# Clinical Trial Protocol

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| | **Document Number: c11975084-02** |
| **EudraCT No.:** | 2018-001192-21 |
| **BI Trial No.:** | 1346-0016 |
| **BI Investigational Product:** | BI 425809 |
| **Title:** | Metabolism and pharmacokinetics of BI 425809 after administration of BI 425809 XX (C-14) as oral solution in healthy male volunteers |
| **Lay Title:** | A study in healthy men to find out how BI 425809 is taken up and handled by the body |
| **Clinical Phase:** | I |
| **Trial Clinical Monitor:** | Phone: +<br>Fax: + |
| **Principal Investigator:** | Phone: +<br>Fax: + |
| **Status:** | Final Protocol |
| **Version and Date:** | Version: 2.0 Date: 25 Sep 2018 |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

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|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br>Not applicable | | | |
| **Name of active ingredient:**<br>BI 425809 | | | |
| **Protocol date:**<br>29 June 2018 | **Trial number:**<br>1346-0016 | | **Revision date:**<br>25Sep2018 |

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|---|---|
| **Title of trial:** | Metabolism and pharmacokinetics of BI 425809 after administration of BI 425809 XX (C-14) as oral solution in healthy male volunteers |
| **Principal Investigator:** | |
| **Trial site:** | |
| **Clinical phase:** | I |
| **Objectives:** | To determine the basic pharmacokinetics of BI 425809 and [$^{14}$C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 25 mg BI 425809 XX (C-14) given to healthy male subjects |
| **Methodology:** | Non-randomized, open-label, single period, single arm |
| **No. of subjects:** | |
| **total entered:** | 6* |
| **each treatment:** | 6*<br>* In case a subject vomits within 8 hours after administration of trial drug on day 1 an additional subject may be entered and dosed in order to have 6 evaluable subjects, i.e. the actual number of subjects entered may increase up to 8 |
| **Diagnosis:** | Not applicable |
| **Main criteria for inclusion:** | Healthy male subjects, age of 18 to 65 years, body mass index (BMI) of 18.5 to 29.9 kg/m$^2$ |
| **Test product** | BI 425809 XX (C-14) as oral solution |
| **dose:** | 25 mg (calculated as free base BI 425809)<br>– in 12.5 mL oral solution (2 mg/mL)<br>– corresponding to 25 mg BI 425809 XX<br>containing a radioactive dose of 3.7 MBq |
| **mode of admin.:** | Oral with 240 mL of water after an overnight fast of at least 10 h |
| **Duration of treatment:** | Single dose |

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|---|---|---|---|
| **Name of company:**<br><br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br><br>Not applicable | | | |
| **Name of active ingredient:**<br><br>BI 425809 | | | |
| **Protocol date:**<br>29 June 2018 | **Trial number:**<br>1346-0016 | | **Revision date:**<br>25Sep2018 |
| **Criteria for pharmacokinetics:** | *Primary endpoints:*<br>Mass balance recoveries of total radioactivity in urine and faeces:<br>Amount of radioactivity excreted as a percentage of the administered dose ($fe_{0-t2}$) for urine and faeces<br>*Secondary endpoints:*<br>Assessment of the oral pharmacokinetics of a solution formulation of BI 425809 XX (C-14) by calculation of the following parameters for total radioactivity and BI 425809 in plasma: $C_{max}$ and $AUC_{0-tz}$ | | |
| **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:** | Descriptive statistics and graphical displays. | | |

# FLOW CHART

| Visit | Day | Planned time (relative to 1st drug administration [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory | $PK_{blood/plasma}$ [2] | $PK_{urine}$ [6] | $PK_{faeces}$ [7] | 12-lead ECG | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [9] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | -21 to -2 | | | Screening (SCR)[1] | x | | | | x | x | |
| 2 | -1 | -18:00 | 14:00 | Admission to trial site | x[5] | | | | | | x |
| | | -14:00 | 18:00 | Dinner | | | | | | | |
| | | -10:30 | 21:30 | Snack (voluntary)[15] | | | | | | | |
| | 1 | -2:00 | 06:00 | | x[3] | x[3] | x[3] | x[14] | x[3] | x[3] | x[3] |
| | | 0:00 | 08:00 | Drug administration | | | ⊤ | ⊤ | | | |
| | | 0:30 | 08:30 | | | x | \| | \| | | | |
| | | 0:45 | 08:45 | | | x | \| | \| | | | |
| | | 1:00 | 09:00 | | | x | \| | \| | | | |
| | | 1:30 | 09:30 | | | x | \| | \| | | | |
| | | 2:00 | 10:00 | 240 mL fluid intake | | x | \| | \| | | | |
| | | 4:00 | 12:00 | 240 mL fluid intake, thereafter lunch[4] | x[8] | x | + | \| | x | x | x |
| | | 6:00 | 14:00 | | | x | \| | \| | | | |
| | | 8:00 | 16:00 | Snack (voluntary)[4] | | x | + | \| | | | |
| | | 11:00 | 19:00 | Dinner | | | \| | \| | | | |
| | | 12:00 | 20:00 | | | x | + | \| | x | x | x |
| | | 13:30 | 21:30 | Snack (voluntary) | | | \| | \| | | | |
| | 2 | 24:00 | 08:00 | | | x | + | + | | x | x |
| | | 36:00 | 20:00 | | | x | \| | \| | | | |
| | 3 | 48:00 | 08:00 | | x[8] | x | + | + | | | x |
| | 4 | 72:00 | 08:00 | | | x | + | + | | | x |
| | 5 | 96:00 | 08:00 | | | x | + | + | | | x |
| | 6 | 120:00 | 08:00 | | | x | + | + | | | x |
| | 7 | 144:00 | 08:00 | | | x | + | + | | | x |
| | 8 | 168:00 | 08:00 | | x[8] | x | + | + | | | x |
| | 9 | 192:00 | 08:00 | | | x | + | + | | | x |
| | 10 | 216:00 | 08:00 | | | x | + | + | | | x |
| | 11 | 240:00 | 08:00 | | | x | + | + | | | x |
| | 12 | 264:00 | 08:00 | | | x | + | + | | | x |
| | 13 | 288:00 | 08:00 | | | x | + | + | | | x |
| | 14 | 312:00 | 08:00 | | | x | + | + | | | x |
| | 15 | 336:00 | 08:00 | Discharge from trial centre | x | x | ⊥ | ⊥ | x | x | x |
| | 20 | 461:00 | 13:00 | Start home collection | | | | ⊤ | | | |
| | 21 | 485:00 | 13:00 | Admission to trial site[11,12] | | x | ⊤ | + | | | x |
| | 22 | 509:00 | 13:00 | Discharge from trial site[11] | | | ⊥ | ⊥ | | | x |
| | 27 | 629:00 | 13:00 | Start home collection | | | | ⊤ | | | |
| | 28 | 653:00 | 13:00 | Admission to trial site[11,12] | | x | ⊤ | + | | | x |
| | 29 | 677:00 | 13:00 | Discharge from trial site[11] | | | ⊥ | ⊥ | | | x |
| | 34 | 797:00 | 13:00 | Start home collection | | | | ⊤ | | | |
| | 35 | 821:00 | 13:00 | Admission to trial site[11,12] | x | x | ⊤ | + | | | x |
| | 36 | 845:00 | 13:00 | Discharge from trial site[11] | | | ⊥ | ⊥ | | | x |

