# Clinical Trial Protocol

**Doc. No.: c01691934-10**

| | |
|---|---|
| **EudraCT No.:** | 2013-005031-24 |
| **BI Trial No.:** | 1289.5 |
| **BI Investigational Product:** | BI 409306 |
| **Title:** | A multi-centre, double-blind, parallel-group, randomized controlled study to investigate the efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with Alzheimer's Disease |
| **Clinical Phase:** | II |
| **Trial Clinical Monitor:** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] |
| **Co-ordinating Investigator:** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] |
| **Status:** | Final Protocol (Revised Protocol based on global amendment No. 4) |
| **Version and Date:** | **Version: 5.0** **Date: 17 February 2017** |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

| | | | |
|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br>NA | | | |
| **Name of active ingredient:**<br>BI 409306 | | | |
| **Protocol date:**<br>27 June 2014 | **Trial number:**<br>1289.5 | | **Revision date:**<br>17 Feb 2017 |
| **Title of trial:** | A multi-centre, double-blind, parallel-group, randomized controlled study to investigate the efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with Alzheimer's Disease. | | |
| **Co-ordinating Investigator:** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] | | |
| **Trial site(s):** | 60 | | |
| **Clinical phase:** | II | | |
| **Objective(s):** | To assess the efficacy, safety and tolerability of different doses of BI 409306 compared to placebo in treatment of prodromal AD | | |
| **Methodology:** | Placebo-controlled, double-blind, randomized parallel-design with 5 treatments over 12 weeks of treatment duration | | |
| **No. of patients:**<br>**total entered:**<br>**each treatment:** | <br>288<br>96 for placebo group and 48 per treatment group | | |
| **Diagnosis :** | Patients with diagnosis of prodromal Alzheimer's Disease according to criteria recommended by the International Working Group (IWG, Dubois et al., 2014) | | |
| **Main criteria for inclusion:** | The study population will include male and female patients with AD who are at least 55 years old and who have not received prescribed drugs for treatment of AD including acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine, phenserine) and memantine within three months prior to screening. A Mini-Mental-State-Examination (MMSE) score of $\geq 24$ and a global CDR score 0 or 0.5 combined with episodic memory dysfunction (demonstrated in the Free and Cued Selective Reminding Test (FCSRT) or the Wechsler Memory Visual Paired Associates test) and evidence of AD biomarker pathology based on measurements in CSF or on amyloid deposition in PET scan are required for inclusion. | | |
| **Test product(s):**<br>**dose:** | BI 409306<br>10mg QD, 25mg QD, 50mg QD, 25mg BID | | |

| | | | |
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| **Name of finished product:**<br>NA | | | |
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| | |
|---|---|
| **mode of admin.:** | Tablet, Oral |
| **Comparator products:** | Placebo to match BI 409306 |
| **dose:** | NA |
| **mode of admin.:** | Tablet, Oral |
| **Duration of treatment:** | 12 weeks |
| **Criteria for efficacy:** | Primary endpoint:<br>- Change in cognition as measured by change from baseline in Neuropsychological Test Battery (NTB) total score after 12-week treatment.<br><br>Secondary endpoints include:<br>- Change from baseline in ADCS-MCI-ADL total score after 12-week treatment<br>- Change from baseline in CDR-SB total score after 12-week treatment<br>- Change from baseline in ADAS-$cog_{11}$ (Alzheimer's Disease Assessment Scale-cognitive subscale) total score after 12-week treatment |
| **Criteria for safety:** | Adverse events, vital signs, 12-lead electrocardiograms (ECG) and routine laboratory tests, Columbia-Suicide Severity Rating Scale (C-SSRS). |
| **Statistical methods:** | Restricted Maximum Likelihood Estimation based Mixed-effects Model for Repeated Measures (MMRM) will be used to obtain adjusted means for the treatment effects. This model will include fixed, categorical effects of treatment, visit and treatment by visit interaction, as well as continuous fixed covariates of baseline and baseline-by-visit interaction. Patient will be considered as random effect. The unstructured covariance structure will be used as covariance structure for within-patient variation<br><br>Descriptive statistics |

# FLOW CHART

| **Trial Period** | **Screening** | **Placebo Run-in Period** | **Treatment Period** | | | | | | | **Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3[14] Baseline** | **4a[12]** | **4b[12]** | **4c[12]** | **5** | **6** | **EOT/ED[11]** | **FU** |
| **Studyweeks** | **-7** | **-2** | | **1** | **2** | **3** | **4** | **8** | **12** | **16** |
| **Study-Day** (or duration during screening/ run-in) | Dura-tion 1-35 days | Duration at least 14 and at most 21 days after screening period | **1** | **8** | **15** | **22** | **29** | **57** | **85** | **EOT +28** |
| **Visit window (in days)** | | | | ±1 | ±1 | ±1 | ±3 | ±3 | +3 | ±3 |
| Patient information & informed consent signed [redacted] | [redacted] | | | | | | | | | |
| Register Patient in IRT | X | | | | | | | | | |
| Randomisation (via IRT) | | | X | | | | | | | |
| Demographics | X | | | | | | | | | |
| Medical history / baseline conditions | X | | | | | | | | | |
| In-/exclusion criteria | X | X | X | | | | | | | |
| Imaging of the Brain[2] | X | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Height (screening only)/weight | X | | | | | | | | X | X |
| Vital signs | X | | X | X | X[12] | X[12] | X | X | X | X |
| Post Dose Heart Rate Procedure[3] | | | X | | | | | | | |
| Physical examination | X | | | | | | | | X | |
| Neurological examination | X | | | | | | | | X | |
| Resting ECG (digital) | X | | X | X | X[12] | X[12] | X | X | X | X |
| Adverse events | X | X | X | X | X[12] | X[12] | X | X | X | X |
| Dispense trial medication[4] | | X | X | | | | X | X | | |
| Collect study drug | | | X | | | | X | X | X | |
| Medication Compliance Check | | | X | | | | X | X | X | |
| **Laboratory tests:** Chemistry, haematology, urinanalysis | X | | X | | | | X | X | X | X |
| Blood Glucose (Onsite)[5] | X | | X | | | | X | | X | |
| [redacted] | | | [redacted] | | | | | [redacted] | | |
| [redacted] | | | [redacted] | | | | | | [redacted] | |
| [redacted] | [redacted] | | | | | | | | [redacted] | |
| Urine drug screen | X | | | | | | | | X | |
| Urine pregnancy test[8] | X | | X | | | | X | X | X | |
| Vitamin B12 and folate | X | | | | | | | | X | |
| RPR (FTA, if RPR positive) | X | | | | | | | | | |
| A-ß and tau-protein assessment in CSF or amyloid deposition in PET[13] | X | | | | | | | | | |
| **Prospective Suicidality Monitoring** | | | | | | | | | | |
| C-SSRS | X[9] | X[10] | X[10] | X[10] | X[10] | X[10] | X[10] | X[10] | X[10] | X[10] |

| **Trial Period** | **Screening** | **Placebo Run-in Period** | **Treatment Period** | | | | | | | **Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3**[14] **Baseline** | **4a**[12] | **4b**[12] | **4c**[12] | **5** | **6** | **EOT/ED**[11] | **FU** |
| **Studyweeks** | **-7** | **-2** | | **1** | **2** | **3** | **4** | **8** | **12** | **16** |
| **Study-Day** (or duration during screening/ run-in) | Dura-tion 1-35 days | Duration at least 14 and at most 21 days after screening period | **1** | **8** | **15** | **22** | **29** | **57** | **85** | **EOT +28** |
| **Visit window (in days)** | | | | ±1 | ±1 | ±1 | ±3 | ±3 | +3 | ±3 |
| **Neuropsychological Rating Scales** | | | | | | | | | | |
| MMSE | X | | | | | | | | | |
| FCSRT | X | | | | | | | | | |
| Wechsler Memory Paired Associates[15] | X | | | | | | | | | |
| CDR | X | | | | | | | | | |
| CDR-SB | | | X[14] | | | | X | | X | |
| NTB | | | X[14] | | | | X | | X | |
| MCI-ADSC-ADL | | | X[14] | | | | | | X | |
| ADAS-cog$_{11}$ | X | | X[14] | | | | | | X | |

[1] Prior to any study related procedure

[2] Results of a MRI or CCT-scan have to be available before visit 2. Please refer to exclusion #1 ( section 3.3.3) for further details.

[3] The baseline vital signs (supine pulse rate after 5 minutes of rest and systolic/diastolic blood pressure) will be measured before the first dose is taken and at 70-110 minutes post dose. Additional supine pulse rate assessments will be performed at the time points of post-dose PK sampling given in table 10.1.1:1 until 70-110 minutes post-dose (See section 5.2.5.2 and section 6.2 for details).

[4] At all visits, the respective kit number has to be allocated to the patient via IRT

[5] Only for patients with antidiabetic therapy (see section 6.2 for details).

[redacted]

[8] Local urine pregnancy test (or blood test if required by local regulations) in women of child bearing potential. More frequent testing may be performed if required by local regulations.

[9] Columbia Suicide Severity Rating Scale baseline/screening scale

[10] Columbia Suicide Severity Rating Scale baseline since-last-visit scale

[11] Also to be completed for patients who are withdrawn or who have discontinued the trial early: in case of early termination visit 7 should be performed no later than 7 days after the last study drug intake (visit FU four weeks later).

[12] If the assessments at visit 4a do not show clinically relevant findings compared to baseline and if deemed clinically acceptable by the investigator then visits 4b and 4c may be performed as phone contacts. Attendance of the study partner is not necessarily required during visits 4 a-c. ECG and vital signs are only to be performed at clinic visits.

[13] Lumbar puncture or PET scans should only be performed after general eligibility is most probably given based on medical status and results of neuropsychological screening assessments. Results from CSF sampling or PET scans must be available before start of visit 2 (run-in period). CSF samples collected in the past 4 months prior to informed consent can be considered for use in the study and for further details please refer to section 3.3.2, section 5.6.1 and appendix 10.2. Results of a PET scan performed in the past according to the recommendations in section 5.3.2.1can be used.

[14] The neuropsychological assessments may be done on the day before the randomisation visit (last day of the screening period) if agreed between site staff and patient. In any case it needs to be ensured that the recommendations for the conduct of the neuropsychological assessments (refer to section 6.2 for details) are followed.

[15] Back-up test for patients that do not reach the required scores in FSCRT

# TABLE OF CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| ABCB1 | ATP-binding cassette sub-family B member 1 (gene encoding for P-gp) |
| AChE-Is | Acetylcholine Esterase Inhibitor |
| AE | Adverse Event |
| AESI | Protocol-specified Adverse Event of Special Interest |
| AD | Alzheimer's Dementia |
| ADAS-cog | Alzheimer's Disease Assessment Scale-cognitive subscale |
| ADCS-MCI-ADL | Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients |
| ANCOVA | Analysis of Covariance |
| [redacted] | [redacted] |
| AUC | Area under the Curve |
| BPM/bpm | Beats per minute |
| BCRP | breast cancer resistance protein |
| [redacted] | [redacted] |
| CDR-SB | Clinical Dementia Rating Scale–Sum of Boxes |
| CI | Confidence Interval |
| CIAS | Cognitive Impairment Associated with Schizophrenia |
| CML | Local Clinical Monitor |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CT | Computer Tomography |
| CCT | Cranial Computer Tomography |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| CSF | Cerebro-spinal Fluid |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTMF | Clinical Trial Master File |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| CYP | Cytochrome P450 |
| DAT | Dementia of Alzheimer Type |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic Acid |
| DSM | Diagnostic and Statistical Manual |
| eCRF | Electronic Case Report Form |
| ED | Early Discontinuation |
| EDC | Electronic Data Capture |
| EEG | Electroencephalogram |
| EM | Extensive Metabolizer |
| EOT | End Of Treatment |
| EudraCT | European Clinical Trials Database |
| FAS | Full Analysis Set |

| | |
|---|---|
| FCSRT | Free and Cued Selective Reminding Test |
| FTA | Fluorescent treponemal antibody absorbent test |
| GCP | Good Clinical Practice |
| gMean | Geometric Mean |
| [redacted] | [redacted] |
| IB | Investigator's Brochure |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| [redacted] | [redacted] |
| IRT | Interactive Response Technology |
| ISF | Investigator Site File |
| i.v. | intravenous |
| IWG | International Working Group |
| LTP | Long Term Potentation |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| MMSE | Mini-Mental-State-Examination |
| MST | Medical Subteam |
| MRI | Magnetic Resonance Imaging |
| NTB | Neuropsychological Test Battery |
| NDMA | N-methyl-D-aspartate |
| OPU | Operative Unit |
| P-gp | P-glycoprotein |
| p.o. | Per os (oral) |
| PCC | Protocol Challenge Committee |
| PDE9A | Phosphodiesterase 9A |
| PET | Positron Emission Tomography |
| [redacted] | [redacted] |
| PK | Pharmacokinetic |
| PM | Poor Metabolizer |
| PTM | Placebo to Match |
| RDC | Remote Data Capture |
| RPR | Rapid Plasma Reagin |
| q.d. | Quaque die (once a day) |
| SAE | Serious Adverse Event |
| s.c. | Subcutaneous |
| SPC | Summary of Product Characteristics |
| STORM | Storage Conditions for Trial Medications |
| TCM | Trial Clinical Monitor |
| TDMAP | Trial Data Management and Analysis Plan |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| TMM | Team Member Medicine |
| TMW | Trial Medical Writer |
| TSAP | Trial Statistical Analysis Plan |

# 1. INTRODUCTION

## 1.1 MEDICAL BACKGROUND

Alzheimer's disease (AD), a chronic progressive mental disorder, is the most common cause of dementia and accounts for 50 to 70 % of all cases. AD is mainly a disorder of the elderly; however it can also affect patients below the age of 60. More than 36 million people (R14-0163) in the world are currently affected by dementia, most of them suffering from AD, with around 5 million new cases occurring every year (R10-5095; R10-5106). The age-specific prevalence of AD almost doubles every 5 years after age 65. Among developed nations, approximately 1 in 10 elderly people (65+ years) is affected by dementia to some degree, whereas more than one third of the very old people (85+ years) may have dementia-related signs and symptoms (R10-5105).

