Clinical Trial Protocol

	Document Number: c09116705-03
EudraCT No.:	2017-004798-14
BI Trial No.:	1289-0025
BI Investigational Product:	BI 409306
Title:	Absolute bioavailability and pharmacokinetics of BI 409306 using a single oral dose of BI 409306 co-administered with an intravenous stable labeled isotope BI 409306 (C-13/N-15) in healthy male and female subjects (Non-Randomised, open-label, single arm, single period design)
Lay Title:	This study in healthy men and women tests how the body takes up BI 409306
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	Version: 3.0 Date: 04 May 2018

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: 14 February 2018	**Trial number:** 1289-0025		**Revision date:** 04 May 2018

Title of trial:	Absolute bioavailability and pharmacokinetics of BI 409306 using a single oral dose of BI 409306 co-administered with an intravenous stable labeled isotope BI 409306 (C-13/N-15) in healthy male and female subjects (Non-Randomised, open-label, single arm, single period design)
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objective:	To investigate the absolute bioavailability of BI 409306
Methodology:	Non-Randomised, open-label, single arm, single period design
No. of subjects:	
Total entered:	Up to 12 6 subjects with CYP 2C19 non-PM status and up to 6 subjects with 2C19 PM status
Each treatment:	Up to 12 6 subjects with CYP 2C19 non-PM status and up to 6 subjects with 2C19 PM status
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male/female subjects, age of 18 to 55 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2, known CYP2C19 metabolizer status
Reference product:	Stable labeled isotope BI 409306 (C-13/N-15) Solution for infusion 6mL (0.1 mg/mL) (R)
dose:	0.1 mg
mode of admin.:	intravenous (infusion over 30 minutes)
Test product:	BI 409306 film-coated tablets, 1 tablet containing 50 mg (T)
dose:	1 x 50 mg
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

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 409306			
Protocol date: 14 February 2018	**Trial number:** 1289-0025		**Revision date:** 04 May 2018
Criteria for pharmacokinetics:	Primary endpoints: $AUC_{0-\infty}$ and C_{max} for BI 409306 and stable labeled isotope BI 409306 (C-13/N-15) (after oral and intravenous administration) Secondary endpoints: $t_{1/2}$, $t_{max.}$ for BI 409306 and stable labeled isotope BI 409306 (C-13/N-15). Cl (total clearance of the analyte) and V_z (Apparent volume of distribution during the terminal phase after intravascular administration) for stable labeled isotope BI 409306 (C-13/N-15), F (absolute bioavailability) for BI 409306		
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])		
Statistical methods:	Absolute bioavailability (F) will be estimated by the ratios of the geometric means (test/reference) for the dose normalized primary endpoints $AUC_{0-\infty}$ and $C_{max.}$ Additionally, their two-sided 90% confidence intervals (CI) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be an ANOVA on the logarithmic scale including the fixed effect for 'formulation' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints		

FLOW CHART

Period	Visit	Day	Planned time (relative to oral drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood BI 409306	BI 409306 (C-13/N-15)	Intravenous infusion	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy 6
SCR	1	-21 to -1			Screening (SCR)[1]	x				x	x	
1	2	-1	-12:00	20:00	Admission to trial site[10]	x[5]						x
		1	-1:30	06:30	Allocation to treatment		x[2]	x[2]		x[2]	x[2]	x[2]
			0:00	08:00	50 mg BI 409306 p.o.							
			0:10	08:10			x					
			0:20	08:20			x					x
			0:30	08:30	0.1 mg BI 409306 i.v.		x[8]		▲			
			0:35	08:35				x				
			0:45	08:45			x	x				
			0:50	08:50				x				
			1:00	09:00			x[9]	x[9]	▼			
			1:10	09:10				x				
			1:20	09:20			x	x			x	x[7]
			1:30	09:30				x				
			1:45	09:45			x	x				
			2:00	10:00	240 mL fluid intake		x	x		x	x	x
			2:30	10:30			x	x				
			3:00	11:00			x	x				
			3:30	11:30			x	x				
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	x			x	x
			5:00	13:00			x	x				
			6:00	14:00			x	x				
			7:00	15:00			x	x				
			8:00	16:00	Snack (voluntary)[3]		x	x				
			9:00	17:00			x	x				
			10:00	18:00			x	x				
			11:00	19:00	Dinner							
			12:00	20:00			x	x			x	x
		2	24:00	08:00	Discharge from trial site Breakfast (voluntary)[3]		x	x				x[7]
EOT	3	2	n.a.	n.a.	End of trial (EOT) examination[4]	x[4]				x[4]	x[4]	x[4]