| Visit | Day | Planned time (relative to 1st drug administration [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory | $PK_{blood/plasma}$ [2] | $PK_{urine}$ [6] | $PK_{faeces}$ [7] | | 12-lead ECG | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [9] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 41 | 965:00 | 13:00 | Start home collection | | | | ┼ | | | | |
| | 42 | 989:00 | 13:00 | Admission to trial site[11,12] | | x | ┼ | ┼ | | | | x |
| | 43 | 1013:00 | 13:00 | Discharge from trial site[11] | | | ┼ | ┼ | | | | x |
| | 48 | 1133:00 | 13:00 | Start home collection | | | | ┼ | | | | |
| | 49 | 1157:00 | 13:00 | Admission to trial site[11,12] | | x | ┼ | ┼ | | | | x |
| | 50 | 1181:00 | 13:00 | Discharge from trial site[11] | | | ┼ | ┼ | | | | x |
| 3 | 15-50 | | | End of trial (EOT) examination[10,13] | x | | | | | x | x | x |

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. Pharmacokinetics (PK): BI 425809 and metabolites in plasma; [$^{14}$C]-radioactivity in whole blood and plasma (see Section 5.5.2.1). Blood sampling for an individual subject can be stopped if [$^{14}$C]-radioactivity in plasma is below limit of detection (< LLOQ 10 dpm/mL) at two consecutive sampling time points for this subject (earliest stop on day 15).
3. The time is approximate; the procedure is to be performed and completed within 2 h prior to drug administration.
4. If several actions are indicated at the same time point, the intake of meals will be the last action.
5. Safety lab including urine drug screening and alcohol test.
6. Urine collection intervals (for PK/[$^{14}$C]-radioactivity assessment and metabolic profiling; planned time): on Day -1 or Day 1 predose (blank) sample within 2 h before drug administration, on Day 1 prior to start of urine collection voiding of the bladder, 0-4 , 4-8, 8-12, 12-24; 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, 240-264, 264-288, 288-312 and 312-336 hours after drug administration. Thereafter, if warranted, 24 h collections are to be performed every 7 days starting on day 21.When the release criteria for radioactivity recovery have been met then urine sampling for PK will be stopped (earliest stop on day 15).
7. All stools (for PK and metabolic profiling) will be collected quantitatively in portions up to 336 hours (sampling intervals of 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, 240-264, 264-288, 288-312 and 312-336 hours) after drug administration. Thereafter, if warranted, 24 h collections are to be performed every 7 days starting on day 20. A blank sample will be collected before drug administration on Day -1 or Day 1. Collection of the predose faeces sample will start from approximately -48 h before admission (see Section 5.5.2.3). When the release criteria for radioactivity recovery have been met then faeces sampling for PK will be stopped (earliest stop on day 15).
8. Only measurement of haematocrit
9. 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.
10. End-of-trial (EOT) examination to be performed within 1 to 7 days after last discharge from the study centre, or, if all once-weekly 24 h sampling periods are needed, prior to discharge on Day 50. End of trial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
11. The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of +/- 4 h to the planned time.
12. Subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Day 20-21, 27-28, 34-35, 41-42, and 48-49. If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis.
13. For definition of the individual subject's end of trial see Section 6.2.3
14. Subjects will collect a predose faeces sample at home in specific containers provided by
15. To be consumed within 30 min to allow 10h fast prior drug administration

# TABLE OF CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| AD | Alzheimer's disease |
| ADME | Absorption, distribution, metabolism, and excretion |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ALT | Alanine amino transferase |
| AST | Aspartate amino transferase |
| $AUC_{0-tz}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point |
| BA | Bioavailability |
| BI | Boehringer Ingelheim |
| BLQ | Below limit of quantification |
| BMI | Body mass index (weight divided by height squared) |
| BP | Blood pressure |
| CA | Competent authority |
| CI | Confidence interval |
| CIAS | Cognitive impairment associated with schizophrenia |
| CL/F | Apparent clearance of the analyte in plasma after extravascular administration |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| CLR, t1-t2 | Renal clearance of the analyte from the time point t1 to t2 |
| CML | Clinical Monitor Local |
| CNS | Central nervous system |
| CRA | Clinical Research Associate |
| CRO | Clinical Research Organization |
| CRF | Case report form |
| CTP | Clinical trial protocol |
| CTR | Clinical trial report |
| DILI | Drug induced liver injury |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| EDTA | Ethylenediaminetetraacetic acid |
| ENTS | Entered set |
| EOT | End of trial |

| | |
|---|---|
| EU | European Union |
| FDA | Food and Drug Administration |
| $fe_{faeces,\ 0\text{-}t2}$ | Fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point |
| $fe_{urine,\ 0\text{-}t2}$ | Fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point |
| GCP | Good Clinical Practice |
| gCV | Geometric coefficient of variation |
| GLYT1 | Glycine transporter 1 |
| gMean | Geometric mean |
| GMP | Good Manufacturing Practice |
| HR | Heart rate |
| IB | Investigator's brochure |
| ICH | International Conference of Harmonization |
| ICRP | International Commission on Radiological Protection |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| IPV | Important protocol violation |
| $\lambda_z$ | Terminal rate constant of the analyte in plasma |
| LLOQ | Lower limit of quantification |
| LC-MS/MS | Liquid chromatography tandem mass spectrometry |
| MBq | MegaBequerel |
| MedDRA | Medical Dictionary for Regulatory Activities |
| $MRT_{po}$ | Mean residence time of the analyte in the body after oral administration |
| NMDA | N-methyl-D-aspartate |
| NOA | Not analysed |
| NOP | No peak detectable |
| NOR | No valid result |
| NOS | No sample available |
| PK | Pharmacokinetic(s) |
| PKS | Pharmacokinetic set |
| PR | Pulse rate |
| QT | Time between start of the Q-wave and the end of the T-wave in an electrocardiogram |

| | |
|---|---|
| QTc | QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB) |
| R | Reference treatment |
| REP | Residual effect period |
| SAE | Serious adverse event |
| SCR | Screening |
| SOP | Summary of Product Characteristics |
| SRD | Single-rising dose |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial master file |
| TS | Treated set |
| $t_z$ | Time of last measurable concentration of the analyte in plasma |
| TDMAP | Trial Data Management and Analysis Plan |
| TSAP | Trial statistical analysis plan |
| ULN | Upper limit of normal |
| VAS | Visual Analog Scale |

# 1. INTRODUCTION

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

## 1.1 MEDICAL BACKGROUND

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

## 1.2 DRUG PROFILE

BI 425809 is a potent and selective inhibitor of GlyT1 and does not show species selectivity regarding inhibition of human, rat and pig GlyT1. In vivo proof-of-mechanism (i.e. target engagement in brain) is demonstrated by a dose dependent increase of glycine in rat cerebrospinal fluid. Results from pre-clinical studies with BI 425809 have demonstrated pro-cognitive properties in relevant animal models of learning and memory impairment. Therefore it is expected that treatment with BI 425809 has the potential to improve cognitive functioning in patients with AD and CIAS.
BI 425809 has been administered to healthy volunteers in so far 7 Phase 1 trials and 2 Phase 2 trials in patients are currently ongoing. In addition, BI 425809 is not a first in class compound. Other GLYT1 inhibitors (e.g. Bitopertin and sarcosine) have been tested in clinical trials before [R13-4447], [R13-4508].