In the prodromal stage of the disease, clinical symptoms may include impairment of episodic memory and/or other cognitive domains, like executive function, orientation and judgment. Patients with these prodromal clinical symptoms showed an increased risk of developing Alzheimer's dementia with progressive decline in the ability to perform activities of daily living and the appearance of behavioral changes and/or psychiatric symptoms (mood disturbances, hallucinations, personality changes). Subsequently and in accordance with the further progression of the disease there is an increasing utilization of resources and medical care finally leading to the need for full-time assisted living or nursing home care before death. The median time from onset of symptoms to death is estimated to be around 10 years.

The pattern of cognitive and functional decline is not uniform over the course of the disease and differs according to the measure in question and the scales used. Cognitive decline, for example, seems to be more rapid in the moderate and severe stages than in the mild and very severe stages, yielding a sigmoid curve of progression.

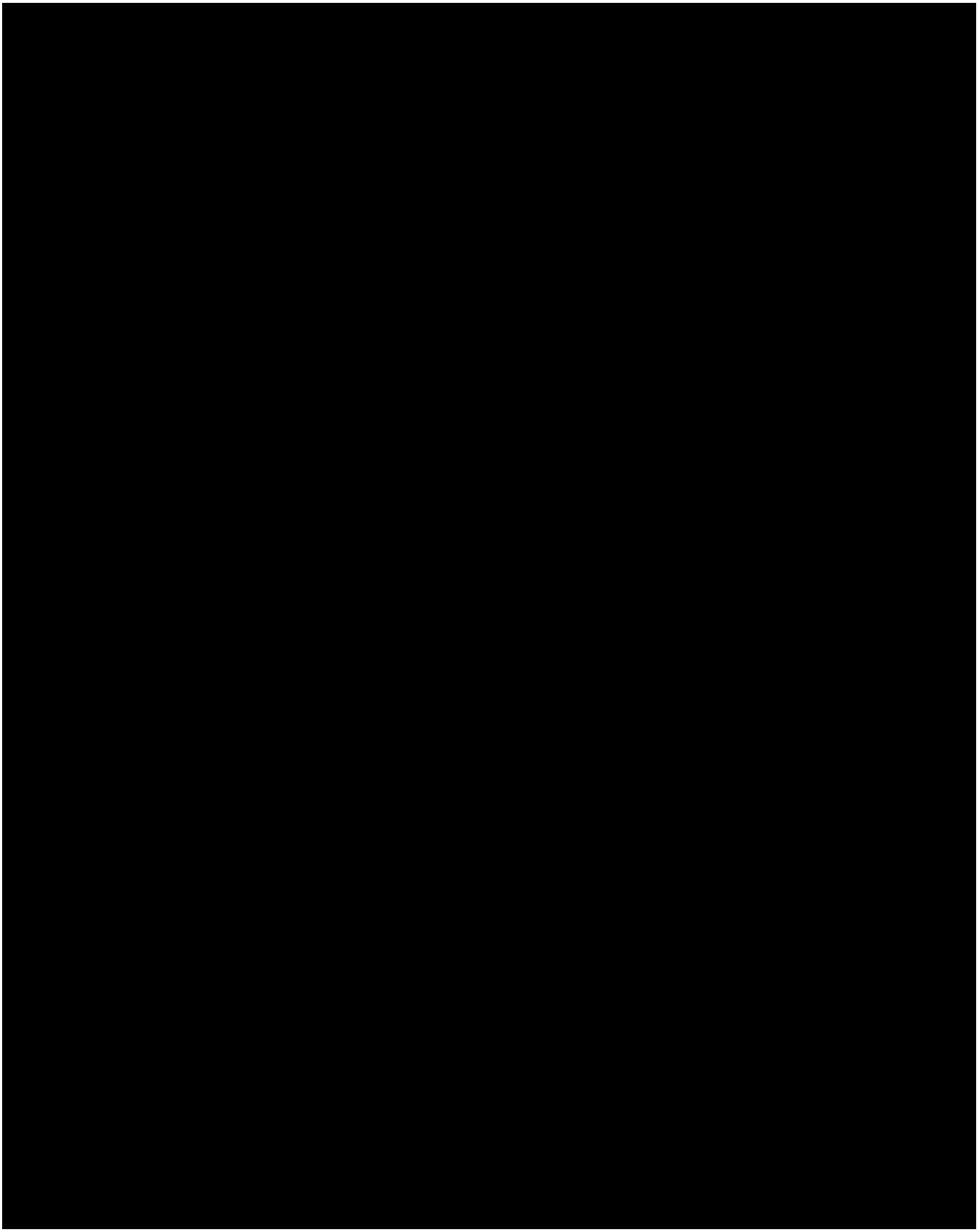
On the cellular level, AD is characterized by a progressive loss of synapses and neurons. Affected transmitter systems mainly include cholinergic and glutaminergic neurons. Glutamate as the major excitatory neurotransmitter in the human brain is most prominently associated with functions of memory formation and learning. Glutaminergic transmission is mediated by various receptors with the post-synaptic N-methyl-d-aspartate (NMDA) receptor playing an essential role. Upon activation, a cascade of intracellular, post-synaptic signaling events is triggered through elevation of second messengers such as cAMP and cGMP with subsequent activation of protein kinases and manifestation of long-term potentiation (LTP) and synaptic plasticity. LTP is regarded as a validated physiological model for cellular processes underlying learning and memory formation (R10-5109; R10-5092; R10-5102).

## 1.2 DRUG PROFILE

BI 409306 - a potent selective phosphodiesterase 9 (PDE9A) inhibitor – is being developed for symptomatic treatment of Alzheimer's disease (AD) and cognitive impairment associated with schizophrenia (CIAS).

PDE9A inhibition is supposed to improve NMDA receptor signalling cascade by increasing cGMP levels with subsequent activation of protein kinases and manifestation of long-term potentiation (LTP) and synaptic plasticity. LTP is regarded as a validated physiological model for cellular processes underlying learning and memory formation. BI 409306 has demonstrated pro-cognitive properties in relevant animal models of learning and memory impairment. Therefore it is expected that treatment with BI 409306 will result in relevant cognition enhancing effects in AD and CIAS.

For full details on drug profile, please refer to the latest version of the IB [U11-1079].



[redacted]

Clinical safety

In healthy volunteer trials [U12-1034-01, U13-1182-01, U12-2165-01, U13-1303-01, c02098989-02] , the most frequent drug related adverse events were visual side effects (such as sensation of flashing lights, altered color perception, photophobia / increased sensitivity to light or blurred vision) that occurred shortly after dosing and mostly resolved within 1 h, i.e., in close connection to maximum BI 409306 plasma concentrations as the concentration-time profile sharply and steeply peaks within the first 1-2 hours and then rapidly declines afterwards. Overall, there were no relevant changes observed for laboratory, ECG recordings, and vital signs following treatment with BI 409306 when compared to placebo. Only a rapid and short lasting increase in supine pulse rate of 12.9 ± 4.4 bpm was detected in Chinese CYP2C19 poor metabolizers subjects treated with BI 409306 (100 mg single dose) in study 1289.4 [c02098989-02]. Following this observation, pharmacometric analysis of all available human data revealed a BI 409306 plasma concentration dependent increase in supine pulse rate reaching a maximum of 7-13 bpm (median) at high exposure end in CYP2C19 poor metabolizers treated with BI409306 at 100 mg. The maximum effects of BI 409306 on pulse rate were generally achieved at maximum BI 409306 plasma concentrations (20-30 minutes post dose) and disappeared rapidly with declining concentrations. Altogether, good to satisfactory safety and tolerability were observed in single doses of BI 409305 (up to 350mg in CYP2C19 extensive metabolizers (EM); up to 100mg in CYP2C19 poor metabolizers (PM)) in healthy young volunteers and multiple doses (14 days up to 100mg EM/50mg PM) of BI 409306 in healthy young and elderly subjects. None of the safety data presented a safety issue for further clinical trials.

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

## 2.1 RATIONALE FOR PERFORMING THE TRIAL

Currently approved AD treatment is purely symptomatic. Registered symptomatic treatment consists of acetylcholinesterase inhibitors (AChE-Is) and memantine. AChE-Is in general and donepezil in particular can be currently regarded as gold standard for treatment of mild-to-moderate DAT and is considered as reference drug. This treatment isn't approved for prodromal stages of the disease.

Prodromal AD is described as a slight but noticeable and measurable decline in cognitive abilities, including memory and thinking skills. These declines of functional capabilities in patients with prodromal AD are not severe enough to allow the diagnosis of dementia according to the current guidelines. However, those with prodromal AD have an increased risk of eventually developing Alzheimer's dementia. Therefore, a symptomatic treatment that delays the progress of these first symptoms caused by the underlying pathology might provide a substantial benefit to such patients.

In addition to the ongoing efforts in the development of more effective symptomatic treatment options, new compounds with a disease-modifying potential are in the center of interest in the AD research field. However, no drug with a proven disease modifying potential is presently available. Furthermore, it cannot be expected that a putative disease modifying drug would have the potential to restore lost cognitive function. Therefore, a symptomatic treatment that proves to be more efficacious than the currently available compounds (AChE-Is, memantine) in improving both existing cognition deficits and the ability to better perform activities of daily living would provide a substantial benefit to patients.

The study is designed to compare the effects of 4 different doses of orally administered BI 409306 to placebo (see section 3.2 for further details) because there is no approved treatment for prodromal AD available so far.

## 2.2 TRIAL OBJECTIVES

The primary objective of this study is to assess efficacy and safety of BI 409306 at doses of 10 mg, 25 mg and 50 mg once daily, 25 mg twice daily compared to placebo over a 12-week treatment period in male and female patients at least 55 years of age with prodromal AD who have not received prescribed drugs for treatment of AD including acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine, phenserine) and memantine) within three months prior to screening. The criteria for inclusion of these patients will consist of an MMSE score of 24 or higher, an CDR-score of 0 or 0.5, and an FCSRT score of 20 or lower for the free recall and of 42 or lower for the total recall and, if the FCSRT fails; performing the Wechsler Memory Visual Paired Associates test. Evidence of A-ß and tau protein pathology in the brain is based on measurements in CSF or, alternatively, on amyloid deposition in PET scan. The study endpoints are listed in section 5.1.1.

## 2.3 BENEFIT - RISK ASSESSMENT

The currently available safety data, including first results from a recently performed phase I trial with single doses orally administered up to 350 mg in healthy subjects, indicate that BI 409306 has a broad safety margin and is well tolerated.