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures includes physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history and pregnancy test in women), 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 (oral) 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 including pregnancy test in women, recording of AEs and concomitant therapies
   Date of EOT coincides with day 2 of visit 2. All EOT activities take place *after* the formal discharge from the trial site. Exception: blood for the EOT safety lab is taken in the context of the 24:00 hours post-dose sampling to avoid two separate punctures
5. Only urine drug screening and alcohol breath test, and pregnancy test in women.
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. includes assessment of local tolerability
8. PK sampling within 2 minutes prior start of infusion
9. PK sampling within 2 minutes prior to end of infusion
10. Admission to the trial site should not be later than 10 hours prior to oral drug administration

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ABBREVIATIONS

AD	Alzheimer's Disease
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
APS	Attenuated Psychosis Syndrome
AUC_{0-24h}	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
BA	Bioavailability
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
bpm	Beats per minute
CA	Competent authority
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP	Cytochrom P 450
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EM	Extensive metabolizer
EOT	End of trial
F	Absolute bioavailability factor
GCP	Good Clinical Practice

GLP	Good laboratory Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
HPC	Human Pharmacology Centre
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
IB	Investigator's brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LTP	Long term potentiation
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time of the analyte in the body after intravenous bolus administration
MRT_{po}	Mean residence time of the analyte in the body after oral administration
NMDA	N-methyl-D-aspartate
NOA	Not analysed
NOAEL	No adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PDE	Phosphodiesterase
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PM	Poor metabolizer
PR	Pulse rate
QD	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard Operating Procedure
SRD	Single-rising dose
Ss	(at) steady state
T	Test product or treatment

TDMAP	Trial Data Management and Analysis Plan
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
V_{ss}	Apparent volume of distribution at steady state after intravascular administration
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
YLD	Years lived with disability

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a non-randomised, open-label, single arm, single period trial in healthy male and female subjects in order to compare the test treatment (T) to the reference treatment (R).
The treatments will be 0.1 mg isotope BI 409306 (C-13/N-15), intravenous administration (R) and one 50 mg film-coated tablet BI 409306, oral administration (T). Both treatments are given in fasted state. For details refer to Section 4.1.

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.

The trial medication will be provided by the

The trial will be conducted at the
under the supervision of the Principal Investigator. Safety laboratory tests will be performed by

The prespecified genotyping of CYP2C19 will be performed at the

The analyses of BI 409306 concentrations in plasma will be performed

On-site monitoring will be performed by BI or a contract research organisation appointed by BI. Data management will be done by BI according to BI SOPs.

Statistical tasks and programming will be performed by
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 GROUP

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

- Day to day variability within a subject is eliminated as potential confounding variable in addition to the intrasubject variabilities in drug dissolution, absorption rate, and metabolism
- Expected favourable safety due to very low exposures after an intravenous microdose
- Radiopharmacy is not required with the stable isotopes. Subjects are not exposed to radioactivity. The stable isotope labeled compound used in this study, BI 409306 (C-13/N-15)-BI 409306 is unlikely to exhibit any detectable isotope effects (see section 2.3).
- Reduced duration of the clinical trial

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

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that up to 12 healthy male and female subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.
To explore potential differences in absolute bioavailability based on 2C19 metabolizer status, it is planned to include 6 subjects with CYP2C19 non-PM status, and up to 6 subjects with 2C19 PM status, if feasible.