### 1.2.3 Residual Effect Period

The Residual Effect Period (REP) of BI 425809 is 11 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

### 1.2.4 Clinical experience in humans

At the time of preparation of this clinical trial protocol, BI 425809 has been investigated in seven Phase 1 trials. Two Phase 2 trials (1346-0009 and 1346-0023) have been re-initiated recently and are ongoing.

A total of 245 healthy subjects have received one or more doses of BI 425809 (single doses of 0.5 mg to 150 mg and multiple doses of 5 mg to 75 mg bid (150 mg/day)), including 18 subjects aged 65 years or older (for details please refer to Investigator's Brochure [c02155957-08], Table 6.1:1).

Altogether, BI 425809 was generally well tolerated in young and elderly healthy male and female volunteers. No deaths or serious adverse events (SAEs) and no AEs of special interest (AESI) were reported. Across all BI 425809 treatment groups, there were 3 subjects with severe, but self-limiting AEs. Overall, drug-related AEs have been seen more frequently in the subjects treated with BI 425809 (33.5% vs 26.9% on placebo). Across all BI 425809 treatment groups, 3 subjects discontinued treatment due to an AE (2x nausea and vomiting, 1x procedural headache), all subjects recovered (for details please refer to Investigator's Brochure [c02155957-08], Table 6.3.1.1:3).

The most frequent AEs for BI 425809 were nervous system disorders (25.3%), with headache being the most common (18.0%). These AEs appear to be dose-related, with a tendency for greater frequency at higher doses and can be clinically monitored.
In addition, transient visual disturbances (at doses ≥ 25 mg BI 425809 qd, mainly blurred vision) and somnolence (drowsiness) were observed. These effects are mostly mild to moderate and transient.

In general, there were no clinically relevant findings in the clinical laboratory evaluation, 12-lead ECG, vital signs. No suicidal ideation or behaviour was observed. No notable decrease in haemoglobin or haematocrit was noted in the BI 425809 treatment groups compared with placebo.

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

# 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

## 2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the metabolism in humans, the mass-balance of excretion, plasma and urinary concentrations of BI 425809 and its metabolites (as appropriate), the resulting PK parameters, and [$^{14}$C]-radioactivity in blood, plasma, urine and faeces after a single oral dose of 25 mg BI 425809 XX (C-14). Major tasks involve metabolite profiling and structure elucidation. This study will also help to determine the metabolic pathways following oral administration of BI 425809 XX (C-14) in healthy volunteers.

The data are necessary for in-depth understanding of the pharmacokinetics of BI 425809 including quantitative determination of elimination pathways and drug metabolites and are required for submission to regulatory authorities.

## 2.2 TRIAL OBJECTIVES

This trial intends to investigate the basic pharmacokinetics of BI 425809 and [$^{14}$C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 25 mg BI 425809 XX (C-14) given to healthy male subjects

The primary objective is:

- To assess the mass balance recovery of [$^{14}$C]-radioactivity from urine and faeces after a single oral dose of 25 mg BI 425809 XX (C-14) given to healthy male subjects

The secondary objective is:

- To assess $C_{max}$ and $AUC_{0\text{-}tz}$ for total [$^{14}$C]-radioactivity and BI 425809 in plasma

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

## 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 to the development of BI 425809. The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication and the intake of BI 425809 XX (C-14).

Procedure-related risks

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.

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 paraesthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venepuncture for blood sampling.

Drug-related risks and safety measures

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

*Risks related to BI 425809 administration*

The currently available data from 7 phase I trials in healthy young and elderly subjects with single oral administration of up to 150 mg BI 425809 and multiple doses of up to 75 mg BI 425809 twice daily (150 mg/d) indicate that BI 425809 has a broad safety margin and is generally well tolerated. The most frequent AEs were adverse CNS symptoms, most commonly headaches but also somnolence (drowsiness) that showed a trend for dose dependency, were reversible and can be clinically monitored. In addition, BI 425809 may be

associated with visual disturbances. These effects are understood to be mostly mild to moderate and transient. Decreased haemoglobin is a potential risk based on preclinical data and class effect; however, no clear decrease in haemoglobin was seen in BI 425809 treated subjects compared to placebo in phase I trials so far.

*Risks related to M232 (BI 761036) and M530 (BI 758790)*

The major human metabolites of BI 425809, M530 (BI 758790) and M232 (BI 761036), have been evaluated in nonclinical studies with no evidence of pharmacological activity, genotoxicity, effects on embryo-foetal development, or adverse effects in repeat-dose toxicity in studies of 13 – 15 weeks duration.
Furthermore, multiple doses of up to 75 mg twice daily (150 mg/d) were well tolerated in previous clinical trials. Based on this human data there is no indication of a metabolite-mediated safety concern for a single dose administration of 25 mg BI 425809 in the present trial.

*Risks related to administration of BI 425809XX (C-14)*

BI 425809 XX (C-14) is labelled with the isotope [$^{14}$C] which is necessary for the purposes of this mass balance trial. Therefore, subjects will be exposed to ionizing radiation. The effective dose that each subject receives from one administration of 3.7 MBq is approx. 0.41 mSv.

The radioactive dose proposed for administration in the planned human ADME study, 0.41 mSv, is lower than the limit specified by:

WHO Category 1, (<0.5mSv – within variations of natural background radioactivity)

And lower than the limit proposed by:

ICRP Category 2a, (<1 mSv – risk defined as minor)

For details on the radiation burden calculation please refer to Appendix 10.1.

For clinical investigations to study the disposition, metabolism and excretion of new pharmaceutical compounds in man an effective dose of 0.1 – 1.0 mSv is considered acceptable [R15-3219].

Summary of benefit-risk assessment

In previous trials in healthy subjects, administration of single oral doses up to 150 mg BI 425809 and multiple oral doses up to 75 mg BI 425809 once or twice daily was safe and well tolerated (Section 1.2.4). In the current trial, healthy male volunteers will receive a single oral dose of 25 mg BI 425809. Each participating subject will receive only one radioactive dose.

The trial design is optimized to collect as much relevant information as possible on the pharmacokinetics of BI 425809 without exposing participating volunteers to undue risk. However, there is always the potential for subjects receiving medication to experience

adverse events (AEs), and rarely also serious adverse events (SAEs). Risks to subjects will be minimized and addressed by eligibility criteria, safety laboratory examinations, ECG and vital sign measurements, in-house observation periods and verbal communication concerning AEs.

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

The risk associated with the expected maximal radiation burden falls in ICRP category 2a with minor level risk and in WHO Category 1, i.e. within variations of natural background radioactivity. This is considered to be acceptable.