In summary, the toxicological profile of BI 409306 is characterised by cardiac effects which seem to be consistent with those described for phosphodiesterase inhibitors in general. All adverse effects were generally restricted to high dose levels and were reversible. It is recommended to carefully monitor cardiac function in clinical trials.

Consistent with the FDA draft guidance entitled "Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials", prospective assessment of suicidal ideation and behavior is included in this study using the C-SSRS.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patient safety.

This is an experimental drug at an early stage of testing and therefore an individual benefit cannot be guaranteed. Only patients who have not received prescribed drugs for treatment of AD including acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine, phenserine) and memantine) within three months prior to screening will be included in this trial of short duration. Therefore, the assignment to the placebo arm is not associated with a higher risk for the patient. Also all study procedures (e.g. AD assessment, safety and suicidality monitoring etc.) may be a benefit for the patient e.g. intensive medical care, a potentially better knowledge of the underlying disease which may lead to a better handling of this disease. As stated above prodromal AD has an increased risk for developing into AD. AD is not reversible and can last more than 20 years. Even if there is no direct benefit for the patient during participation in this trial, it can be assumed that the trial results may contribute to better drug development in future. In addition due to the long duration of AD the patient may directly benefit from the drug development based on the results of this trial.

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

This is a 12-week, multi-center, randomized, double-blind, double dummy placebo controlled, parallel group study in patients with prodromal AD.

In total, 288 patients with prodromal AD who meet the entry criteria are planned to be randomized in this trial. The randomized treatment will be double blind. Each patient will receive active treatment with BI 409306 (each patient will receive one active treatment and placebos to match the alternative active treatment) or placebos (each patient will receive placebos to match each of the active treatments).

After obtaining informed consent, patients will undergo a screening period of a maximum of 5 weeks. All patients who successfully complete the screening period and are eligible for the study, then enter a minimum of 2 weeks of single blinded placebo run-in before randomization.

Patients who successfully complete the single-blinded phase and who fulfil both the inclusion and exclusion criteria will be randomized to the 12-week double blind treatment period at visit 3 and will be assigned to one of the 5 treatment groups namely: once daily (QD) 10 mg, 25 mg, or 50 mg BI 409306, or 25 mg BI 409306 twice daily (BID), or placebo.

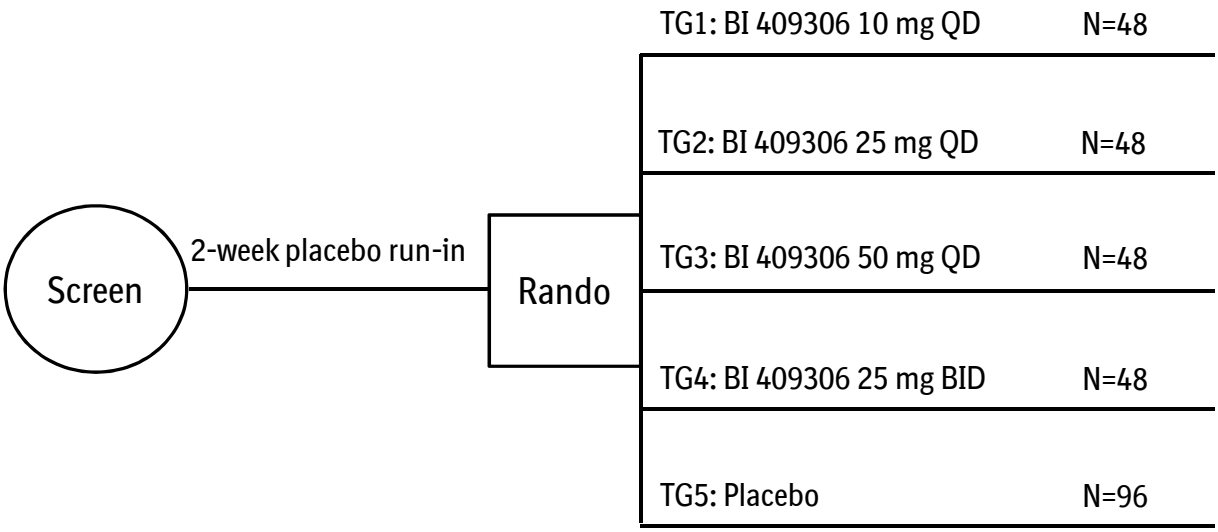



Figure 3.1:1 Study design

After the end of the double-blind treatment period, patients will be followed up for an additional 4 weeks without study medication. Patients will be evaluated for efficacy at randomization, at visit 5 (week 4) and at visit EOT (week 12). Safety will be formally evaluated at each visit until end of the observational period which is 28 days after end of treatment or for an appropriately longer time in case of unresolved adverse events.

Adverse events will be collected throughout the trial according to section 5.2.2.2.

### 3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI). Boehringer Ingelheim will appoint a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs), directing the clinical trial team in the preparation, conduct and reporting of the trial, order the materials as needed for the trial, ensures appropriate training and information of local clinical monitors (CMLs), CRAs and investigators in participating countries.

Data management and statistical evaluation will be done by BI according to BI SOPs. For these activities, a Trial Data Manager and a Trial Statistician will be appointed. Tasks and functions assigned in order to organize, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons will be given in the Clinical Trial Master File (CTMF) document.

[redacted] has been selected as a service provider to support the following tasks related to the neuropsychological assessments: rater prequalification, rater training (online and at investigator meeting), provision of rater materials and central review of assessments (see section 5.1.2 and section 8.2 for details).

A central laboratory and central ECG service vendor will be used for this trial. The organization of the trial in the participating countries will be done by the respective local BI organization (OPU) or by a Contract Research organization (CRO) with which the responsibilities and tasks have been agreed and a written contract has been filed before initiation of the clinical trial. In each local BI-organisation (OPU) participating in this study, a local clinical monitor (CML) will be appointed who will be responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU.

A Coordinating Investigator will be nominated to coordinate investigators at different sites participating in this multi-centre trial. Tasks and responsibilities for the Coordinating Investigator will be defined in a contract filed before initiation of the trial. Documents on participating (Principal) investigators and other important participants as defined in the monitoring manual, especially their curricula vitae, will be filed in the CTMF.

The Investigator Site File (ISF) will be kept at the sites as far as required by local regulations and BI SOPs. A copy of the ISF documents will be kept as an electronic Clinical Trial Master File.

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

All patients who successfully complete screening and are eligible for the study will undergo a single blinded placebo run-in phase in order to generally familiarize with the clinical setup of the neuropsychological tests as well as the regular intake of study drug to ensure compliance with study procedures.

A parallel group design is the appropriate design as the inherent within-patient variability and the progressive nature of the disease makes it difficult if not impossible to employ a cross-over design.

To assess a comparative benefit/risk ratio treatment BI 409306 patients will randomly be allocated to one of 4 active doses or placebo only in a 1:1:1:1:2 ratio (for rationale of allocation of treatments refer to section 7.1 and for justification of doses refer to section 4.1.3).

In order to estimate the absolute drug effect on cognition and function, a double-blind comparison against placebo is included in this trial. With this approach we follow the EMA guideline on medical products for the treatment of Alzheimer's disease and other dementias (CPMP/EWP/553/95 Rev. 1, 2008).

The current standard treatment of cognitive and functional impairment in AD shows substantial treatment effects during the first three months of treatment. Therefore, a 12-week treatment period is considered to also be sufficient to assess the efficacy, safety and tolerability of BI 409306 in prodromal stages of this disease.

The data collected in this double-blind, randomized, placebo-controlled trial are standard in diagnosed Alzheimer's disease and therefore regarded to also provide important information in terms of efficacy, safety and tolerability on the use of BI 409306 maintenance treatment in patients with prodromal AD.

## 3.3 SELECTION OF TRIAL POPULATION

About 1000 patients will be screened for the study in approximately 12 countries. About 60 study centres will be participating to ensure approximately 288 patients are randomised to study treatment.

Recruitment will be competitive and participating sites are expected to randomize at least 288 patients. Patients who fail to complete all assessments in terms of primary and secondary endpoints according to the study protocol will not be considered study completers (see section 6.2 and section 7.3 for details). Patients who discontinue following randomization may not be re-enrolled at a later date. A record is kept of all patients failing to complete all trial visits and their reasons for discontinuation.

This trial (1289.5) investigates patients with cognitive impairment caused by the Alzheimer's disease. In parallel BI is investigating the effect of BI 409306 in patients with mild Alzheimer's dementia in the study 1289.7. It is expected that both trials share a high percentage of trial sites. The Mini Mental Stage Examination (MMSE) evaluates the severity of cognitive impairment and this assessment is used in both trials as part of the eligibility assessments with the following requirements:

1. 1289.5 – MMSE score ≥ 24
2. 1289.7 – MMSE score ≥ 18 - 26

Patients who do not reach the required scores of ≥24 in MMSE and CDR total score 0 or 0.5 are not eligible for this study and must be registered as screen failure in IRT. If the result of the MMSE and CDR fulfill the requirements of the parallel trial 1289.7 and the patient and his study partner agree to alternatively participate in 1289.7 after giving a new consent then the results of the MMSE and CDR can be transferred into the database of 1289.7 without repeated performance of the MMSE and CDR and vice versa. This prevents the risk of unwanted learning effects which would be a consequence of repeating the MMSE and CDR in the same patient. This rule only applies if the screening visit for 1289.7 is no later than 7 days after the MMSE/CDR for 1289.5 was performed. The patient will then be registered as a new patient in the IRT of 1289.7. This does not apply to sites participating in only one of the 1289.5/1289.7 studies.

Permission to randomize more than 15 patients per site must be obtained in writing from the TCM at Boehringer Ingelheim. This will only be allowed after a careful review of the enrolment status.

Re-screening of not yet randomised patients can be allowed in exceptional cases but should be discussed on a case-by-case basis between the study site, Monitor staff and with the TCM.

A log of all patients included into the study (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

Patients with diagnosis of prodromal AD in accordance with the recommendation of the International Working Group (IWG), Dubois et al. 2014) [R14-2556]):

- Symptoms noticed by the patients or informant
- Cognitive testing confirming prodromal symptoms
- Biomarker evidence of AD pathology
- No evidence of other forms of dementia
- No other concomitant illness or medication which could confound or prohibit completion in the trial by the patient

### 3.3.2 Inclusion criteria

Patients will be included in this study if they meet all of the following criteria:

1. Male and female patients with an age ≥ 55 years. Patients older than 85 years may be included based on an acceptable general health status, (e.g. concomitant diseases, physical capability to follow the required study procedures [visits etc.]) per investigators judgement.

2. Body weight ≥ 50 kgs.

3. Patients with a confirmed diagnosis of prodromal AD on neuropsychological testing defined as:

    - Mini-Mental State Examination (MMSE) score: ≥ 24
      and
    - a global CDR-score of 0 or 0.5
      and
    - Free and Cued Selective Recall Reminding Test (FCSRT) score:

        - free recall test: ≤ 20 (out of 48) and
        - total recall test: ≤ 42 (out of 48)

    Patients who do not reach the required score in FCSRT will additionally perform the Wechsler Memory Visual Paired Associates test. If the Wechsler Memory Visual Paired Associates test shows a cognitive deficit worse than 1 standard deviation to the mean (compared to the reference values of age and educational norms for inclusion), then the patients can be considered to be eligible for the study. [R14-4676]

4. Confirmation of abnormal markers of AD pathology either via a), or alternatively b) mentioned below:*

    a) Presence in cerebrospinal fluid of (samples taken within past 4 months may be eligible, refer to section 5.6.1 and appendix 10.2 for full details):

        - low Aβ1-42 concentrations (< 640 pg/mL) and increased total tau concentrations (>375 pg/ml),

          or / and

        - low Aβ1-42 concentrations (< 640 pg/mL) and increased phospho-tau concentrations (> 52 pg/mL in cerebrospinal fluid),

    or

    b) Abnormal amyloid deposition in a cerebral PET scan. Scans performed in the past according to the recommendations in section 5.3.2.1 are acceptable.

    * Note – CSF or PET could be the procedure of choice as per local regulations or IRBs/ IECs or site practices (as applicable).

5. Patients who have not received prescribed drugs for treatment of AD (including acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine, phenserine) and Memantine) within three months prior to screening.

6. Patients must have at least 6 years of formal education and fluency in the test language as verbally confirmed by the patient and documented by the study investigator.