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

3.3.1 Main diagnosis for study entry

The study will be performed in male and female 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 ECG, and clinical laboratory tests
2. Age of 18 to 55 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
5. Known CYP 2C19 metabolizer status
6. 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 (follicle stimulating hormone) 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 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)

12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Current smoker or ex-smoker who quit smoking less than 30 days prior to screening
14. Alcohol abuse (consumption of more than 20 g per day for females and 30 g per day for males)
15. Drug abuse or positive drug screening
16. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
17. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
18. Inability to comply with dietary regimen of trial site
19. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 msec in males or repeatedly greater than 470 msec in females) or any other relevant ECG finding at screening
20. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
21. 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

Female subjects will not be allowed to participate if any of the following applies:

22. Positive pregnancy test, pregnancy or plans to become pregnant within 30 days after study completion
23. Lactation period
24. Concomitant use of hormonal replacement therapy or hormonal contraceptives

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as pregnancy, surgery, adverse events, or diseases)

4. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.

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

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

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.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational products have been manufactured by BI Pharma GmbH & Co. KG.

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
Route of administration:	p.o.

The characteristics of the reference product are given below:

Substance:	stable labeled isotope BI 409306 (C-13/N-15) Solution for infusion
Pharmaceutical formulation:	i.v. solution
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	6 mL (0.1 mg/mL, 0.6mg/vial)
Posology:	0.1 mg-0-0
Route of administration:	i.v.
Duration of use:	intravenous infusion over 30 min

BI 409306 (C-13/N-15) is a ready for use i.v. solution provided in a glass vial. Sodium chloride (0.9%) has been chosen as tonicifier for the BI 409306 (C-13/N-15) solution. The aseptically prepared solution is tested for sterility and bacterial endotoxins as part of the release testing.

BI 409306 (C-13/N-15) will be administered as short infusion using a syringe infusion pump (Perfusor fm® B.Braun, Melsungen, Germany) based on the handling instructions (see section 10). For intravenous drug administration and PK sampling two different intravenous cannulas will be used. They must not be on the same arm during the drug administration.

4.1.2 Method of assigning subjects to treatment groups

The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, the subjects will be allocated to a study subject number by drawing lots.

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

4.1.3 Selection of doses in the trial

The oral dose of 50 mg BI 409306 was selected since it is expected to be a therapeutic dose and was well tolerated in previous studies (section 1.2).
Using the microtracer approach for investigating the absolute bioavailability the intravenous dose should not significantly add to the systemic drug concentrations arising from the oral administration [R17-1799].

The oral dose (50 mg BI 409306) is 500 times higher than the intravenously infused dose (0.1 mg BI 409306 [C-13/N-15]). Therefore the exposure to BI 409306 (C-13/N-15) originating from the infused microdose is considered negligible (see section 2.3).
With the bioanalytical methods described in section 5.5.3, the anticipated drug concentrations are expected to be detectable.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a non-randomised, open-label, single arm, single period study. All subjects will receive both treatments, orally administered BI 409306 (T) as well as intravenously administered BI 409306 (C-13/N-15) (R). The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R (Reference)	BI 409306 (C-13/N-15)	i.v. solution	0.1 mg/mL	1 ml	0.1 mg
T (Test)	BI 409306	film-coated tablet	50 mg	50 mg single dose	50 mg

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

During the first 2 h after oral drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The intravenous medication will be administered as a continuous intravenous infusion over 30 minutes under supervision of the investigating physician or an authorised designee. Start and end time of the infusion will be recorded.

The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation, if correct dosage cannot be ensured

otherwise. Administration will be performed following an overnight fast starting no later than 10 h before scheduled dosing.

4.1.5 Blinding and procedures for unblinding

No blinding was performed because the treatments are distinguishable from each other. This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Emergency envelopes will not be provided, since all subjects receive the same dose of different formulations in an open label design.

4.1.6 Packaging, labelling, and re-supply

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

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

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

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

No re-supply is planned.

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 (labeled) storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

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

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

Only authorised personnel as documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial subjects. The investigator will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorise symptomatic therapy. 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. CYP2C19 or 1A2 inhibitors or inducers are not allowed due to their interaction potential with BI 409306. Acetylsalicylic acid is not allowed due to potential for CYP2C19 induction. Ibuprofen may be used as analgesic drug if need be.

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 oral drug intake.

From 1 h before oral 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.

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

Smoking is not allowed.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 24 h before until 24 h after oral trial medication.

