can be rejected. Note that it is sufficient to reject only one of the three single null hypotheses in order to reject the overall null hypothesis stated in Section 7.2 (i.e., the intersection of the three single hypotheses), and hence to show assay sensitivity.

7.3.2.2 Analyses of the heart rate

For each dose of BI 409306, the HR changes from baseline at each time point between 20 min to 24 hours after dosing will be analysed by applying the same model as in the primary analyses and calculating the corresponding 90 % CIs for the mean difference between BI 409306 and placebo. For these analyses, only the HR data from the respective BI 409306 dose and placebo will be used.

7.3.2.5 Heart rate corrections of QT interval

Precise heart rate correction of the QT interval is one of the most important factors in increasing the precision for the detection of drug induced QT prolongation. In the absence of relevant effects of a drug on the heart rate, the Fridericia correction formula is accepted as the primary correction method (see e.g. the FDA "Scientific white paper on concentration-QTc modeling" [R18-0143]). For a given pair (QT, RR), it is defined as

$$QTcF[\text{msec}] = QT[\text{msec}] * \left(\frac{1000\ \text{msec}}{RR[\text{msec}]}\right)^{\frac{1}{3}}.$$

QTcF will be selected as the primary correction method for the present trial, as it is not expected that the mean of the placebo-corrected HR change from baseline will be larger than 10 beats/min for both doses of BI 409306.

7.3.3 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 24 hours after the last dose of trial medication (in treatment periods with BI drug or placebo) or a period of 4 days after the last dose of trial medication (in moxifloxacin treatment period), will be assigned to the on-treatment period for evaluation. The safety analysis will be done by 'treatment at onset'.

All treated subjects will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Laboratory data will be listed only. Values outside the reference range as well as values defined as clinically relevant will be flagged.

Vital signs, physical examinations, 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.

7.3.4 Interim analyses

No interim analysis is planned.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

If it is not possible to estimate an individual correction factor for a subject, e.g. if the range of observed off-drug heart rates is too narrow, the correction factor will be imputed by the correction factor estimated from the entire study population instead, referred to as QTcN correction method.

7.5 RANDOMISATION

Subjects will be randomised to the 15 treatment sequences (see Section 7.1) in a balanced ratio.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

The randomisation list will contain additional blocks to allow for subject replacement (refer to 3.3.5).

Access to the codes will be controlled and documented according to the standard procedures in place at BI.

7.6 DETERMINATION OF SAMPLE SIZE

The following sample size considerations are performed for the MMRM based analysis of the primary endpoint.

Based on the results of trial 1289.28 [c03808525-02], the maximum effect of BI 409306 on the QTc interval can be expected within the first 3 hours after drug administration. Except for one outlier at 8 hours after drug administration, the maximum (over all remaining time points) estimated standard deviation of the mean difference between BI 409306 and placebo in QTc changes from baseline was 11.3 msec, and the estimated maximum difference (over all time points) was less than 5 msec for both QTcF and QTcN.

In case of a QT prolonging drug effect of BI 409306, the higher effect would be expected for the higher dose, while the effects of the two doses on QTc should be highly correlated, especially since all comparisons are done with the same comparator. Therefore, the sample size determination will be based on the assumptions for the higher dose. Hence, in the following, we focus only on one single testing problem (i.e. for only one dose).

Further, since the above worst case scenarios (maximum effect over time, maximum standard deviation of the difference over time) will be used, the following power calculations are performed only for the univariate testing problem of non-inferiority at a single time point.

Since all assessments in tQT trials are based on the comparisons between active treatment and placebo, these treatment contrasts should be estimated with the highest statistical efficiency. To account for this, the selected crossover design for this trial will include a second placebo period instead of only one, following the arguments in [R12-0517]. The sample size for the resulting 4-treatment 5-period crossover design can be determined as 3/4 of the sample size for the corresponding 4-period crossover design (i.e., with the number of treatments and periods being equal); see formula (2) in [R12-0517].