7. Patients must have given written informed consent in accordance with GCP and local legislation prior to any study procedures. All patients must be able to give informed consent personally and have capacity for such consent. An informed consent given by a legal representative will not be accepted.

8. Patients must have a reliable study partner (per investigator judgement, for instance a family member, partner etc., guardian). This person should be in close contact with the patient and agree to accompany the patient on all scheduled visits. The person should also agree to be reachable by phone and should be able to contribute to the neuropsychological assessments of the patient, wherever necessary. This person should be able to communicate in the language in which the patient is being assessed and should also serve as a back-up contact for the study site. This person must sign a separate informed consent form which describes their contribution during the study.

### 3.3.3 Exclusion criteria

Patients must be excluded from this study if they meet any of the following criteria:

1. Mild cognitive impairment with any etiology other than prodromal AD (for example: neurosyphilis, craniocerebral trauma, small vessel disease) based on clinical data and/or current laboratory findings and/or a pre-existing MRI or CT of the brain (CCT). If previous cranial imaging is not available or older than 12 months prior to screening then a CCT or MRI needs to be performed at screening*

   *Please check your local regulations if the use of radiations for a CCT scan is allowed in your country. If performing of a CCT is not allowed in the frame of this trial (e.g. Germany, France, United Kingdom), a MRI must be performed.

2. Substantial concomitant cerebrovascular disease (defined by a history of a stroke / intracranial haemorrhagia) temporally related to the onset of worsening of cognitive impairment per investigator judgement.
3. Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years.
4. Medical history or diagnosis of any of the following symptomatic and unstable/uncontrolled conditions per investigator judgement:
   a. Uncontrolled cardiovascular illnesses such as chronic congestive heart failure (with or without oedema), tachycardia, arrhythmias, uncontrolled hypertension.
   b. Significant ischemic heart disease, myocardial infarction within the last two years and/or with residual angina, orthopnea, conduction defects (ECG), or any other clinical significant heart disease classified as New York Heart Association (NYHA) III or IV.
   c. Significant liver disease (for example cirrhosis, active hepatitis B and C, primary or metastatic liver neoplasm).

d. Significant gastrointestinal disorders as per investigator's judgement (for example gastrointestinal bleeding within the last two years, malabsorption syndromes, post-gastrectomy, or active peptic ulcer disease).

e. Uncontrolled endocrine disease such as uncontrolled diabetes mellitus or hyperthyroidism.

f. Unstable/Uncontrolled major depression.

g. Significant pulmonary disease predisposing to hypoxia.

h. Immunological disorders such as clinically significant allergies, Lupus erythematosus, or scleroderma.

i. Unstable/uncontrolled haematological disease (regardless of etiology) such as refractory anaemia or refractory myelosuppression.

j. Systemic or multiple organ dysfunctions which, in the opinion of the investigator, would impact on the primary and secondary endpoints of the trial such as clinically relevant dehydration.

5. Severe renal impairment defined with a GFR < 30ml/min/1.73m$^2$ in the screening central lab report.
6. Any other psychiatric disorders such as schizophrenia, or mental retardation.
7. Any suicidal actions in the past 2 years (per investigator judgement i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).
8. Any suicidal ideation of type 4 or 5 in the Columbia Suicide Severity Rating Scale (C-SSRS) in the past 3 months (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent).
9. Previous participation in investigational drug studies of mild cognitive impairment within three months prior to screening. Having received active treatment in any other study targeting disease modification of AD like Aß immunization and tau therapies. Previous participation in studies with non-prescription medications, vitamins or other nutritional formulations is allowed however these should be captured in the eCRF.
10. Significant history of drug dependence or abuse (including alcohol, as defined in Diagnostic and Statistical Manual of Mental Disorders [DSM-V] or in the opinion of the investigator) within the last two years, or a positive urine drug screen for cocaine, heroin, or marijuana.
11. Known history of HIV infection.
12. Any planned surgeries requiring general anaesthesia, or hospitalisation for more than 1 day during the study period.
13. Pre-menopausal women (last menstruation ≤ 1 year prior to informed consent) who:

    • are nursing or pregnant or
    • are of child-bearing potential and are not practicing an acceptable method of birth control, or do not plan to continue using this method throughout the trial until 28 days after the last treatment administration, and do not agree to submit to periodic

pregnancy testing during participation in the trial. Acceptable methods of birth control include tubal ligation, vasectomized partner (and this has to be the patient's sole partner), transdermal patch, intra uterine devices/systems (IUDs/IUSs), combined estrogen-progestin oral contraceptives as well as implantable or injectable hormonal contraceptives unless they are a moderate to strong CYP1A2 inhibitor – see section 4.2.2.1. Complete sexual abstinence (if acceptable by local health authorities) is allowed when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Double barrier methods are permissible (if acceptable by local health authorities, note that this is not an acceptable method in EU countries).

14. For male patients: Men who are able to father a child, unwilling to be abstinent or to use an adequate form of effective contraception for the duration of study participation and for at least 28 days after treatment has ended.
15. Use of any investigational drug or procedure for other indications within 3 months or 6 half-lives (whichever is longer) prior to randomization.
16. Intake of the following medications within 3 months prior to randomization and intended to be initiated during the duration of the trial:
    a. tricyclic antidepressants,
    b. antidepressants that are monoamine oxidase inhibitors,
    c. neuroleptics with moderate or greater anticholinergic potency (e.g. chlorpromazine, fluphenazine, loxapine, perphenazine, thioridazine),
    d. anticholinergic medications

    The following drugs may be given as needed if the total daily dose was stable 8 weeks prior to randomisation and is expected to be for the duration of the trial:
    a. neuroleptics listed in section 4.2.2.,
    b. benzodiazepines and sedatives listed 4.2.2.
17. Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined during visit 1.
18. Any other clinical condition that, in the opinion of the Investigator, would jeopardize patient safety whilst participating in this clinical trial.
19. Non-compliance with study drug intake during placebo run-in phase defined as compliance < 75 %.
20. Clinically significant uncompensated hearing loss in the judgment of the investigator. Use of hearing aids is allowed.
21. Known hypersensitivity to the drug product excipients (lactose monohydrate, microcrystalline cellulose, pregelatinized starch, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate, hypromellose, propylene glycol, titanium dioxide, talc and iron oxide yellow).

### 3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from the trial if:

- The patient withdraws consent, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other study medications(s), refer to section 4.2.2.
- The patient is no longer able to participate for other medical reasons (e.g. surgery, AEs, or other diseases).
- If a patient becomes pregnant during the trial, the investigational drug will be stopped, the patient will be discontinued from the trial and the patient will be followed up until birth or otherwise termination of the pregnancy.
- At visit 3, if the patient experiences sinus tachycardia (defined as resting pulse rate >100 BPM measured in supine position after a minimum of 5 minutes rest) at any time point up to 90±20 minutes post dose or if a pulse rate increase greater than 20 BPM over the pulse rate taken before the first dose administration (baseline) has persisted at 90±20 minutes post-dose. Pulse rate is generally to be measured in a supine position after 5 min rest. See also section 5.2.5.2, and section 6.2.2.
- The patient exhibits serious suicidality, in the clinical judgement of the investigator or according to criteria below:
  - Any suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
  - Any suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent

A patient can be discontinued after discussion between sponsor and investigator if eligibility criteria have been violated, or if the patient fails to comply with the protocol (e.g. non-attendance at study assessments).

Patients who drop out during screening or during placebo run-in phase prior to randomization (Visit 3) will be considered as screening failure. For patients that screen fail, data will be collected for signed IC, demographics, AE, concomitant medications and randomization and recorded in the eCRFs. No further follow-up is required.

Patients who discontinue or withdraw from the study after randomization (Visit 3) will be considered as “early discontinuations” and the reason for premature discontinuation must be recorded in the eCRFs. The data will be included in the trial database and will be reported.

Patients who withdraw or discontinue from the trial after randomization will not be replaced.

If a female patient is suspected to be or becomes pregnant during treatment, the patient must inform the investigator immediately and stop taking all study drugs. For the reporting, follow up and documentation of pregnancy cases refer to section 5.2.2.2.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial and/or invalidate the earlier positive benefit-risk-assessment,
3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

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

# 4. TREATMENTS

## 4.1 TREATMENTS TO BE ADMINISTERED

The trial medication will be provided by Boehringer Ingelheim. Following an initial screening visit and a single blinded 2-week placebo run-in period, patients who qualify according to in- and exclusion criteria will be randomized to one of the five following treatment groups of investigational drugs:

Table 4.1:1 Treatment groups

| Group | Treatment Regimen | Treatment | tbl./d |
|---|---|---|---|
| **1** | **10 mg BI 409306 QD** | **BI 10 mg** | 1-0-0 |
| | | BI 25/50 mg PTM | 1-0-1 |
| **2** | **25 mg BI 409306 QD** | **BI 25 mg** | 1-0-0 |
| | | BI 10 mg PTM | 1-0-0 |
| | | BI 25/50 mg PTM | 0-0-1 |
| **3** | **50 mg BI 409306 QD** | **BI 50 mg** | 1-0-0 |
| | | BI 10 mg PTM | 1-0-0 |
| | | BI 25/50 mg PTM | 0-0-1 |
| **4** | **25 mg BI 409306 BID** | **BI 25 mg** | 1-0-1 |
| | | BI 10 mg PTM | 1-0-0 |
| 5 | PTM BI 409306 | BI 10 mg PTM | 1-0-0 |
| | | BI 25/50 mg PTM | 1-0-1 |

(PTM = Placebo to Match)

Note: The 25mg and 50 mg tablets active drug and PTM are visibly identical.

### 4.1.1 Identity of BI investigational product and comparator product(s)

Table 4.1.1: 1 BI 409306

| Substance: | BI 409306 |
|---|---|
| Pharmaceutical form: | Tablet |
| Source: | Boehringer Ingelheim Pharma GmbH & Co KG [redacted] |
| Unit Strength: | 10 mg, 25 mg, 50 mg |
| Daily Dose: | 10 mg QD (1-0-0) in Gr.1,<br>25 mg QD (1-0-0) in Gr.2,<br>50 mg QD (1-0-0) in Gr.3,<br>25 mg BID (1-0-1) in Gr.4 |
| Route of administration: | Per os |
| Posology: | QD or BID |
| Duration of use: | 12 weeks |

Table 4.1.1: 2 Placebo matching BI 409306, 10 mg tablet

| Substance: | Placebo matching BI 409306, 10 mg tablet |
|---|---|
| Pharmaceutical form: | Tablet |
| Source: | Boehringer Ingelheim Pharma GmbH & Co KG [redacted] |
| Unit Strength: | - |
| Daily Dose: | n.a |
| Route of administration: | Per os |
| Posology: | QD (1-0-0) in Gr.2, 3, 4, 5 and run-in |
| Duration of use: | 12 weeks |

Table 4.1.1: 3 Placebo matching BI 409306, 25 mg or 50 mg tablet

| Substance: | Placebo matching BI 409306, 25 mg or 50 mg tablet |
|---|---|
| Pharmaceutical form: | Tablet |
| Source: | Boehringer Ingelheim Pharma GmbH & Co KG [redacted] |
| Unit Strength: | - |
| Daily Dose: | n.a |
| Route of administration: | Per os |
| Posology: | QD (0-0-1) in Gr. 2 and 3; BID (1-0-1) in Gr.1, 5 and run-in |
| Duration of use: | 12 weeks |

### 4.1.2 Method of assigning patients to treatment groups

Patients eligible for the trial will be assigned at random to one of the five treatment groups at Visit 3 by Interactive Response Technology (IRT). Details on randomization are provided in section 7.5. Assignment and drug supply management of study drug will be done via IRT. Note that the medication numbers assigned to the patient by the IRT are different from the patient number; each medication box has a different medication number. The patient number is assigned at study entry, i.e. signing informed consent at Visit 1.

To facilitate the use of IRT, each study site will receive an information manual describing the steps to randomize a patient, to obtain a medication kit assignment and to acknowledge receipt of study medication. The manual will be part of the ISF. Medication kits (including single blinded placebo run-in kits) will be assigned at Visits 2, 3, 5 and 6 for each patient.

The access to the randomization codes will be controlled, documented and limited to a pre-specified group of users in order to ensure the blinding of the treatments groups.