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

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

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 and/or urinary excretion will provide additional confirmation of compliance.

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

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

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

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

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

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

or

- 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'

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.

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

The latest list of 'Always Serious AEs' can be found in the eDC (electronic data capture) 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 in chapter 5.2.2.2.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. 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 are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - 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
  - 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 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 diminished).

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

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

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

5.2.2.2 Adverse event collection and reporting

AEs collection

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

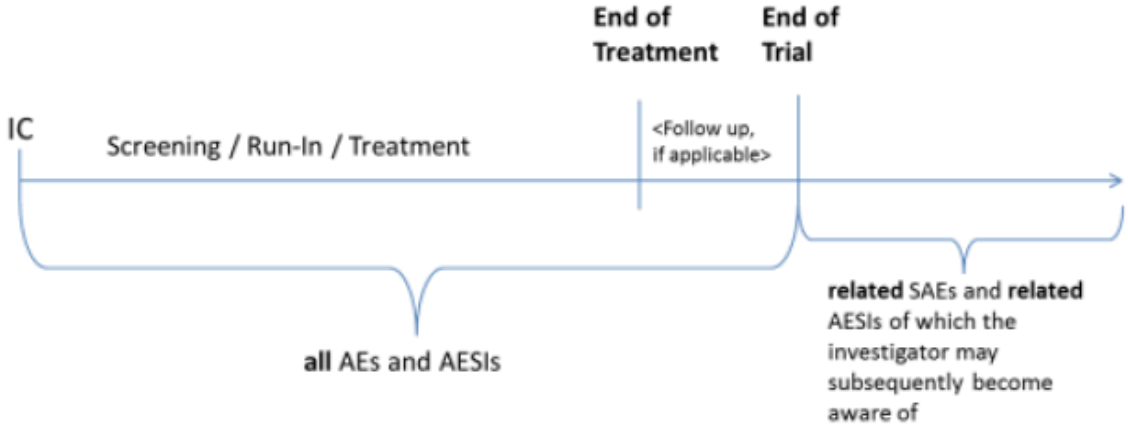
A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.
If subjects report a change in perception or any 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 principal 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 AEs but should only report 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.

Figure 5.2.2.2: 1 Collection of AEs and AESIs



The REP refers to the oral drug administration. The REP of the BI 409306 (13-C/15-N) is considered to be negligible. Therefore, all AEs that occur through the treatment phase and throughout the REP will be considered as on treatment (without differentiation of intravenous or oral administration); please see Section 7.3.3. Events that occur after the REP until the end of trial examination will be considered to be follow-up events.

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.

Upon receipt of any further information relevant to the reported AEs, the investigator is to provide a follow-up SAE form to the sponsor. For follow-up information, the same rules and timelines apply as for the initial information.

Information required

For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable.

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

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

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been sufficiently characterised, 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).

Pregnancy itself is not 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 as well.

5.2.3 Assessment of safety laboratory parameters

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

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. Creatine kinase-MB will only be performed if creatine kinase is increased.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name	Screening	End-of- trial
Haematology	Haematocrit	x	x
	Haemoglobin	x	x
	Red blood cell count /Erythrocytes	x	x
	White blood cell count /Leucocytes	x	x
	Platelet count/Thrombocytes/ (quant)	x	x
Automatic WBC differential (relative and absolute)	Neutrophils/Leucocytes	x	x
	Eosinophils/Leucocytes	x	x
	Basophils/Leucocytes	x	x
	Monocytes/Leucocytes	x	x
	Lymphocytes/Leucocytes	x	x
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	x	x
	ALT [Alanine transaminase] /GPT, SGPT	x	x
	Alkaline Phosphatase	x	x
	Gamma-Glutamyl Transferase	x	x
Hormones	Thyroid stimulating hormone	x	-
Substrates	Glucose Plasma	x	x
	Creatinine	x	x
	Bilirubin total	x	x
	Bilirubin direct	x	x
	C-Reactive Protein (Quant)	x	x
Electrolytes	Sodium	x	x
	Potassium	x	x
Urinalysis (Stix)	Urine Nitrite (qual)	x	-
	Urine protein (qual)	x	-
	Urine Glucose (qual)	x	-
	Urine Ketone (qual)	x	-
	Urobilinogen (qual)	x	-
	Urine Bilirubin (qual)	x	-
	Urine erythrocytes (qual)	x	-
	Urine leukocytes (qual)	x	-
	Urine pH	x	-
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	x	-

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, after admission to the trial site on day -1, and as part of the end of trial examination.
Drug screening will be performed at screening and after admission to the trial site on day -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 (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
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 treatment 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.
Laboratory data will be transmitted electronically from the laboratory to the trial site.