The results of this trial are necessary for the further development of BI 425809. Successful development of BI 425809 is expected to provide a new valuable treatment to improve cognitive functioning in patients with AD and CIAS.
The risks of the participating volunteers are minimized and justified when compared to the potential benefits of this trial.

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

This trial will be performed as a non-randomized, open-label, single period, single arm trial in healthy male volunteers to investigate the basic pharmacokinetics of BI 425809 and [$^{14}$C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 25 mg BI 425809 XX (C-14).

The planned radioactive dose per subject is 3.7 MBq (0.41 mSv). This is equivalent to 0.111 mSv/MBq (reference: Appendix 10.1).

On Day 1, subjects will receive the [$^{14}$C]-labelled drug substance, i.e. 25 mg BI 425809 XX (C-14) and will then stay in the study centre up to the morning of Day 15 for collection of samples of blood, urine, and faeces. Subjects will be readmitted to the study centre for 24 h collection intervals of urine and faeces on Days 21, 28, 35, 42, and 49, if release criteria as specified below have not been met on Day 15. Within 24 h before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24 h interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval. Otherwise it will be discarded.

For determination of whether release criteria have been reached for individual subjects, [$^{14}$C]-radioactivity will be measured in excreta (urine and faeces). The actual recovery results will be reported as a percentage of the administered dose.

If one of the following release criteria is true (i.e., release criteria have been met), 24 h collection intervals after Day 15 will not be performed / will be stopped:

- Greater than or equal to 90% of the administered dose has been recovered in urine and faeces combined over the investigational period, *or*
- If <1% of the dose administered has been collected in urine and faeces within 2 separate, consecutive 24 h intervals, *and*
- Concentration of total radioactivity in plasma and in blood <5% of $C_{max}$ of total radioactivity in plasma

If a subject is unable to attend one of these visits, they may be allowed to reschedule the visit if needed.

Irrespective of whether release criteria have been met or not after collection interval Day 49-50, no further collections are planned.

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

### 3.1.1 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 radiolabelled trial medication (BI 425809 XX (C-14)) will be provided by

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

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

The analyses of BI 425809 (and its metabolites) concentrations in plasma, the metabolite profiling and the identification in urine, plasma, and faeces will be performed at BI and/or at a suitable Contract Research Organisation (CRO) under the responsibility of the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany .

Blood, plasma, urine, and faeces (and vomit if applicable) concentrations of [$^{14}$C]-radioactivity will be determined at

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

Data management and statistical evaluation will be performed by BI according to BI SOPs and/or by a suitable CRO under the responsibility of the Department of Biostatistics and Data Sciences, BI Pharma GmbH & Co. KG, Biberach, Germany.

Tasks and functions assigned in order to organize, 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

This is a standard study design for a [$^{14}$C] human study of absorption, metabolism, and excretion including determination of mass balance.

Inclusion of a control group is not required for this investigation. Due to the prolonged half-life of the metabolite BI 761036 (M232) (~170h), that contains the radioactive [$^{14}$C] label, it cannot be excluded that prolonged sampling is necessary in humans. Therefore, following 14 days in-house excreta collection after dosing, subjects will return on a weekly basis for in-house 24-h collection intervals for up to 7 weeks after dosing as long as release criteria are not met (Section 3.1).
Blinding is not necessary, because all subjects receive the same treatment.

## 3.3 SELECTION OF TRIAL POPULATION

It is planned that 6 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site or, if necessary, via advertisement. In case a subject vomits within 8 h after trial drug administration assuming an incomplete absorption of the radiolabelled compound an additional subject may be entered and dosed to assure that 6 evaluable subjects will complete the study as per protocol. Thereby, the actual number of subjects entered may increase up to 8.

The current trial is designed to investigate the basic pharmacokinetics of BI 425809 including absorption, metabolism, and elimination and quantitative determination of excretion by mass balance. Samples will be generated for additional metabolic profiling and structural identification. Healthy male subjects are an ideal population for the objectives of this trial, since they provide relatively stable physiological, biochemical and hormonal conditions, i.e. the absence of disease-related variations and relevant concomitant medications.

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

### 3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

### 3.3.2 Inclusion criteria

Subjects will only be included into the trial, if they meet the following criteria:

1. Healthy male subjects according to the investigator’s assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 65 years (incl.)
3. BMI of 18.5 to 29.9 kg/m$^2$ (incl.)

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

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

   Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, with their partner, they must comply with the contraceptive requirements detailed above.

### 3.3.3 Exclusion criteria

Subjects will not be allowed to participate if any of the following general criteria apply:

1. Any finding in the medical examination (including BP, PR or ECG) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 139 mmHg, diastolic blood pressure outside the range of 45 to 89 mmHg, or pulse rate outside the range of 40 to 100 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Clinically significant gastrointestinal, hepatic, renal, respiratory (including but not limited to interstitial lung disease), cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections

10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation). Use of CYP3A4 inhibitors and inducers 1 week prior to administration of trial medication
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Smoker (more than 5 cigarettes or 1 cigars or 1 pipes per day)
14. Inability to refrain from smoking on trial days
15. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 35 ml of spirits)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within 4 days prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

23. Participation in another ADME study with a radiation burden of >0.1 mSv in the period of 1 year prior to screening or 1.1-2.0 mSv in the past 2 years or 2.1-3.0 mSv in the past 3 years etc.
24. Exposure to radiation for diagnostic reasons (except dental X-rays and plain X-rays of thorax and bony skeleton (excluding spinal column)) in the period of 1 year prior to screening
25. Irregular defecation pattern (less than a mean of one bowel movement every day)

For study restrictions, refer to Section 4.2.2.

### 3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events, or diseases)
4. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.

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

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 1.2.3), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

#### 3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP, or the contract with BI 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.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

### 3.3.5 Replacement of subjects

In case a subject vomits within 8 h after trial drug administration assuming an incomplete absorption of the radiolabelled compound an additional subject may be entered and dosed to assure that 6 evaluable subjects will complete the study as per protocol.

In case some subjects do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. Replacement of subjects and dosing of additional subjects as described above should always be done in mutual agreement with the principal investigator. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he replaces.

# 4. TREATMENTS

## 4.1 TREATMENTS TO BE ADMINISTERED

BI 425809 XX is a neutral molecule exhibiting no ionizing centre. Therefore 25 mg BI 425809 equals to 25 mg BI 425809 XX.
Radiolabelled BI 425809 is administered as oral solution of BI 425809 (C-14). The oral solution contains a mixture of [C-14] BI425809 XX and unlabelled BI 425809 XX and is manufactured by BI Pharma GmbH & Co. KG. The solution from this mixture is made by

### 4.1.1 Identity of BI investigational product

The characteristics of the test product are given below:

| | |
|---|---|
| Name: | BI 425809 XX (C-14) oral solution 2 mg/mL (12.5 mL; 3.7MBq) |
| Substance: | BI 425809 XX mixed with [C-14] BI425809 XX |
| Pharmaceutical formulation: | Oral Solution |
| Source: | |
| Unit strength: | 25 mg BI 425809 calculated as free base<br>- Corresponding to 25 mg BI 425809 XX<br>- Containing [C-14] BI 425809 XX corresponding to a radioactive dose of 3.7 MBq (0.41mSv)<br>- In a solution of 12.5 mL volume (concentration of BI 425809: 2 mg/mL, dissolved in 12.5 mL PEG (polyethylene glycol 400) as solvent) |
| Posology: | 1-0-0 |
| Route of administration: | p.o. |
| Duration of use: | Single dose |

### 4.1.2 Method of assigning subjects to treatment groups

This is an open-label, phase I, single-dose study. All subjects receive the same treatment.