### 4.1.3 Selection of doses in the trial

BI409306 has been tested in animal models to assess cognitive effects. On the basis of the described mode of action and the presented experimental efficacy in these animal memory tests, peak levels of BI 409306 in CSF in the range of 1x PDE9 IC50 need to be targeted for memory enhancing efficacy in humans. In a PoC study in healthy volunteers [U12-2165-01], it was shown that BI 409306 is able to cross the human blood-brain barrier (plasma to CSF) with a concentration corresponding to IC 50 (65 nmol/L) in CSF reached at 25 mg in 2 out of 4 subjects and exceeded IC 50 in all subjects at the higher doses. CSF exposure to BI 409306 increased with increasing dose and the CSF to plasma ratio for BI 409306 Cmax in humans is comparable to the one observed in rats and is constant over the entire dose range tested. CSF concentration-time profiles of BI 409306 peak approx. 0.5 to 1 hour later than in plasma and decline mono-exponentially and roughly in parallel to plasma concentrations afterwards with BI 409306 concentrations in CSF decreasing beyond the quantification limit (0.5 nmol/L) after 8 to 14 hours post dosing.

Therefore, the 25mg dose is anticipated to be the effective dose and will be tested once daily (QD) and twice daily (BID). To study the dose-response relationship, a lower dose (10mg) and a higher dose (50mg) will also be tested. For further details to the preclinical data as well to the human proof of mechanism study, please refer to the current version of the IB [U11-1079].

Patients will be randomized to one of five treatment groups as follows during the treatment period:

- BI 409306 10mg QD (Treatment Group 1)
- BI 409306 25mg QD (Treatment Group 2)
- BI 409306 50mg QD (Treatment Group 3)
- BI 409306 25mg BID (Treatment Group 4)
- Placebo (Treatment Group 5)

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

All patients who fulfil both inclusion and exclusion criteria until visit 2 will be assigned to a single blinded placebo run-in kit at the beginning of the run-in period (Visit 2).

The medication assignment will be provided through IRT. The assigned medication number must be entered in the eCRF, and the corresponding medication kit must be given to the patient. The amount of trial medication dispensed and returned will be recorded on drug accountability forms.

IRT will allocate medication kit numbers at Visit 2, 3, 5 and 6.

For blinding reasons all treatments will consist of two tablets of active drug or placebo for the morning dose and one tablet of active drug or placebo for the evening dose depending on the treatment arm. This will not be changed during the entire study.

During the run-in period patients will take 3 placebo tablets daily (2 tablets in the morning and 1 tablet in the evening) to mimic the dosing schedule during the treatment period.

Following the run-in period patients will be randomized (Visit 3) to one of the 5 treatment arms as outlined in figure 3.1:1

The first dose of the study medication will be taken at visit 2 under supervision of the investigator or site staff. At all applicable clinic visits the investigational drug will be taken during the visit under supervision of the investigator or relevant site staff. The actual visit date and time of study drug administration at the trial visit will be recorded in the eCRF.

Patients should be instructed to take the tablets orally with water at approximately the same time every day in the morning and in the evening with or without food. If a dose is missed by more than 4hrs, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken and dose reductions are not permitted. Patients should be instructed to bring all unused drug and empty study blister / bottles to the study site.

Patients should be instructed not to take their study medication on the morning of visit days. Patients are allowed to have a light breakfast/meal before the scheduled visit. Patients who erroneously take the morning dose of study medication before coming to the clinic at visit 6 should have the visit rescheduled as soon as possible, ideally on the following day [redacted] The actual date and time of administration of the medication at the trial visit will be recorded in the eCRF.

### 4.1.5 Blinding and procedures for un-blinding

#### 4.1.5.1 Blinding

Administration of the placebo run-in will be single blinded, meaning patients will not know during which period of the trial they will be receiving placebo.

This trial incorporates a double-blind, double-dummy trial design, meaning that treatments are indistinguishable according to the scheme as shown in Table 4.1:1. Placebo tablets are identical in the size and appearance to the corresponding active tablet and are combined with active drug tablets as needed in each treatment group to maintain the blinding.

After randomization at visit 3, patients, investigators and everyone involved in analysing or with a potential interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after database lock. However, due to the requirements to report Serious Unexpected Suspected Adverse Reactions (SUSARs), it may be necessary for a representative from BI's drug safety group to access the randomization code for individual patients during trial conduct. In such cases, access to the code will only be permitted by authorised drug safety representatives. Access to the code will be via the IRT system.

The randomization code will be kept secret by clinical trial support at BI up to database lock. The access to randomization codes will be controlled, documented and limited to a pre-specified group of users who are not involved into the capturing, processing and evaluation of the clinical data unless defined differently or in case of an emergency in order to ensure the blinding of the treatments. For details of the rules of breaking the codes in case of an emergency refer to section 4.1.5.2. The random code will be transferred to the trial data manager only after the Blinded Report Planning Meeting (BRPM) and after locking of the trial database.

The randomization codes will be provided to the sponsor's bioanalytic department prior to last patient out to allow them to perform appropriate pharmacokinetic analytical determination. Bioanalytics' will not disclose the randomization code or the results of their measurements until the study is officially unblinded. Prior to unblinding of the trial database, any pharmacokinetic results or data may only be communicated in a way that does not provide any direct or indirect link between patient number and treatment.

#### 4.1.5.2 Procedures for emergency unblinding

The IRT will be available for the unblinding of patients by the investigator in an emergency situation.

Detailed information on the IRT un-blinding procedures is described in the IRT manual that will be provided to the sites. The code break may only be performed in emergency situations when the identity of the trial medication must be known to the investigator in order to provide appropriate medical treatment or if required to assure the safety of trial participants.

The reason for un-blinding must be documented on the appropriate e-CRF page and in the patient source data.

If possible, the monitor must be contacted and informed prior to the site un-blinding a patient's treatment.

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

For details of packaging and the description of the label, refer to the Investigator Site File (ISF).

### 4.1.7 Storage conditions

Study medication (BI 409306 or placebo) will be stored in a secure, locked compartment under the supervision of the site staff. Store tablets in the original package in order to protect them from moisture and light. For storage conditions refer to the locally approved medication label and the STORM document in the ISF.

### 4.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The investigator / pharmacist/ investigational drug storage manager will receive the investigational drugs delivered by the sponsor when 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 the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol,
- if applicable, availability of the proof of a medical licence for the principal investigator,
- for the USA availability of the Form 1572.

The investigator / pharmacist / investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient and the return to the sponsor or alternative disposition of unused product(s).

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

## 4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

### 4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

No rescue medication, emergency procedure or additional treatments are foreseen for this study.

### 4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Intake of the following medications with the mentioned exceptions is prohibited during the entire duration of the trial including follow-up:

a. Tricyclic antidepressants, other drugs which are active on the central nervous system (CNS) i.e. psychotropics (tricyclic antidepressants and monoamine oxidase inhibitors, mood stabilisers, neuroleptics, atypical antipsychotics, antiepileptics, benzodiazepines, other hypnotics or sedatives (including sedative antihistamines), muscle relaxants, or central analgesics, e.g., opioids.

   **Note:** Zolpidem (10 mg/day), chloral hydrate (1 g/day), triazolam, quetiapine, temazepam and oxazepam if needed for sleep is allowed. If they are taken occasionally, then dosing on the night prior to cognitive testing is not allowed.

b. Agents having central dopamine antagonist activity, i.e. reserpine, methyldopa, antiemetic's etc. However, the serotonin and combined serotonin/noradrenalin Re-Uptake Inhibitors (SSRIs/SNRIs) like fluoxetin, es-citalopram, citalopram, sertalin, venlafaxin, duloxetin are allowed, but paroxetine is excluded. Other antidepressant drugs without anticholinergic and without dopaminergic effects may be given as needed if the total daily dose was stable 8 weeks prior to randomization and is expected to be maintained for the duration of the trial.

c. Intake of other phospodiesterase inhibitors (for example theophyllin, roflumilast, sildenafil, tadalafil, vardenafil, avanafil).

d. Intake of St. Johns wort, Carbamazepine, extracts from Gingko, artemisinin, enzalutamide, efavirenz, lopinavir, ritonavir, tipranavir, rifampicin as they are relevant CYP2C19 inducers

e. Intake of prescribed drugs for treatment of AD including acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine, phenserine) and memantine)

f. Use of medications that are known to be moderate or strong CYP1A2 inhibitors is not permitted. (For a list of moderate or strong CYP1A2 inhibitors, please consult the ISF Section 11 "Safety Information").

The drugs listed below may be used as needed:

Non-prescription drugs or vitamins including medical nutrition formulations that have been initiated before visit 1 can be continued concomitantly during the study. However initiation of such medication after visit 1 is prohibited.

4.2.2.2 Restrictions on diet and life style

There are no other restrictions on diet, exercise, alcohol consume or smoking except that the patient's usual habits, including nicotine and caffeine intake, should be within acceptable daily amounts in discretion of the investigator and not be drastically changed throughout the study conduct.

Drastic weight-loss dieting during the study is not permitted.

## 4.3 TREATMENT COMPLIANCE

Patients will be asked to bring all trial medication containers (with or without any remaining tablets) with them to each trial visit. The tablets will be counted and compliance will be calculated according to the formula:

$$\text{Compliance}(\%) = \frac{\text{Number of tablets actually taken since last tablet count}}{\text{Number of tablets which should have been taken in the same period}} \times 100\,\%$$

Compliance during the placebo run-in period should be between 75% and 120%.

Compliance during the randomized treatment period should be between 80 % and 120 %. Patients who are not compliant according to this definition should be carefully interviewed and re-informed about the purpose and the conduct of the trial.

# 5. VARIABLES AND THEIR ASSESSMENT

## 5.1 EFFICACY - CLINICAL PHARMACODYNAMICS

### 5.1.1 Endpoint(s) of efficacy

The following efficacy measures are completed at the times shown in section 6.2 and the Flow Chart.

Primary endpoint:

- The primary endpoint is Neuropsychological Test Battery (NTB) response, defined as change from baseline in total z-score after 12-week treatment.

Secondary endpoints:

- Change from baseline in the ADCS-MCI-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living for mild cognitive impairment) score after 12-week treatment.

- Change from baseline CDR-SB (Clinical Dementia Rating – Sum of Boxes) after 12-week treatment

- Change from baseline in ADAS-Cog11 (Alzheimer's Disease Assessment Scale-cognitive subscale) total score after 12-week treatment.

### 5.1.2 Assessment of efficacy

Established neuropsychological assessments will be used to capture individual changes in memory, cognitive function and activities of daily living. Detailed instructions how to administer the assessments can be found in the respective user manuals which will be filed in the ISF.

The NTB consists of 9 validated components:

- Wechsler Memory Scale visual immediate (score range, 0-18)
- Wechsler Memory Scale verbal immediate (score range, 0-24)
- Rey Auditory Verbal Learning Test (RAVLT) immediate (score range, 0-105)
- Wechsler Memory Digit Span (score range, 0-24)
- Controlled Word Association Test (COWAT)

- Category Fluency Test (CFT)
- Wechsler Memory Scale visual delayed (score range, 0-6)
- Wechsler Memory Scale verbal delayed (score range, 0-8)
- RAVLT delayed (score range, 0-30). The RAVLT delayed measure is composed of delayed recall and recognition performance components that are summed to yield a score ranging from 0 to 30.

Raw scores on each of the 9 NTB tests will be converted to z-scores using the baseline means and standard deviations (SDs) for each test. The resultant z-scores will be averaged to obtain a total z-score, incorporating all 9 NTB tests [R13-2645].

**ADCS-MCI-ADL**

This is a functional scale based on the information provided by an informant/caregiver that describes the performance of patients in several activities of daily living for MCI patients. This is a 24 item scale with 6 items related to complex abilities. The sum score could range from 0 to 69. Higher scores indicate better function [R13-2647].

**CDR-SB** is obtained through semi structured interviews of patients and informants, and cognitive functioning is rated in 6 domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment (personal care is scored on a 4-point scale without a 0.5 rating available). The CDR-SB score is computed [R03-0748].

**ADAS-cog/11** is an 11-item cognitive subscale that objectively measures memory, language, orientation and praxis with a total score range of 0 to 70 [R96-2608].

[redacted] has been selected as service provider to support tasks related to the neuropsychological assessments.

The services of [redacted] include:

- Necessary Rater prequalification
- Central Rater training for neuropsychological assessments used as primary and secondary endpoints (online and at investigator meeting)
- Provision of Rater materials

- Central Quality Review of Assessments

Details of rater prequalifications, Rater Training, Rater Materials (including Assessments) and of the Central review procedures will be available in a separate document filed in the ISF.