5.2.4 Electrocardiogram

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

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

All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

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

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) 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. Additional (unscheduled) BP data may be collected by the investigator for safety reasons. However, BP measurement on the arm where i.v. drug is administered must be avoided during the 30 min infusion period.

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.

5.2.5.3 Local tolerability

Local tolerability at the injection site will be assessed by the investigator according to ‘swelling’, ‘induration’, ‘heat’, ‘redness’, ‘pain’, or ‘other findings’ as specified in the flowchart.

5.4 APPROPRIATENESS OF MEASUREMENTS

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoint

The following primary endpoints will be determined for BI 409306 and BI 409306 (C-13/N-15):

- $AUC_{0-\infty}$ and C_{max}

5.5.1.2 Secondary endpoints

The following secondary endpoints will be evaluated.

For BI 409306 and BI 409306 (C-13/N-15):

- $t_{1/2}$ (terminal half-life of the analyte in plasma)
- t_{max} (time from dosing to maximum measured concentration of the analyte in plasma)

For BI 409306 (C-13/N-15):

- CL (total clearance of the analyte)
- V_z (Apparent volume of distribution during the terminal phase after intravascular administration)

For BI 409306

- F (absolute bioavailability)

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

BI 409306
For quantification of BI 409306 plasma concentrations and its metabolites (CD 13896 and CD 14084), 4.9 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and at 4 to 8 °C. Three plasma aliquots will be obtained and stored in polypropylene tubes. The first and second aliquot should contain at least 0.5 mL plasma whereas the third aliquot should contain the remaining plasma (0.5 mL or less). The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 minutes, with interim storage of blood samples and aliquots at room temperature. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. The third aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first and second aliquot. At the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

BI 409306 (C-13/N-15)
For quantification of the BI 409306 (C-13/N-15) plasma concentrations, 4.9 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 1 mL plasma whereas the second aliquot should contain 1 mL or less plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min, with interim storage of blood samples and aliquots at room temperature. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

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

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

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 409306 and the BI 409306 (C-13/N-15) plasma concentration

Analyte concentrations in plasma will be determined by validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assays [All details of the analytical method will be available prior to the start of sample analysis.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min for the first 4 hours after oral drug administration and ± 45 min thereafter.

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

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

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the 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 pregnancy test, drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

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

6.2.2 Treatment period

Each subject is expected to participate in one treatment period (Days -1, 1, and 2).

On Day -1 study participants will be admitted to the trial site in the evening prior to drug administration. Study participants will be kept under close medical surveillance for at least 24 hours following oral drug administration (Day 1). The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness on day 2.

Due to the short half-life of BI 409306, end-of-trial examination will take place on day 2. (see 6.2.3).

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.5.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on time points for all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 End of trial period

Due to the short half-life of BI 409306, end-of-trial examination will take place on day 2 after the last PK sample has been taken.

For AE assessment, laboratory tests (including pregnancy test in women), recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.

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

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained. The end of the trial as a whole is defined by the 'last regular visit completed by last subject' or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the absolute bioavailability of BI 409306 by comparing 50 mg of orally administered unlabeled BI 409306 (Test, T) with 0.1 mg intravenously administered stable labeled isotope BI 409306 (C-13/N-15) (Reference, R). The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of an appropriate linear model.
The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between the formulations. The secondary objectives will be assessed by descriptive statistics.

The assessment of safety and tolerability will be an additional objective of this trial, and will be evaluated by descriptive statistics.

7.1.2 Endpoints

Absolute bioavailability is to be determined on the basis of the dose normalized primary pharmacokinetic endpoints (see Section 5.5.1.1). All pharmacokinetic endpoints (see Section 5.5.1) will be calculated and analysed descriptively.