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

The randomization procedure is described in Section 7.5.

### 4.1.3 Selection of doses in the trial

The dose of 25 mg BI 425809 is below the already tested highest doses (single doses up to 150 mg, multiple doses up to 75 mg bid (150 mg/d)) of BI 425809 in healthy subjects. In healthy volunteers, a single dose of 25 mg was safe and well-tolerated (Section 1.2). A dose of 25 mg corresponds to the maximum dose tested in the ongoing phase II studies 1346-0023 [c03632269-04], 1346.9 [c03559983-03]. A dose of 25 mg is considered adequate for the objectives of the current trial.

This dose administered as oral solution will include 3.7 MBq of BI 425809 XX (C-14). The radiolabelled dose of 3.7 MBq is required for the objectives of the study providing good detection limits for measurement of radioactivity in urine, faeces and plasma. The total effective dose (radiation burden) amounts to 0.41 mSv. This is below the limit of ICRP Category 2a and considered acceptable. Radiation burden calculations are presented in Appendix 10.1. For risk-benefit assessment, see Section 2.3.

### 4.1.4 Drug assignment and administration of doses for each subject

In the morning of Day 1, following an overnight fast of at least 10 h, all subjects will receive one single oral dose of the radiolabelled trial drug (BI 425809 XX (C-14) oral solution 2 mg/mL (12.5 mL; 3.7 MBq)).

The radiolabelled medication will be administered as a single oral dose together with 240 ml of water to a subject in the sitting position under supervision of the investigator or an authorised designee. The amount of administered radiolabelled medication will be calculated based on pre- and postdose weight of the syringe used for oral administration.

The so-called four-eye principle (two-person rule) should be applied for administration of trial medication.

During the first 4 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 or if necessary for any medical reasons (e.g., adverse events). For restrictions with regard to diet and fluid intake see Section 4.2.2.2.

After drug administration subjects will be kept under close medical surveillance until planned discharge from the unit on Day 15. In case release criteria for radioactivity recovery have not been met on Day 15, subjects will come back to the unit for once-weekly 24 h sampling periods until discharge criteria are met or after the last collection interval day 49-50 was completed (see Section 3.1).

### 4.1.5 Blinding and procedures for unblinding

This is an open-label study.

### 4.1.6 Packaging, labelling, and re-supply

Drug product manufacturing is done by . The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The final container

will be an oral syringe holding the Investigational Drug Products and will be labelled according to GMP Annex 13 / EU GMP Guideline and local drug law.

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

### 4.1.8 Drug accountability

pharmacy will deliver the investigational drugs to the investigator upon availability of a valid prescription from the investigator.

The investigator will not order the drugs from the pharmacy before the following requirements are fulfilled:

- Approval of the study protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol
- Availability of licence for clinical research using radioactive isotopes

Only authorised personnel as documented in the form 'Site Delegation Log' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused trial medication must be returned to the sponsor or disposed locally by the trial site upon written authorisation by the clinical monitor. Appropriate retention samples will be kept at until finalization of the clinical trial report. Receipt, usage and return or 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 return to the sponsor or alternative 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 or return to the sponsor (and/or) appointed CRO, 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 specific rescue drugs foreseen for the treatment of AEs. No special emergency procedures are to be followed. No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorize 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 except for paracetamol. Limited doses of paracetamol (up to 2 grams per day) are allowed prior to entry in the clinic and during the clinical stay after prescription by a physician to treat aches and pains. However, in case of adverse events in need of treatment, a concomitant therapy will be permitted. The use of moderate or potent CYP3A4 inhibitors should be avoided. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardized meals will be served at the time points described in the Flow Chart. On Day 1 no food is allowed for at least 4 h after drug intake.

For fasting times before drug administration see Section 4.1.4. For fasting times before safety laboratory investigations see Section 5.2.3.

From 1 h before drug intake until lunch, fluid intake is restricted to the 240 ml of 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 should be within about 1000 to 3000 mL.

During the days of urine collection, subjects will be advised that total fluid intake should be at least 1.5 liters and should not exceed 3.5 liters.

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

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

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

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

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

Excessive physical activity (such as competitive sport) should be avoided starting 4 days before the first administration of trial medication until the end of trial examination.

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

## 4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations and urinary and faeces 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.

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 CRF 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 hospitalization
- requires prolongation of existing hospitalization,
- 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 jeopardize 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 hospitalization 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 Section 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 are considered as AESIs:

- 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 trial 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, intensity of the event, and any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for 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.

### 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 Table5.2.3: 1 and Table 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

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

Table 5.2.3: 1 Routine laboratory tests

| Functional lab group | Test name |
|---|---|
| Haematology | Haematocrit |
| | Haemoglobin |
| | Red blood cell count (RBC) |
| | Reticulocyte count |
| | White blood cell count (WBC) |
| | Platelet count |
| Automatic WBC differential (relative and absolute) | Neutrophils, eosinophils, basophils, monocytes, lymphocytes |
| Manual differential WBC (if automatic differential WBC is abnormal) | Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes |
| Coagulation | Activated partial thromboplastin time (aPTT) |
| | Prothrombin time (Quick's test and INR) |
| | Fibrinogen |
| Enzymes | Aspartate transaminase (AST/GOT) |
| | Alanine transaminase (ALT/GPT) |
| | Alkaline phosphatase (AP) |
| | Gamma-glutamyl transferase (GGT) |
| | Creatine kinase (CK) |
| | CK-MB, only if CK is elevated |
| | Lactate dehydrogenase (LDH) |
| | Lipase |
| | Amylase |
| Hormones[1] | Thyroid stimulating hormone (TSH) |
| | fT3, fT4 |
| Substrates | Plasma glucose |
| | Creatinine |
| | Total bilirubin |
| | Direct bilirubin |
| | Total protein |
| | C-Reactive Protein (CRP) |
| | Uric acid[1] |
| | Total cholesterol[1] |
| | Triglycerides[1] |
| Electrolytes | Sodium |
| | Potassium |
| | Magnesium |
| | Calcium |

[1] Only at screening and end of trial.

Table 5.2.3: 1 Routine laboratory tests (cont).

| Functional lab group | Test name |
|---|---|
| Urinalysis[1] (Stix) | Urine nitrite<br>Urine protein<br>Urine glucose<br>Urine ketone<br>Urobilinogen<br>Urine bilirubin<br>Urine haemoglobin<br>Urine leukocytes<br>Urine pH |
| Urine sediment[1] (microscopic examination if haemoglobin, 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) |

[1] Only at screening and end of trial.

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and on Day-1 prior to the treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, an alcohol test in urine will be performed at screening and on Day-1 prior to the treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

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

The drug and alcohol screening tests will be performed using the ADVIA Chemistry XPT system.