These members of the site staff conducting the neuropsychological assessments have to be adequately trained (either at the investigator training or individually) and training documentation has to be filed in the ISF. The training standards and standards for the conduct of the assessments will be defined for each assessment individually and can be found in the ISF. It is the responsibility of the Principal Investigator at the site to ensure proper training of all members of the site staff involved in the neuropsychological assessments.

## 5.2 SAFETY

### 5.2.1 Endpoint(s) of safety

No additional study specific important safety endpoints will be assessed in this study.

### 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, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of adverse event

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

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event

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. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

If a SAE is reported from a still blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (i.e. any active comparator or placebo according to the trial design).

Worsening of the underlying disease or other pre-existing conditions (except worsening of suicidal ideation and behavior)

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF, if they are judged clinically relevant by the investigator.

Protocol-specified Adverse Events of Special Interest (AESI)

The following are considered as AESIs:

Hepatic injury defined by the alterations of liver parameters as defined below:

- an elevation of AST and/or ALT $\geq$ 3 fold ULN combined with an elevation of total bilirubin $\geq$ 2 fold ULN measured in the same blood draw sample.

Patients showing these lab abnormalities need to be followed up according to Appendix 10.4 of this clinical trial protocol and the "DILI checklist" provided in the ISF.

Adverse Events of Special Interest are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria – for details please see section 5.2.2.2.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the REP/follow-up period) will be collected, documented and reported to the sponsor by the investigator on the appropriate CRF(s) / eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in section 5.2.2.1.

If a patient reports a change in visual perception or any vision-related AE, site staff must record the patient's verbatim description in the source documents to be reported in the eCRF. A local ophthalmology assessment will be required if any visual AE that is rated as moderate or severe by the subject or at the discretion of the PI. The ophthalmologist will act as a consultant to the Investigator and may offer advice on the proper management and treatment for the reaction.

The residual effect period (REP) for BI 409306 is 7 days and hence the time period for which adverse events will still be considered on-treatment, is ≤ 7 days following last intake of trial medication. All adverse events will be reported up until the last per protocol visit (follow-up visit) which is 28 days after the last dose of trial medication. The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant.

If not stipulated differently in the ISF, the investigator must report the following events 1) if using paper process SAE form via telephone/fax or 2) if available for the trial, using the electronic submission process (RDC) immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs relevant to the SAE(s) and Adverse Events of Special Interest.

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

The list of these adverse events can be found via the RDC-system.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File) or by using the electronic submission process. This immediate report is required irrespective of whether the

investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or Adverse Events of Special Interest becomes available.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

### 5.2.3 Assessment of safety laboratory parameters

The laboratory tests listed in Table 5.2.3:1 will be performed at the central laboratory service provider. Patients don't have to be fasted for the blood sampling for the safety laboratory. Instructions on collection, handling/ processing, and shipping of the samples will be provided in the investigator site file by the central laboratory. For time points of laboratory sampling refer to the Flow Chart.

The following lab parameters will not be determined at each study visit:

- TSH, HIV and syphilis testing: at screening only
- Vitamin B12 and folate at screening and EOT only
- Urine drug screen at screening and EOT only
- Human urine chorionic gonadotropin for women of child bearing potential only

Table 5.2.3: 1 Safety laboratory parameters

| Category | Test name | |
|---|---|---|
| **Haematology** | Hematocrit (Hct)<br>Hemoglobin (Hb) (Reticulocyte Count (reflex test if Hb outside normal ranges)<br>Red Blood Cells (RBC) Erythrocytes<br>Reticulocyte Count<br>White Blood Cells / Leukocytes<br>Platelet Count/ Thrombocytes | |
| | Diff. Automatic<br>(manual if diff. automatic is abnormal) | - Neutrophils<br>- Eosinophils<br>- Basophils<br>- Monocytes<br>- Lymphocytes |
| **Chemistry** | AST(GOT)<br>ALT(GPT)<br>Alkaline Phosphatase (AP)<br>- γ-GT (gamma-glutamyl transferase) reflex test triggered by elevated alkaline phosphatase on two sequential measures<br>Albumin<br>Creatine Kinase (CK)<br>CK-MB, troponin (reflex tests if CK is elevated)<br>Lactic Dehydrogenase (LDH)<br>Calcium<br>Sodium<br>Potassium<br>Chloride<br>Vitamin B12 | Bicarbonate<br>Creatinine<br>Phosphate<br>Urea (BUN)<br>Bilirubin Total (if increased:)<br>Bilirubin Direct<br>Bilirubin Indirect<br>Lipase<br>Magnesium<br>Potassium<br>Protein, Total<br>TSH<br>Folate |
| **Serology** | HIV testing and Syphilis testing (Rapid plasma reagin (RPR), if RPR positive, then performing Fluorescent Treponemal Antibody test (FTA) | |
| **Urine Pregnancy test** | Human urine chorionic gonadotropin | |
| **Urinalysis** | Urine Nitrite<br>Urine Protein<br>Urine Glucose | Urine Ketone<br>Urine WBC/ Leukocytes<br>Urine pH |
| **Urine-Sediment (microscopic examination)**, (only if urine analysis abnormal) | Urine Sediment Bacteria<br>Urine Cast in Sediment<br>Urine Squamous Epith Cells | Urine Sediment RBC/ Erythrocytes<br>Urine Sediment WBC/ Leucocytes |
| **Drug screening (urine)** | Cannabis<br>Benzodiazepine<br>Barbiturates<br>Opiates | Cocaine<br>Amphetamines<br>Methadone<br>Phencyclidine (PCP) |

### 5.2.4 Electrocardiogram

ECG-recordings will be made at the time points described in the Flow Chart. Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using equipment provided by a central ECG vendor. The ECGs will be recorded for at least 10 second duration after the subjects have rested for at least 5 minutes in a supine position. Electrode placement will be performed according to the method of Einthoven/Goldberger (ankles and wrists). At all-time points, indicated in the Flow Chart, single ECGs will be recorded. ECG recordings at planned time points may be repeated for quality reasons like alternating current artefacts, muscle movements and electrode dislocation.
All locally printed ECGs will be evaluated by the investigator or a designee. Additional (unscheduled) ECGs can be recorded for safety reasons at any time based on the judgment of the investigator. Any ECG abnormalities will be carefully monitored and if necessary the subject will be removed from the trial and medically treated.
All ECGs will be transmitted electronically to the central ECG vendor in order to enable a centralized re-evaluation of all 12-lead ECGs by an independent ECG laboratory (only if needed). Abnormalities detected during this centralized ECG evaluation will not necessarily qualify as AE.

### 5.2.5 Assessment of other safety parameters

#### 5.2.5.1 Physical examination (PE) and Neurological Examination

A standard physical examination will be carried out as described in the Flow Chart.

A physical examination including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes and extremities will be performed. The physical examination will include examination of known and suspected sites of disease.

A standard neurological examination will be carried out as described in the Flow Chart.

A neurological examination including, but not limited to, mental status, cranial nerves, reflexes, motor strength and coordination will be performed. The neurological examination will include examination of known and suspected sites of disease.

Clinically relevant abnormal findings noticed after baseline assessment will be reported as (S)AEs.

#### 5.2.5.2 Vital signs (orthostatic blood pressure & pulse rate)

Vital signs (orthostatic measurements of systolic/diastolic blood pressure and pulse rate) will be recorded at all the study visits as described in the Flow Chart, including the early End of Treatment Visit and the Follow-up visit (4 weeks after the end of treatment). Body weight will be measured at the visits indicated in the Flow Chart and the same scale has to be used for all measurements. The height is measured only at visit 1 (screening).

Measuring Orthostatic Blood Pressure

1. Have the patient lie down for 5 minutes.

2. Measure blood pressure and pulse rate.
3. Have the patient stand and immediately measure blood pressure and pulse rate.
4. Repeat blood pressure and pulse rate measurements after 3 minutes of standing.

Only at visit 3 the following additional measurements need to be performed which include:

- pulse rate is to be measured in a supine position after 5 minutes of rest pre-dose and at the time points of post-dose PK sampling until 90±20 mins post-dose. Pulse rate should be taken before the respective blood for PK sampling is drawn.
- Orthostatic measurements of systolic/diastolic blood pressure and pulse rate are to be done pre-dose and at 90±20 minutes post-dose.

This procedure is to be performed in a quiet environment and unexpected disturbances have to be avoided. In case of an unexpected disturbance (for example slamming door) this measurement may be repeated.

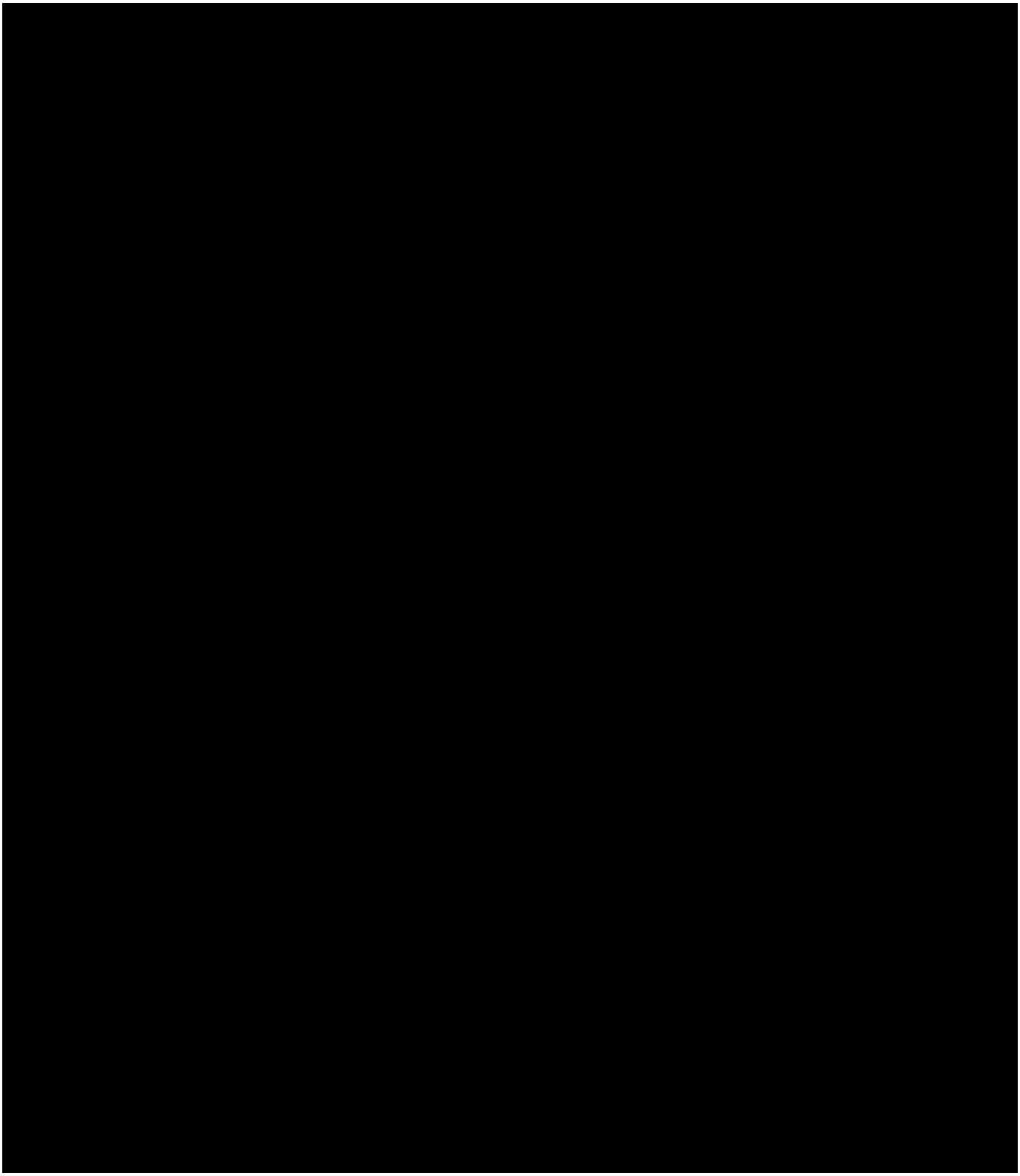
If there is a finding which meets any withdrawal criterion (See section 3.3.4.1), the subject should be removed from study participation.