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

7.1.3 Model

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

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

y_{km} = logarithm of response (dose normalized primary endpoint, see Section 5.5.1.1) measured on subject m receiving formulation k,

μ = the overall mean,

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

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

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

The absolute bioavailability of 50 mg of orally administered unlabeled BI 409306 compared to 0.1 mg intravenously administered stable labeled isotope BI 409306 (C-13/N-15) will be estimated by the ratios of the geometric means (test/reference) for the dose normalized primary PK endpoints. Additionally, their two-sided 90% confidence interval (CI) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified, that is, no hypothesis will be tested.

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

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The primary pharmacokinetic endpoints (see Section 5.5.1.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

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

Relevant protocol violations may be

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

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

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

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

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

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

Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic mean, geometric mean and the planned blood sampling times will be used.

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

Point estimates of bioavailability, the intra-subject ratios of the geometric means (test/reference) for the dose normalized primary endpoints (see Section 5.5.1.1), and the corresponding two-sided 90% CIs will be provided.

To this end, the dose normalized PK endpoints will be log transformed (natural logarithm) prior to fitting the ANOVA model (cf. Section 7.1.3). For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (LeastSquares Means), and a two-sided 90% CI based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CI for each endpoint.

The response variables used in the ANOVA model are the following:

for C_{max}: $C_{max,\ norm,\ po}$ and $C_{max,\ norm,iv}$

for AUC: $AUC_{0-\infty,\ norm,\ po}$ and $AUC0-\infty_{,\ norm,iv}$

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

7.3.2 Secondary analyses

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

If an adequate number of PM subjects is reached within the study a subgroup analysis will be done for the primary PK endpoints to compare PM subjects with non-PM subjects.

The following descriptive statistics will be calculated for primary and secondary PK parameters and for further endpoints: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with 3 significant digits in the clinical trial report.

The secondary parameters (refer to Section 5.5.1.2) will be calculated according to the BI SOP ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics’ (001-MCS-36-472).

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI standards.

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

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

Measurements (such as vital signs or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs).

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

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

Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline (screening measurements) will be evaluated.

For vital signs, the differences from baseline (last value before oral drug administration) will be evaluated.

Relevant ECG findings will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

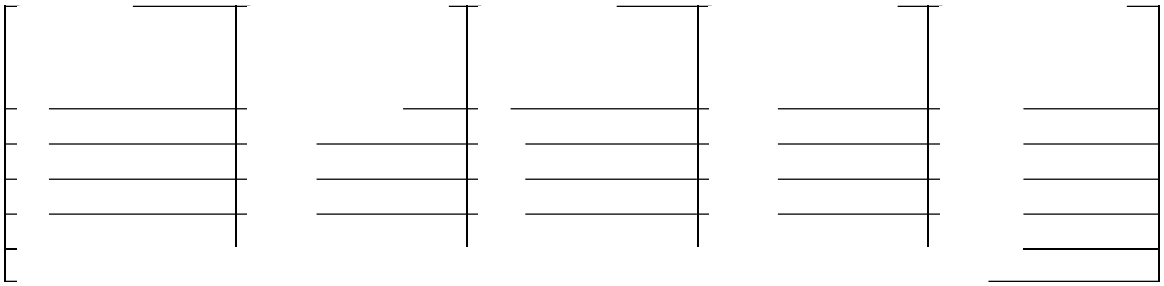
For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period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