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

### 5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (Mortara ELI 250 Rx) at the 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. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

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

### 5.2.5 Assessment of other safety parameters

#### 5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap CareScape VC150 from GE Healthcare) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

#### 5.2.5.2 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.

## 5.3 OTHER

## 5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of

administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure in human mass-balance trials.

## 5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

### 5.5.1 Pharmacokinetic endpoints

#### 5.5.1.1 Primary endpoints

Primary endpoints will be the mass balance recoveries of [$^{14}$C]-radioactivity in urine and faeces after a single oral dose of 25 mg BI 425809 XX (C-14) given to healthy male subjects:

- $fe_{urine,\ 0\text{-}t2}$ (fraction of [$^{14}$C]-radioactivity excreted in urine as percentage of the administered oral dose over the time interval from 0 to the last quantifiable time point)
- $fe_{faeces,\ 0\text{-}t2}$ (fraction of [$^{14}$C]-radioactivity excreted in faeces as percentage of the administered oral dose over the time interval from 0 to the last quantifiable time point)

Timeframe: The timeframe for determination of these endpoints depends on discharge of radioactivity from each individual subject and is predicted to vary between 2-7 weeks after drug administration.

#### 5.5.1.2 Secondary endpoints

The following secondary endpoints will be evaluated for [$^{14}$C]-radioactivity and BI 425809 in plasma:

- $C_{max}$ (maximum measured concentration of the analyte)
- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable time point)

### 5.5.2 Methods of sample collection

5.5.2.1 Sampling of whole blood and plasma

Whole blood and plasma will be collected at time points shown in the Flow Chart:

- to determine [$^{14}$C]-radioactivity concentrations in whole blood and plasma
- to determine concentrations of BI 425809 and its metabolites in plasma
- to identify the metabolites of BI 425809 in plasma
- to determine the blood cell/plasma and blood/plasma ratios of [$^{14}$C]-radioactivity

5.5.2.2 Sampling of whole blood and plasma for [$^{14}$C]-radioactivity analysis in whole blood and plasma and quantification of BI 425809 and its metabolites in plasma

Blood for pharmacokinetics and metabolite identification purposes will be taken from an antecubital or forearm vein into a $K_2$-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart.

At each time point listed in the Flow Chart, 5 mL (for time points 0.5h – 240 h (inclusive)) or 8 mL (for the pre-dose sample and from time points 264 h to the last) of whole blood will be drawn.

It is planned that aliquots of all time points are prepared for the determination of [$^{14}$C]-radioactivity in whole blood and plasma.

Bioanalysis of BI 425809 and its metabolites in plasma are planned to be prepared as long as PK blood sample are collected for total radioactivity after 336 h.

*Premature stopping of blood sampling*

In case [$^{14}$C]-radioactivity in plasma samples is not detectable (<LLOQ 10 dpm/mL) at two consecutive time points for a subject, blood sampling can be stopped for this subject. However, all samples until and including the 336 h sample for single dose have to be taken.

*Laboratory manual*

For detailed description of blood sampling, sample handling, sample preparation, sample storage, tube labelling and sample shipment refer to the laboratory manual.

#### 5.5.2.5 Urine sampling

Urine will be collected during the trial as indicated in the Flow Chart:

- to determine the concentration and amount of BI 425809 and its metabolites M530 (BI 758790), M232 (BI 761036), and M312 (IN 79211) in urine
- to determine total [C-14] BI 425809 related material in urine
- to investigate the metabolic profile of BI 425809 in urine

A blank urine sample will be collected within approximately 14 hours prior to drug administration. All urine voided will be collected in containers, according to intervals, given in the Flow Chart. Addition of Tween 20 resulting in a final concentration of at least 0.05% Tween 20 is required. For urine collection, the weight of the empty containers has to be determined prior to and at the end of the collection interval. The urine volume (weight will be set equal to volume, i.e. 1 kg = 1 L, without correction for specific gravity of urine) for each collection interval will be documented. Volunteers will empty their bladders at the end of each sampling interval. The exact start and end times of the urine collection intervals will be recorded in the CRF.

All samples are planned to be used for determination of [$^{14}$C]-radioactivity.

Samples until and including the collection interval 312-336 h are planned to be used for analysis of BI 425809 and its metabolites.

Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each urine sample.

For a detailed description of urine sampling, preparation of collection containers, sample storage, sample handling, labelling, and sample shipment refer to the laboratory manual.

#### 5.5.2.6 Faeces sampling

Faeces will be collected for the analysis of [$^{14}$C]-radioactivity and for metabolic profiling in intervals as indicated in the Flow Chart. A blank faeces sample will be collected prior to drug administration.

All faeces samples after intake of BI 425809 XX (C-14) are planned to be used for determination of [$^{14}$C]-radioactivity.

Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each faeces sample interval.

All stools will be collected quantitatively in portions up to 336 hours after drug administration. The weight of the faeces and the exact times of faeces collection will be recorded in the eCRF.

*Laboratory Manual*

For a detailed description of faeces sampling, sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

5.5.2.7 Collection of vomit

If vomiting occurs in a volunteer within 12 h after radioactive drug administration, the vomit will be collected for determination of weight and [$^{14}$C]-radioactivity.

For a detailed description of vomit sampling, sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

## 5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 425809 and its metabolites plasma and urine concentrations

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

The analysis will be performed at:

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

5.5.3.3 Radiokinetic and Excretion Balance

Determination of [$^{14}$C]-radioactivity concentrations in plasma, whole blood, urine, and faeces (and vomit, if applicable) will be done by means of validated liquid scintillation counting methods at

The blood, plasma, urine and faeces (and vomit, if applicable) concentrations of radioactivity will be determined in agreement with relevant Standard Operating Procedures (SOPs).

## 5.6 BIOMARKER

No biomarker will be determined.

## 5.7 PHARMACODYNAMICS

No pharmacodynamic sampling will be performed.

## 5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

# 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 2 h-period prior to the trial drug administration.

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

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

For planned individual plasma concentration sampling times and urine/faeces sampling times/ collection intervals 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 beginning or end of a urine/faeces collection interval and a blood sample are scheduled for the same time point, urine/faeces collection should be done first, with withdrawal of the blood sample as closely to the planned time point as possible.

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

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

### 6.2.1 Screening period

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

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

### 6.2.2 Treatment period

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

On Day -1 of Visit 2 study participants will be admitted to the trial site and kept under close medical surveillance for at least 336 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. In case release criteria have not been met on the Day 15 (Section 3.1), subjects will return to the trial site for up to 5 weekly 24-h collection intervals of urine and faeces until release criteria

have been reached. For these additional 24-h collection intervals, subjects will be admitted to the trial site as indicated in the Flow Chart and discharged after formal assessment and confirmation of their fitness.

Within 24 h before each once-weekly in-house collection interval, subjects are to collect faeces at home (beginning of home collections on Days 20, 27, 34, 41, and 48). Faeces collected in these 24-h home-collection intervals will be used for analysis in case no defecation occurs in the subsequent 24-h in-house collection interval. E.g., if no defecation occurs in in-house collection interval Day 21-22, faeces of home-collection interval Day 20-21 will be used for analysis. If however faeces are collected in the subsequent 24-h in-house collection interval, faeces collected at home will be discarded. E.g., if defecation occurs in in-house collection interval Day 21-22, faeces of home-collection interval Day 20-21 will be discarded. Once release criteria are reached, home collections will be stopped.