Thus, in a first step the sample sizes for a crossover tQT trial with equal number of treatments and periods will be determined, which then lead to the sample size for the selected 5-period design through multiplication by 0.75 in a second step.

Using a one-sided confidence level of $\alpha = 0.05$ and a power of 90%, Table 7.6: 1 displays the required sample sizes for showing that the mean difference between BI 409306 and placebo in the QTcF change from baseline is smaller than 10 msec under various assumptions for the within-subject variability and expected differences between the means.

Table 7.6: 1 Sample sizes assuming a power of 90% for concluding that the mean difference between BI 409306 and placebo is less than 10 msec

LEL for difference	-999	-999	-999	-999	-999	-999	-999	-999	-999
UEL for difference	10	10	10	10	10	10	10	10	10
Expected difference	3	3	3	4	4	4	5	5	5
Standard deviation of differences	10	11	12	10	11	12	10	11	12
Total N	20	24	28	26	32	36	36	44	52

LEL: Lower equivalence limit, UEL: Upper equivalence limit (one-sided $\alpha = 0.05$)
The calculations were performed using the MTE1co routine from commercial software nQuery Advisor® 7.0[R15-1331].

Therefore, in a standard crossover design with equal number of treatments and periods, a total sample size of 52 subjects will provide a power of 90% to conclude that the mean difference between BI 409306 and placebo in QTcF change from baseline is smaller than 10 msec, if the true difference is up to 5 msec and the standard deviation of the differences is at most 12 msec. Accounting for up to 8 potential drop outs, a total of 60 subjects would be required.

As the sample size for the 5-period crossover with 2 placebo periods can be determined as 3/4 of the sample size of the corresponding 4-period crossover, the required sample size for this trial is 45 subjects. A power of roughly 90% will be achieved under the assumptions specified above, even if up to 6 subjects are to discontinue the trial prematurely.

Regarding the assessment of assay sensitivity, the maximum difference in the QTcF change from baseline between moxifloxacin and placebo can be expected to be around 12 msec, with a standard deviation of 10 msec, based on previous BI tQT trials. If just one single test (for one time point out of the three; see Section 7.3.2.1) was performed at level α/3=1.667%, and taking into account the design with 2 placebo periods, the power to reject the corresponding null hypothesis given a sample size of 45 would be 99.8%. If the true value of the maximum placebo-corrected change from baseline would be only 10 msec, still the power for the single test would be 93.3%. The power to reject the overall null hypothesis stated in Section 7.2 using the Bonferroni method would be larger than the above values in each scenario, since in that case all three single tests would be performed at level α/3, and only one would have to be significant. The power of the Hochberg method described in Section 7.3.2.1 is again larger than that of the Bonferroni method [R97-1003].

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. See Section 4.1.5.1 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

In the Phase I unit – the validated is operated for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, 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 (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 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 and regulatory reporting obligation in accordance with regulatory requirements.

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 competent authority.

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.

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c22514660-01 A multi-centre, double-blind, parallel-group, randomized controlled study to investigate the efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with Alzheimer's Disease. CTR. Version 1. 1289.5. 13 June 2018.

U12-1034-01 A randomised, 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. CTR. Version 1. 1289.1. 19 Jan 2012.

U12-2165-01 Randomised, double-blind, placebo-controlled, parallel-group proof of mechanism study to assess the pharmacokinetics and to evaluate the pharmacodynamic effect of different single oral doses of BI 409306 in healthy male volunteers. CTR. Version 1. 1289.3. 17 Sep 2012.

U13-1182-01 Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple-rising doses of BI 409306 film-coated tablets given orally q.d. or bid for 14 days in young healthy and elderly healthy male/female volunteers (randomised, double-blind, placebo-controlled within dose groups Phase I study). CTR. Version 1. 1289.2. 20 Feb 2013.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		12 Feb 2019
EudraCT number		2018-001335-44
BI Trial number		1289-0038
BI Investigational Product(s)		BI 409306
Title of protocol		Thorough QT study to evaluate the effects of BI 409306 as single doses on cardiac safety parameters in healthy male and female subjects. A randomized, placebo controlled, double-blind, five-period crossover study with (open-label) moxifloxacin as positive control.
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		2.3 Benefit-risk assessment
Description of change		Risks related to moxifloxacin administration were updated according to the current German SmPC for Avalox® [R19-0482]; a typing error was corrected.
Rationale for change		Version 1.0 of the CTP did not reference the currently valid version of the German SmPC for Avalox®.