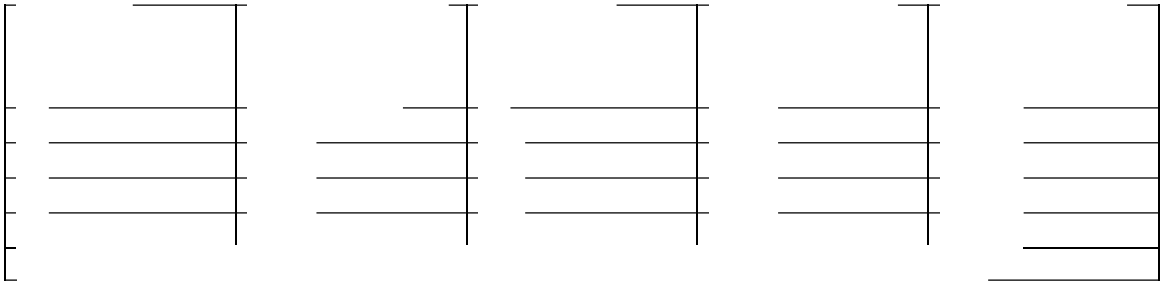
7.5 RANDOMISATION

Randomisation is not applicable in this open-label, single arm, single period clinical study. All subjects will receive the same treatment. A list of consecutive subject numbers will be provided for procedural reasons (see Section 4.1.2).

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to enter up to 12 subjects in the trial: 6 subjects with CYP2C19 non-PM status, and up to 6 subjects with CYP2C19 PM status.





8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be

personally dated by each signatory and the informed consent and any additional subject information form are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

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

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

8.2 DATA QUALITY ASSURANCE

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

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.

8.3 RECORDS

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

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

8.3.1 Source documents

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal 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 CA.

8.6 COMPLETION OF TRIAL

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R15-4424 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). 5th ed. Arlington: American Psychiatric Association; 2013.

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9.2 UNPUBLISHED REFERENCES

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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. 1289.1. Clinical Trial Report. 19 January 2012

c01694347-09 BI 409306 in Alzheimer's Disease and Cognitive Impairment associated with Schizophrenia. Investigator's Brochure. 01 June 2017

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). 1289.2. Clinical Trial Report. 20 February 2013

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. 1289.3. Clinical Trial Report. 17 September 2012

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10. APPENDICES

Section 10.1 and 10.2 provides information on preparation of the intravenous stable labeled isotope BI 409306 (C-13/N-15) for infusion and its application.

10.1 DRUG SUPPLY AND EQUIPMENT

10.1.1 Drug supply

BI 409306 (C-13/ N-15) solution for infusion is an intravenous solution consisting of 6 mL of a sterile, clear, colourless solution, containing 0.1 mg/mL BI 409306 BS (C-13/N-15), and presented in a colourless glass vial sealed with a rubber stopper and an aluminum flip-off seal.

10.1.2 Disposables

Material	REF	Company
Mini-Spike® [1)]	4550242	B Braun
Omnifix® 10 mL Luer Lock Solo [2)]	4617100V	B Braun
Original Perfusor® Line Type: IV-Standard-PE, Luer Lock 150 cm [3)]	8722935	B Braun
Discofix®3SC [4)]	4095111	B Braun
Introcan Safety® W Winged-FEP 18G [5)]	4254562-01	B Braun
Combi-Stopper[6)]	4495101	B Braun

[1)] Mini-Spike is a vented dispensing pin for withdrawing fluids from medication vials. Its integrated air-venting channel makes pressure-balancing techniques unnecessary.
[2)] Omnifix 10 mL ,Luer Lock Solo – is a hypodermic syringe for single use with Luer Lock connection to allow the connection with the Perfusor® line.
[3)] Original Perfusor® Line – tube for use with syringe pump “Perfusor® fm”
[4)] Dicofix®3SC is a stopcock system with axially and radially movable swivel lock for secure and speedy connection.
[5)] Introcan Safety® is an intravenous catheter with protection against needlestick injuries.
[6)] Combi-Stopper: sterile closing

Please note: only CE certified disposables are to be used.

10.1.3 Technical equipment

10.2 HANDLING INSTRUCTION

10.2.1 Overview

Prior to intravenous drug administration, 6 mL of the solution is withdrawn from the vials into a syringe "Omnifix® 10 mL Luer Lock Solo". The application system is flushed with the solution for infusion.
Subsequently, 1 mL (i.e. 0.1 mg) of solution for infusion is administered over 30 minutes.
Residual solution for infusion is discarded.
The following description provides a step by step instruction.