Irrespective of whether release criteria have been met or not after collection interval day 49-50, no further collections are planned.

For details on time points and procedures for collection of blood, plasma, faeces and urine samples for PK analysis and mass balance assessment, refer to Flow Chart and Section 5.5.2.

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

### 6.2.3 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see Section 5.2.2 to Section 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 examine the metabolism in humans, the mass-balance of excretion, plasma and urinary concentrations of BI 425809 and its metabolites (as appropriate), the resulting PK parameters, and [$^{14}$C]-radioactivity in blood, plasma, urine and faeces after a single oral dose of 25 mg BI 425809 XX (C-14). The assessment of safety and tolerability will be an additional main objective of this trial, and will be evaluated by descriptive statistics.

### 7.1.2 Endpoints

The basic pharmacokinetics of BI 425809, its metabolites, and [$^{14}$C]-radioactivity, including mass balance, excretion pathways and metabolism is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (see Section 5.5.1).

Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory analysis will be conducted for this study. Data will be reported with descriptive statistics only.

## 7.3 PLANNED ANALYSES

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations (IPVs) will be identified no later than in the Report Planning Meeting and provided in the TSAP.
Plasma/urine/faeces concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol 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:

- 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 following analysis sets will be defined for this trial:

- Treated set (TS)

  This subject set includes all subjects from the ENTS who were documented to have received at least one dose of study drug

- Pharmacokinetic set (PKS)

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

### 7.3.1 Primary analyses

Analysis of the primary endpoints (refer to Section 5.5.1.1) is described in Section 7.3.5.

### 7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' [001-MCS-36-472] and will statistically be assessed using the same methods as described for the primary endpoints.

### 7.3.3 Safety analyses

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to the treatment (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 (REP) (see Section 1.2) will be assigned to the treatment period, and all AEs occurring between the end of REP and trial termination date will be assigned to 'follow-up'. Additionally, further treatment intervals may be defined in order to provide summary statistics for time intervals, such as periods without treatment effects (such

as post-study intervals). These assignments including the corresponding time intervals will be defined in detail in the TSAP. Please note that AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

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

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

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

Relevant ECG findings will be reported as AEs.

### 7.3.4 Interim analyses

No interim analysis is planned.

### 7.3.5 Pharmacokinetic analyses

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

Subjects who are not included in the PKS (refer to Section 7.3) will be reported with their individual plasma/urine/faeces concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma/urine/faeces concentrations, pharmacokinetic parameters or other statistical assessment.

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

Plasma concentrations and whole blood concentrations (when applicable) 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. The primary analysis of primary and secondary endpoints will be based on descriptive statistics only.

The following descriptive statistics will be calculated for concentration-time data as well as for all pharmacokinetic parameters: number, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. Descriptive statistics of pharmacokinetic parameters will be

calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the Clinical Trial Report.

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

## 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 Blood/Plasma/urine/faeces drug concentration - time profiles

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

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

### 7.4.3 Pharmacokinetic parameters

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

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

## 7.5 RANDOMISATION

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

## 7.6 DETERMINATION OF SAMPLE SIZE

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

# 8. INFORMED CONSENT, 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.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in a separate agreement between the investigator or the trial site and the sponsor. 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.

### 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.

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

# 9. REFERENCES

## 9.1 PUBLISHED REFERENCES

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

## 9.2 UNPUBLISHED REFERENCES

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

c02155957-08 BI 425809 Investigators Brochure. 06 Jun 2018

c02820512-01 Safety, tolerability, and pharmacokinetics of single rising oral doses of BI 425809 in healthy male subjects (partially randomised, single-blind, placebo-controlled) and investigation of relative bioavailability and food effect of BI 425809 (open-label, randomised, three-way crossover) 1346.1. 05 May 2015

c03632269-04 . A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy and safety of orally administered BI425809 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease. 1346.23. 12 Dec 2017

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

# 10. APPENDICES

## 10.1 RADIO BURDEN CALCULATION



### Radiation Burden Calculation Report

| | |
|---|---|
| **Title (provisional)** | A phase I, single center, open-label, non-randomized, non-placebo-controlled study to investigate the metabolism, excretion pattern, mass balance, safety, tolerability and pharmacokinetics of orally administered BI 425809 in healthy volunteers |
| **Sponsor:** | Boehringer Ingelheim |
| **Protocol No:** | BID731EC-167311 |
| **PRA Project Id:** | BI 1346-0016 |
| **Version Date:** | 03 May 2018 |

### Calculation of Radiation Burden (Dosimetry)

BI 425809 is a glycine transporter 1 inhibitor under development for the treatment of Alzheimer's disease and for cognitive impairment associated with schizophrenia.
Excretion and pharmacokinetic studies using BI 425809 were conducted on rats[1], and quantitative tissue distribution studies on pigmented and non-pigmented rats[2,3,4]. A radiation dose assessment was made based on these studies. In addition, data from studies in human patients[5] were taken into consideration.
The following assumptions, based on the data from these experiments, and taking the worst-case scenario, were made to be able to estimate the effective radiation dose:

- After oral dosing, BI 425809 and possible metabolites are considered to be distributed more or less homogeneously throughout the body, with the exception of higher exposure of the liver, kidneys and adrenals, which have been calculated separately[2,3,4].
- The major part of the administered amount of $^{14}$C-radiolabeled BI 425809 and possible metabolites show reasonably slow elimination from the body, mostly via fecal and for a smaller part via urinary excretion[1].
- Using the data of the BI 425809 study in rats a half-life of total $^{14}$C-activity of up to 34 hours is estimated[1]. In humans a terminal phase half-life of BI 425809 of 37 to 59 hours is assumed[5]., but for an important human metabolite (M232) a half-life of 170 hours is given[5]. In the current estimation as a worst-case assumption a half-life of total radioactivity of 170 hours is used.
- The absorbed fraction is 1, based on rat data[1].
- Based on the excretion study in rats $^{14}$C-radiolabeled BI 425809 is found to be excreted both in feces and in urine. For the calculation is assumed: 93% of the administered radioactivity is excreted via the gastrointestinal tract in feces and 7% is excreted via the kidneys in urine[1].

Based on these assumptions the estimated effective radiation burden after a single oral radioactivity dose of 3.7 MBq $^{14}$C-radiolabeled BI 425809 is approximately 0.41 mSv. For biomedical investigations in small groups of human volunteers an effective dose of 0.1 – 1.0 mSv is considered acceptable[6].

In the first preclinical studies the $^{14}$C label was at a different place in the molecule than in the later studies. This change was done to be able to follow the important human metabolite M232.
In the planned human ADME study the $^{14}$C-label will also be in the latter position. Because the assumptions with the strongest impact on the dosimetry were taken from the study where the label is at the latter site, this dosimetry is considered to be representative for the assessment of the radiation burden in human volunteers.