Clinically relevant abnormal findings noticed after baseline assessment will be reported as (S)AEs.

#### 5.2.5.3 Suicidal risk assessed by the C-SSRS

The C-SSRS®, developed by leading experts in cooperation with the FDA, is a questionnaire assessing both suicidal behavior and suicidal ideation. The medical qualified clinician administered interview with the questionnaire has a typical administration time of five minutes, can be easily coupled with evaluation of inclusion/exclusion criteria and causes only a low burden on patients and the assessing medical qualified clinician. The interview consists of five questions related to suicidal behavior and five questions related to suicidal ideation, evaluated as either present or not. Patients presenting with any suicidal behavior or suicidal ideation will be excluded from participation in the trial. The C-SSRS® has been widely used in large multinational clinical trials in the past four years and it is available in over 20 languages. The C-SSRS® will be administered by the medical qualified clinician or expert clinician and will be assessed at the screening visit with the aim to exclude patients with active moderate or severe symptomatology prior to the screening visit, or recent (or current) suicidal or suicide attempt according to the C-SSRS® (baseline/screening version). Subsequently, the C-SSRS® “since last visit” assessment will be performed at each clinic visit after visit 3 and as shown in Flow Chart. If there is a positive response of suicide attempt or suicidal ideation by the patient during the administration of the C-SSRS® during the treatment period, the medical qualified clinician is to immediately interview the patient during the clinic visit and determine if the patient will be discontinued from the trial and appropriate actions for the patient’s safety have to be initiated by the investigator. For assessment of the C-SSRS® paper forms will be used and results will be transcribed into the e-CRF.

## 5.3 OTHER



[redacted]

### 5.3.2 Imaging Assessment

5.3.2.1 PET scan examination alternatively to CSF (where applicable)

Pattern for β-amyloid pathology on functional neuroimaging with PET (evaluation of β -amyloid positivity for tracers should be performed according to the prescribing information for display and interpretation provided in the label of the used tracer). Local PET scan specialists who assess the PET scans must have been trained by the manufacturer of the used A-ß tracer. A tracer specific training certificate should have been available for review, which confirms this individual training with name of the rater and when the training was performed.

5.3.2.2 MRI / CCT

Performance and assessment of brain MRI or CT images of the brain (not older than 12 months prior to randomization) to rule out other reasons for dementia should be performed by qualified readers according to radiological standards.

## 5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects and to determine pharmacokinetics of BI 409306 in an appropriate way.

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values, and ECG. The primary and secondary endpoints are widely accepted assessments of function and cognition in Alzheimer's Disease. They have been used in previous phase II and phase III studies in this indication.

[redacted]

[redacted]

## 5.6 BIOMARKER(S)

The following biomarker samples will be collected:

1. CSF samples collected to determine a positive amyloid signature at baseline via evaluation of CSF Aß1-42 and Tau levels (see also section 3.3.2) which is mandatory for all sites and patients that decide for confirmation of diagnosis using CSF. CSF sample aliquots that were not used for the assessment of Aβ1-42, total-Tau and phospho-Tau181 will be destroyed after the final study report is archived at the latest. [redacted].
2. [redacted]

The CSF collection processes is also described here and for details on the timing of collection, please refer to the Flow Chart.

### 5.6.1 Methods of sample collection

Patients for whom the CSF amyloid signature will be acquired as part of the screening procedure for inclusion will undergo a single lumbar puncture (visit 1, see Flow Chart; approximately 8 mL per individual) and collected CSF will be analysed for Aβ1-42, total-Tau and phospho-Tau181.

Detailed instructions for obtaining, handling and shipping of CSF samples are provided in Appendix 10.2.)

[redacted]

### 5.6.2 Analytical determinations

CSF samples will be analysed for Aβ1-42, total-Tau and phospho-Tau181 using validated immunoassays. [redacted]

# 6. INVESTIGATIONAL PLAN

## 6.1 VISIT SCHEDULE

All trial visits should be initiated preferentially in the morning starting before 9:00 AM. Patients should be instructed to avoid intake of the morning dose of the study medication at home at scheduled visit days as they will be dosed whilst at the study site.

All patient visits should be scheduled according to the Flow Chart.

If any visit has to be rescheduled, subsequent visits should follow the original visit schedule. The trial medication packs contain sufficient medication to allow for these time windows.

The end of the trial is defined as “last patient out”, i.e. last visit completed by the last patient.

If the reason for removal of a patient from the treatment is an adverse event or an abnormal laboratory test result, the patient must be followed until complete resolution or stabilization of the event or until follow-up is agreed to be adequate by the Investigator and BI CML.

Blood samples for the optional pharmacogenomics evaluation should be collected only after obtaining separate informed consent.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart. Additional details regarding visit procedures are provided below.

The following section describes recommendations for the conduct of the neuropsychological assessments.

- The assessments should be administered in the same sequence found in the flowchart and approximately at the same time of the day at every applicable visit.
- Assessment of the Neuropsychological Rating Scales should preferentially be done by the same member of the site staff for a given patient throughout the study period.
- It is strongly recommended that a member only performs independent tests (meaning that different assessments of cognition should be performed by different members of the team). The study partner contributing to the functional assessments should not change during the study. If that cannot be avoided this is to be recorded in the source data and as a protocol violation.
- The adverse events should be evaluated by a team member that is not directly involved in the neuropsychological and functional assessments (NTB, CDR, MCI-ADCS-ADL and ADAS-cog$_{11}$) to prevent partial unblinding.

The members of the site staff performing the assessment have to be properly trained (either at the investigator training or individually) and training documentation has to be filed in the ISF. The training standards and standards for the conduct of the assessments will be defined for each assessment individually and can be found in the ISF. It is the responsibility of the

Principal Investigator at the site to ensure proper training of all members of the site staff involved in the neuropsychological assessments.

### 6.2.1 Screening and run-in period(s)

Visit 1 (screening)

- No trial procedures should be done unless the patient and study partner have consented to taking part in the trial.
- Once the patient has consented, the patient is considered to be enrolled in the trial and has started screening. The patient should be recorded on the enrolment log and be registered in the IRT as a screened patient.
- Informed consent for optional pharmacogenomics sampling, if applicable should be obtained.
- For diabetic patients with antidiabetic therapy: exclusion of hypoglycemia for the period of the neuropsychological assessment (documented plasma glucose concentration ≥ 90 mg/dl (5mmol/l) at the beginning and directly after the assessment). If glucose is too low patients need to eat a snack and then be retested to confirm that the blood sugar value is above 90 mg/dl before the tests are started
- The following screening procedures must however be performed in the order of the Flow Chart: MMSE, FCSRT, (Wechsler Memory Visual Paired Associates test, if applicable), CDR, ADAS-cog$_{11}$, MRI/CCT and PET/ CSF sampling (whichever applicable) to ensure that undesirable, invasive screening procedures are deferred until necessary.
- If the patient fails screening due to the results of the MMSE and/or the CDR then an alternative participation in study 1289.7 might be considered, where applicable.
- Administration of C-SSRS (baseline/screening scale)
- Collection of urine and blood for safety laboratory testing including testing for HIV, Syphilis and vitamin B12 and folate levels.
- Collection of blood samples for optional soluble biomarker evaluation from patients who consent.
- If patient does not meet inclusion/exclusion criteria at visit 1 then the patient must be recorded in IRT and CRFs as a screen failure.
- If the patient is eligible according to inclusion/exclusion criteria available at visit 1, the run-in visit (visit 2) should be scheduled. Patient should be reminded to come for visit 2 in the morning.
- Patients are allowed to have a light breakfast/ meal before coming to the study site.
- Patients should be reminded not to take occasionally used sleeping aids (see section 4.2.2.1) in the evening prior to visit 2.
- Patient should be reminded to inform the study site in case of adverse events.

Visit 2 (Run-in period)

- It is recommended to perform study procedures in the order as listed in the Flow Chart.

- Results pending for assessments done at visit 1 for inclusion/ exclusion criteria should be evaluated and if the patient is deemed ineligible, the patient must be recorded in IRT and CRFs as a screen failure.
- If patient does not meet inclusion/exclusion criteria available on visit 2 the patient must be recorded in IRT and CRFs as a screen failure.
- Informed consent for optional pharmacogenomics sampling, if applicable should be obtained
- Administration of C-SSRS (since last visit scale).
- The intake of trial medication and handling of medication blisters should be discussed with the patient and the study partner. The first dose of the trial medication should be taken by the patient under the supervision of the study. Patients should be advised to take the trial medication as per the drug label till the next scheduled visit. The importance of compliance to the study drug intake should be emphasized to the study partner as well.
- Patients should be reminded to get all used and un-used medication including the medication packaging back at visit 3.
- Patients should be reminded not to take occasionally used sleeping aids (see section 4.2.2.1) in the evening prior to visit 3.
- Patients should be reminded to NOT take any study medication on the morning of visit 3.
- Patients are allowed to have a light breakfast/ meal before coming to the study site.
- Patient should be reminded to inform the study site in case of adverse events.

### 6.2.2 Treatment period(s)

Visit 3 (Randomization visit)

Visit 3 is the baseline/randomisation visit and marks the beginning of the treatment period. The neuropsychological assessments may be done on the day before the randomisation visit (last day of the screening period) if agreed between site staff and patient. In any case it needs to be ensured that the recommendations for the conduct of the neuropsychological assessments (refer to section 6.2 for details) are followed.

- It is recommended to perform study procedures in the order as listed in the Flow Chart.
- Study medication provided at visit 2 and returned should be collected and compliance check performed.
- Beginning with Visit 3 until end of treatment (EOT/ ED respectively) the neuropsychological assessments should always be performed approximately at the same time (in the morning) in the order as stated in the Flow Chart
- Eligible patients should be randomised using IRT. If patient does not meet inclusion/exclusion criteria at visit 3 the patient must be recorded in IRT and CRFs as a screen failure.
- Informed consent for optional pharmacogenomics sampling, if applicable should be obtained
- For diabetic patients with antidiabetic therapy: exclusion of hypoglycemia for the period of the neuropsychological assessment (documented plasma glucose concentration ≥ 90 mg/dl (5mmol/l) at the beginning and directly after the assessment). If glucose is too low

patients need to eat a snack and then be retested to confirm that the blood sugar value is above 90 mg/dl before the tests are started

- Administer the neuropsychological assessments in the following order :
  - CDR-SB
  - NTB
  - ADCS-MCI-ADL
  - ADAS-cog11
- Administration of C-SSRS (since last visit scale).
- Pre-dose vital signs (orthostatic measurements of systolic/diastolic blood pressure and pulse rate). Please see section 5.2.5.2.
- [redacted]
- Collection of urine and blood for safety laboratory testing.
- [redacted]
- New medication kits should be dispensed and the intake of trial medication and handling of medication blisters should be discussed with the patient and the study partner.
- The first dose of the study medication from the new kit should be taken under the supervision of the study staff.
- [redacted]
- Post Dose Vital Signs (orthostatic measurements of systolic/diastolic blood pressure and pulse rate) at 70-110 minutes should be performed. Please see section 5.2.5.2.
- Patients should be advised to take the trial medication as per the drug label till the next scheduled visit. The importance of compliance to the study drug intake should be emphasized to the study partner as well. Patients should be reminded to return all used and un-used medication including the medication packaging back to the clinic at visit 5.
- Patients should be reminded not to take occasionally used sleeping aids (see section 4.2.2.1) in the evening prior to visit 5
- Patient should be reminded to NOT take any study medication on the morning of visits 4 and 5.
- Patients are allowed to have a light breakfast/ meal before coming to the study site.
- Patient should be reminded to inform the study site in case of adverse events.

Visit 4 a, b, c

- Visit 4a is a mandatory clinic visit. Visits 4b and Visit 4c may be a phone contact with the patient if (in discretion of the investigator) no clinically relevant abnormalities in ECG and vital signs are observed at visit 4a. Study procedures have to be completed according to the Flow Chart.
- ECG and vital signs are only to be performed at clinic visits.

- The attendance of the study partner is not necessarily required during the visits 4a-c.
- Patients should be advised to take the trial medication as per the drug label till the next scheduled visit. The importance of compliance to the study drug intake should be emphasized
- Administration of C-SSRS (since last visit scale).
- Patients should be reminded to return all used and un-used medication including the medication packaging back to the clinic at visit 5.
- Patient should be reminded to NOT take any study medication on the morning of visit 5.
- Patients are allowed to have a light breakfast/ meal before coming to the study site.
- Patients should be reminded not to take occasionally used sleeping aids (see section 4.2.2.1) in the evening prior to visit 5.
- Patient should be reminded to inform the study site in case of adverse events.