10.2.2 Preparation of i.v. solution for continuous infusion via syringe pump

- **Step 1:** Remove the flip-off seal from the glass vial containing BI 409306 BS (C-13/N-15)
- **Step 2:** Attach the Minispike® on the vial and mount the Omnifix® 10 mL Luer Lock Solo
- **Step 3:** Withdraw 6 ml i.v. solution completely
- **Step 4:** Disconnect the syringe from the Minispike®
- **Step 5:** Remove air bubbles from the Omnifix® 10 mL Luer Lock Solo if applicable
- **Step 6:** Connect the Perfusor® line with the filled Omnifix® 10 mL Luer Lock Solo
- **Step 7:** Connect the Discofix®3SC at the end of the Perfusor® line
- **Step 8:** Remove the air from the Perfusor® line by pushing the syringe plunger and fill the Perfusor® line and the Discofix®3SC completely with i.v. solution.
- **Step 9:** Put a Combi-Stopper to the Discofix®3SC for safe storage of the system until administration
- **Step 10:** Place the filled Omnifix® 10 mL Luer Lock Solo into the syringe pump Perfusor® fm
- **Step 11:** Flush the Perfusor® line **with 1 mL** via Perfusor® fm
- **Step 12:** Enter administration data into syringe pump Perfusor® fm:
  1 ml solution is to be administered over 30 min.

  Please note: The deadspace volume of Introcan Safety® W Winged-FEP 18G was determined as 0.1 mL. Therefore, the volume settings at the syringe pump must be increased from 1.0 mL to 1.1 mL (infusion duration 30 minutes).

The solution for infusion is ready for administration.

10.2.3 In-use stability

After withdrawal of i.v. solution from the glass vial, storage of vial and solution in the Omnifix® 10 mL Luer Lock Solo (including filled Perfusor® line **)** is allowed for 24 hours at

room temperature. Vial and syringe shall be protected from direct sun exposure. No additional light protection measures are required.

10.2.4 Mode of application

The vials are for single use only. Remnants in vial and syringe must be discarded.

10.2.5 General remarks – important

The solution in the vial is ready for use. Because of lacking analytical coverage beyond the preparation procedure described in this document, no further dilutions of the solution is allowed.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		24 April 2018
EudraCT number		2017-004798-14
BI Trial number		1289-0025
BI Investigational Product(s)		BI 409306
Title of protocol		Absolute bioavailability and pharmacokinetics of BI 409306 using a single oral dose of BI 409306 co-administered with an intravenous stable labeled isotope BI 409306 (C-13/N-15) in healthy male and female subjects (Non-Randomised, open-label, single arm, single period design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1. 5.5.2.1 2. 4.1.4
Description of change		1. The term “dipotassium”was replaced with the correct term “tripotassium” 2. Clarification of position after oral drug administration
Rationale for change		1. Correction 2. Correction

Number of global amendment		2
Date of CTP revision		04 May 2018
EudraCT number		2017-004798-14
BI Trial number		1289-0025
BI Investigational Product(s)		BI 409306
Title of protocol		Absolute bioavailability and pharmacokinetics of BI 409306 using a single oral dose of BI 409306 co-administered with an intravenous stable labeled isotope BI 409306 (C-13/N-15) in healthy male and female subjects (Non-Randomised, open-label, single arm, single period design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1. 10.2.2 2. 3.3.3
Description of change		1. Information of amount of deadspace volume of intravenous cather was inserted 2. In exclusion criterion 12 the missing last word (“drug”) was added already in the context of global amendment No 1 but not listed on the description of changes.
Rationale for change		1. Clarification 2. Correction

APPROVAL / SIGNATURE PAGE

Document Number: c09116705 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-2

Title: Absolute bioavailability and pharmacokinetics of BI 409306 using a single oral dose of BI 409306 co-administered with an intravenous stable labeled isotope BI 409306 (C-13/N-15) in healthy male and female subjects (Non-Randomised, open-label, single arm, single period design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		07 May 2018 11:34 CEST
Author-Clinical Pharmacokineticist		07 May 2018 11:39 CEST
Approval-Therapeutic Area		07 May 2018 12:32 CEST
Author-Trial Clinical Monitor		07 May 2018 14:46 CEST
Verification-Paper Signature Completion		07 May 2018 17:44 CEST
Approval-Team Member Medicine		09 May 2018 16:44 CEST

(Continued) Signatures (obtained electronically)

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