## References:

1: Excretion in urine, faeces and bile and pharmacokinetics of radioactivity in plasma after oral and intravenous administration of [14C]BI 425809 to rats; report A070/14SMB; S. Blattner; 05 September 2014.
2.: Quantitative whole-body autoradiography in male albino rats after single intravenous / oral administration of [14C]BI 425809; A091/15JS; J. Sandel; 16 October 2015.
3.: Quantitative whole-body autoradiography in male pigmented rats after single oral administration of [14C]BI 425809; A083/14JS; J. Sandel; 18 July 2014.
4.: Quantitative whole-body autoradiography in male pigmented rats after single oral administration of [14C]BI 761036; A111/16JS; J. Sandel; 11 July 2017.
5.: Investigator's brochure Version 7 Dated 04 December 2017.
6.: Recommendations of the International Commission on Radiological Protection. ICRP publication 60, 1992 and ICRP 103, 2007.

## Appendix A1: Radiation burden of the gastrointestinal tract after oral administration of 3.7 MBq $^{14}$C BI 425809

Using SEE-values, an organ-specific radiation burden can be estimated. The SEE-value is dependent, among other factors, on the mass of the target organ and the type of radiation.
With these SEE-values and the number of disintegrations U in the target organ, the organ dose equivalent $H_I$ is calculated:
$H_I$= constant x U x SEE (mSv); using a target organ-related weight factor, the contribution of the organ burden to the body burden is translated as: $H_{wb,I} = H_I$ x weight factor (mSv)

In order to be able to calculate the radiation burden of the GI tract, this has been divided in five sections, i.e., the stomach (st), the small intestines (si), the right part of the large intestines, the left part of the large intestines (lc) and the rectum / sigmoid (rs).
The SEE-values for these organs are:

| | | |
|---|---|---|
| ST: | 1.0 x 10 -5, | (weight factor = 0.12) |
| SI: | 3.2 x 10 -7, | (weight factor = 0.01) |
| RC: | 2.3 x 10 -10, | (weight factor = 0.048) |
| LC: | 2.9 x 10 -10. | (weight factor = 0.045) |
| RS: | 9.2 x 10 -10. | (weight factor = 0.027) |

The number of disintegrations U in each target organ depends on the amount of radioactivity excreted, or any metabolites that are eliminated via the gall bladder that is standardised for the various compartments of the GI tract (constant). I0 = 3.7 MBq; Excretion via GI tract: 93% of the dose, excretion via urine: 7% of the dose. These assumptions give:

| | |
|---|---|
| $H_{st}$= | 0.0030 mSv |
| $H_{si}$= | 0.0000 mSv |
| $H_{RC}$= | 0.0000 mSv |
| $H_{LC}$= | 0.0000 mSv |
| $H_{RS}$= | 0.0000 mSv |
| total GI: | 0.0030 mSv |

The total contribution of the GI tract to the effective dose (body radiation burden) amounts to 0.0030 mSv.

## Appendix A2: Radiation burden of the central compartment after oral administration of a MBq $^{14}$C BI 425809

Average body weight = 70 kg; SEE = 7.1905 x 10-7; 82% of the dose administered excreted with a half-life of 170 hours. (The remaining 18% is divided over the three organs calculated separately below). Total number of disintegrations in the central compartment after oral administration of 3.7 MBq [$^{14}$C] BI 425809 is 2.65x10$^{12}$ with a tissue weighting factor of 0.93 giving a $H_{tw}$ of 0.2763 mSv.

## Appendix A3: Radiation burden of the liver and kidneys after oral administration of 3.7 MBq $^{14}C$ BI 425809

| Organ | SEE (MeV/g.Bq) | % of dose | $T_{1/2}$ (h) | hto (mGy) | Wt | Htw (mSv) |
|---|---|---|---|---|---|---|
| Liver | 0.0000272 | 14.9 | 170* | 2.0976 | 0.04 | 0.0839 |
| Kidneys | 0.000158 | 3 | 170* | 2.4533 | 0.01 | 0.0245 |
| Adrenals | 0.00613 | 0.05 | 170* | 1.5864 | 0.01 | 0.02 |

*: the value of 170 hours was taken as worst-case assumption

The contribution to the total radiation burden of these three organs is 0.1284 mSv.

The total effective dose (radiation burden), based on the above-mentioned worst-case scenario amounts to 0.0030 + 0.2763 + 0.1284 = 0.41 mSv.

| **Name and Date:** | **Signature:** Signed by: investigator Reason: I am the author of this document. Date & Time: 14 May 2018 04:08 PM +02:00 DocuSign |
|---|---|

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

| | | |
|---|---|---|
| **Number of global amendment** | | 2.0 |
| **Date of CTP revision** | | 25 Sep 2018 |
| **EudraCT number** | | 2018-001192-21 |
| **BI Trial number** | | 1346-0016 |
| **BI Investigational Product(s)** | | BI 425809 |
| **Title of protocol** | | Metabolism and pharmacokinetics of BI 425809 after administration of BI 425809 XX (C-14) as oral solution in healthy male volunteers |
| | | |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | ☐ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | ☒ |
| | | |
| **Section to be changed** | a. Flow Chart<br>b. 4.2.2.2<br>c. 5.2.5.1<br>d. 5.5.2.5 | a. Footnote 6<br>b. Restrictions on diet and lifestyle<br>c. Vital signs<br>d. Urine sampling |
| **Description of change** | a. Flow Chart<br>b. 4.2.2.2<br>c. 5.2.5.1<br>d. 5.5.2.5 | a. Urine predose corrected from 14 to 2h<br>b. Clarified that subjects shall be advised to drink the recommended volume<br>Deletion of a doubled “are not allowed”<br>c. Changed the monitoring system used for blood pressure measurement<br>d. Added “at least” in front of Tween “0.05% Tween 20” |

| | | |
|---|---|---|
| **Number of global amendment** | | 2.0 |
| **Rationale for change** | a. Flow Chart<br>b. 4.2.2.2<br>c. 5.2.5.1<br>d. 5.5.2.5 | a. Inconsistency between Flow Chart and Footnote corrected<br>b. Clarification that on days of urine collection the suggested fluid intake is a recommendation The “doubling” of “are not allowed” was a leftover of the drafting process<br>c. The site has changed equipment since finalization of this protocol<br>d. Clarification that the concentration of Tween 20 in the urine is allowed to be 0.05% or higher |

**APPROVAL / SIGNATURE PAGE**

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**Document Name:** clinical-trial-protocol-revision-1

**Title:** Metabolism and pharmacokinetics of BI 425809 after administration of BI 425809 XX (C-14) as oral solution in healthy male volunteers

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Clinical Trial Leader | | 26 Sep 2018 12:32 CEST |
| Author-Trial Statistician | | 26 Sep 2018 12:44 CEST |
| Approval-Team Member Medicine | | 26 Sep 2018 13:23 CEST |
| Approval-Therapeutic Area | | 26 Sep 2018 13:39 CEST |
| Verification-Paper Signature Completion | | 27 Sep 2018 10:02 CEST |
| Author-Trial Clinical Pharmacokineticist | | 27 Sep 2018 10:17 CEST |

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

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