Number of global amendment		2
Date of CTP revision		25 Mar 2019
EudraCT number		2018-001335-44
BI Trial number		1289-0038
BI Investigational Product(s)		BI 409306
Title of protocol		Thorough QT study to evaluate the effects of BI 409306 as single doses on cardiac safety parameters in healthy male and female subjects. A randomized, placebo controlled, double-blind, five-period crossover study with (open-label) moxifloxacin as positive control.
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	3.3.3 3.3.4.1 3.3.4.2 3.3.5 4.1.2	Exclusion criteria Removal of individual subjects Discontinuation of the trial by the sponsor Replacement of subjects Method of assigning subjects to treatment groups
Description of change	3.3.3 3.3.3 3.3.4.1 3.3.4.2	Changed the lower limit of systolic RR to 100 mmHg (EX No. 2); added EX No. 28 (contraindications for moxifloxacin administration) Deleted “or run-in” in EX No. 20 Added individual removal criterion No. 5 (AST/ALT increase), No. 6 (potential QT findings) and No. 7 (serious adverse reaction, non-serious severe adverse reaction) Re-phrased discontinuation criterion No. 1 to address the case or potential serious adverse reaction or severe non-serious adverse reactions

Number of global amendment		2
	3.3.5 4.1.2	Number of replacement subjects have been specified A description about the planned cohort number, cohort size and dosing regimen as well as justification has been added
Rationale for change	3.3.3 3.3.3 3.3.4.1 3.3.4.2 3.3.5 4.1.2	Request by competent authority (CA) and ethics committee (EC) To reduce redundancy with EX No. 27. Request by CA and EC Request by CA and EC Request by CA and EC Request by CA and EC

Number of global amendment		3
Date of CTP revision		23 Apr 2019
EudraCT number		2018-001335-44
BI Trial number		1289-0038
BI Investigational Product(s)		BI 409306
Title of protocol		Thorough QT study to evaluate the effects of BI 409306 as single doses on cardiac safety parameters in healthy male and female subjects. A randomized, placebo controlled, double-blind, five-period crossover study with (open-label) moxifloxacin as positive control.
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	- 3.3.4.1 5.2.4.4	Flow Chart Removal of individual subjects Safety 12-lead single standard ECG and run-in (Holter) ECG
Description of change	- 3.3.4.1 5.2.4.4	Flow Chart: Inserted safety ECGs at PTM 2:00 and 4:00 Amended individual removal criterion No. 6: Individual subjects will be removed from the trial in case of a QTc increase > 60 msec from baseline in safety ECGs Added the two time-points for additional safety ECGs at PTM 2:00 and 4:00; added information about electrode placement
Rationale for change	- 3.3.4.1 5.2.4.4	Request from health authority to implement an individual stopping criterion based on changes of QTc from baseline > 60 msec

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-revision-3

Title: Thorough QT study to evaluate the effects of BI 409306 as single doses on cardiac safety parameters in healthy male and female subjects. A randomized, placebo controlled, double-blind, five-period crossover study with (open-label) moxifloxacin as positive control.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist		23 Apr 2019 16:04 CEST
Approval-Team Member Medicine		23 Apr 2019 16:09 CEST
Verification-Paper Signature Completion		24 Apr 2019 08:09 CEST
Author-Trial Statistician		25 Apr 2019 09:33 CEST
Approval-Therapeutic Area		26 Apr 2019 13:48 CEST
Author-Clinical Trial Leader		30 Apr 2019 08:20 CEST

(Continued) Signatures (obtained electronically)

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