Visit 5

- It is recommended to perform study procedures in the order as listed in the Flow Chart.
- Study medication provided at visit 3 and returned should be collected and compliance check performed.
- Neuropsychological assessments should always be performed approximately at the same time (in the morning) in the order as stated in the Flow Chart. Neuropsychological assessments and collection of urine and blood for laboratory testing must be performed prior to administration of study medication.
- For diabetic patients with antidiabetic therapy: exclusion of hypoglycemia for the period of the neuropsychological assessment (documented plasma glucose concentration ≥ 90 mg/dl (5mmol/l) at the beginning and directly after the assessment). If glucose is too low patients need to eat a snack and then be retested to confirm that the blood sugar value is above 90 mg/dl before the tests are started
- Administer the neuropsychological assessments in the following order:
  - CDR-SB
  - NTB
- Administration of C-SSRS (since last visit scale).
- New medication kits should be dispensed and the intake of trial medication and handling of medication blisters should be discussed with the patient and the study partner.
- The first dose of the study medication from the new kit should be taken under the supervision of the study staff.
- Patients should be advised to take the trial medication as per the drug label till visit 6. The importance of compliance to the study drug intake should be emphasized to the study partner as well.
- Patients should be reminded to get all used and un-used medication including the medication packaging back at visit 6.
- Patient should be reminded to NOT take any study medication on the morning of visit 6.
- Patients are allowed to have a light breakfast/ meal before coming to the study site.
- Patients should be reminded not to take occasionally used sleeping aids (see section 4.2.2.1) in the evening prior to visit 6.
- Patient should be reminded to inform the study site in case of adverse events.

Visits 6

- It is recommended to perform study procedures in the order as listed in the Flow Chart.
- Study medication provided at visit 5 and returned should be collected and compliance check performed.
- Collection of urine and blood for safety laboratory testing
- C-SSRS (since last visit scale)
- New medication kits should be dispensed and the intake of trial medication and handling of medication blisters should be discussed with the patient and the study partner.
- [redacted]
- The first dose of the study medication from the new kit should be taken under the supervision of the study staff.
- [redacted]
- Patients should be advised to take the trial medication as per the drug label till visit EOT. The importance of compliance to the study drug intake should be emphasized to the study partner as well.
- Patients should be reminded to return all used and un-used medication including the medication packaging back to the clinic at visit EOT.
- Patient should be reminded to NOT take any study medication on the morning of visit EOT.
- Patients are allowed to have a light breakfast/ meal before coming to the study site.
- Patients should be reminded not to take occasionally used sleeping aids (see section 4.2.2.1) in the evening prior to visit EOT.
- Patient should be reminded to inform the study site in case of adverse events.

Visits 7 (End of Treatment/ Early Discontinuation visit)

- It is recommended to perform study procedures in the order as listed in the Flow Chart.
- Study medication provided at visit 6 and returned should be collected and compliance check performed.
- Neuropsychological assessments should always be performed approximately at the same time (in the morning) in the order as stated in the Flow Chart.
- For diabetic patients with antidiabetic therapy: exclusion of hypoglycemia for the period of the neuropsychological assessment (documented plasma glucose concentration ≥ 90 mg/dl (5mmol/l) at the beginning and directly after the assessment). If glucose is too low patients need to eat a snack and then be retested to confirm that the blood sugar value is above 90 mg/dl before the tests are started
- Administer the following neuropsychological assessments in the following order:
  - CDR-SB
  - NTB
  - ADCS-MCI-ADL
  - ADAS-cog11

- C-SSRS (since last visit scale)
- Collection of urine and blood for safety laboratory testing.
- [redacted]
- Visit EOT is the end of treatment visit. Study medication will not be taken at Visit EOT.

### 6.2.3 End of trial and follow-up period

For all patients completing the study according to protocol, a follow-up contact (Visit FU) will be performed at the end of the follow-up phase of 28 days.

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN - MODEL

This is a phase II multi-centre, double-blind, parallel-group, randomized, placebo-controlled study to investigate efficacy, safety and tolerability of orally administered BI 409306 once or twice daily during a 12-week treatment period compared to placebo in patients with prodromal Alzheimer's Disease. The primary endpoint is Neuropsychological Test Battery (NTB) response, defined as change from baseline in total z-score after 12-week treatment.

The primary analysis is the restricted maximum likelihood based mixed model repeated measurement (MMRM) comparing the change from baseline of NTB total z-score after 12-week treatment. Further analysis details are provided in section 7.3 (Planned Analyses).

Another design aspect is the randomization allocation ratio of 1:1:1:1:2 of 10 mg, 25 mg, 50 mg, 25 mg BID of BI 409306 and placebo. Since the literature suggests that higher placebo response is related to the probability of patients receiving trial medication, the randomization allocation ratio is modified from a traditional equal ratio where only about 17 % of patients would receive placebo to an allocation ratio of 1:1:1:1:2 where 33 % of patients would receive placebo [P10-10921]. This is further elaborated in the section 7.5 and the impact on sample size calculation is provided in section 7.6.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

The objective of this exploratory trial is to demonstrate proof-of-concept and also explore the dose response of BI 409306 in NTB total score change from baseline (Visit 3) after 12 weeks treatment. The hypotheses testing will be carried in the following steps. No multiplicity adjustment will be made; hence all the p-values will be descriptive. All tests will be tested at a two-sided alpha 0.05.

- Step 1 for Proof-of-Concept:

$H_{1\text{-}0}$: Mean NTB response of pooled doses of 10 mg QD, 25 mg QD, 25 mg BID and 50 mg QD = Mean NTB response of placebo

$H_{1\text{-}a}$ : Mean NTB response for pooled doses of 10 mg QD, 25 mg QD, 25 mg BID and 50 mg QD ≠ Mean NTB response of placebo

If the null hypothesis $H_{1\text{-}0}$ is rejected in favour of $H_{1\text{-}a}$, then the proof of concept is established.

- Step 2 for dose response finding:

A regression model will be fitted first as the following functional form.

$$\mu(d_i) = \beta_0 + \beta_1 d_i + \beta_2 {d_i}^2,$$

where $\mu(d_i)$ denotes the mean response of NTB of the dose level i group, $d_i$ denotes for dose levels i, for i = 1, 2,..,5 and β's are the coefficients. The dose $d_i$ will be treated as continuous variable.

Testing for linear dose response curve

$H_{2\text{-}0}$: $\beta_1 = 0, \beta_{2=0}$

$H_{2\text{-}a}$: $\beta_1 \neq 0, \beta_{2=0}$

If the null hypothesis $H_{2\text{-}0}$ is rejected in favour of $H_{2\text{-}a}$, then the following test will be tested for quadratic dose response curve.

$H_{3\text{-}0}$: $\beta_2 = 0$

$H_{3\text{-}a}$: $\beta_2 \neq 0$

- Step 3:

Once the dose response curve is determined from Step 2, the dose group with peak response in the selected model will be tested as follows:

$H_{4\text{-}0}$: The dose group with peak response in the respective model Mean NTB response = Mean NTB response of placebo.

$H_{4\text{-}a}$: The dose group with peak response in the respective model Mean NTB response ≠ Mean NTB response of placebo.

In addition to the 3 steps above, the confidence intervals of difference in treatment effect against placebo will be presented for efficacy evaluation.

Note Step 1 and Step 3 the testing will be based on the adjusted means of NTB response from the primary model as described in section 7.3

For the secondary endpoint, all calculated p-values should be considered as descriptive for the analysis of secondary endpoint. Therefore, no alpha correction will be carried out.

## 7.3 PLANNED ANALYSES

Analysis set

**Treated set (TS):** All patients who were randomized and treated with at least one dose of study medication.

**Full analysis set (FAS)**: The full analysis set (FAS) will consist of all randomized patients who were treated with at least one dose of study drug and had a baseline and at least one post baseline on treatment primary endpoint NTB assessment. The FAS will be used for the primary analyses.

### 7.3.1 Primary analyses

Derivation of primary endpoint

The primary endpoint NTB total score will be analysed as change from baseline after 12 weeks of treatment. The NTB includes 9 tests as described in section 5.1. For each patient raw scores on each of the 9 NTB tests will be converted to the standardized z-score using the baseline means and standard deviations (SDs) for each test. The baseline means and SDs will be calculated using all randomized patients. The resultant z-scores will be averaged to obtain a total z-score, incorporating all 9 NTB tests. Change from baseline will be calculated as the post-baseline composite z-score minus the pre-treatment z-score, such that a positive change indicates an improvement from baseline. The measurements taken at Visit 3 will be considered as baseline values [R13-2645].

Primary analysis model

The restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM) will be used for the change from baseline in NTB total score after 12 weeks of treatment. The model will include fixed, categorical effects of treatment, visit and treatment by visit interaction, as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient will be considered as random effect. The unstructured covariance structure will be used to model the within patient errors. If this analysis fails to converge, compound symmetry covariance structure might be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Analyses will be implemented using SAS PROC MIXED. The primary treatment comparisons will be the contrast between treatments after 12 weeks of treatment. Adjusted mean values as well as treatment contrasts will be presented together with the 95 % confidence intervals.

### 7.3.2 Secondary analyses

The REML model as described for the primary endpoint will be performed for the secondary endpoint CDR-SB. An ANCOVA model similar to the primary endpoint model will be performed for the ADAS-$Cog_{11}$ and ADCS-MCI-ADL secondary endpoints. Further details will be provided in the TSAP. The adjusted mean values as well as the treatment contrasts will be presented together with the 95 % confidence intervals.

### 7.3.3 Safety analyses

Standard safety analyses will be performed on the TS.

All safety data will be displayed and analyzed using descriptive statistical methods. No formal inferential analysis is planned for safety comparison.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between first drug intake and end of residual effect period 7 day after last drug intake will be considered ‘treatment-related. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

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

Descriptive statistics of laboratory values over time and for the difference from baseline will be provided. Frequency tables of changes with respect to the reference range between baseline and last value on treatment will also be presented.

*Vital signs, ECG and other safety parameters 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.*

The responses to the C-SSRS will be summarized through descriptive statistics.

More details of these analyses will be included in the TSAP.

### 7.3.4 Interim analyses

No interim analysis is planned during the course of the study.

[redacted]

[redacted]

## 7.4 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at the specified time points.

In general, completely missing visits will be handled through the statistical model.

NTB measurements

- For NTB, if more than 3 out of 9 items are missing, the total score will not be derived and it will be set to missing [R13-2645].
- If all data from a visit is missing at random (i.e. the patient withdraw for any reason or a visit is missed but the patient has not withdrawn), the likelihood based repeated measures mixed effects model described in section 7.3.1 will handle missing data.

Additional details on the imputation of missing data will be specified in the Trial Statistical Analysis Plan (TSAP) prior to un-blinding.

## 7.5 RANDOMIZATION

Eligible patients will be randomly assigned to one of the 5 treatment groups, with an allocation of 2:1:1:1:1 respectively for placebo: BI 409306 10 mg once daily: BI 409306 25 mg once daily: BI 409306 50 mg once daily once daily: BI 409306 25 mg twice daily.

The randomization will not be stratified.

The randomization of patients to the treatment groups will be performed via an interactive response technology (IRT). BI will arrange for the randomization as well as packaging and labeling of study medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation of medication numbers to treatment is both reproducible and non-predictable. The access to the randomization codes will be controlled and documented.

## 7.6 DETERMINATION OF SAMPLE SIZE

The primary efficacy hypothesis will be tested by comparing the dose group of BI 409306 with the peak response in the fitted regression model to the placebo group on the primary

endpoint, the change from baseline in NTB total score after 12-week treatment. (See section 7.2 for the details of hypothesis testing.)

As previously mentioned, the randomization allocation ratio of 1:1:1:1:2 of 10 mg, 25 mg, 50 mg, 25 mg BID of BI 409306, and placebo is used so that 33 % of patients will be randomized to placebo. Since these results in an unequal allocation of treatment to placebo, the sample size required for the active treatment and placebo for various effect size are displayed separately. The sample size calculations in Table 7.6:1 displays the range of effect sizes considered for this trial under these assumptions using a 2-sided alpha of 0.05 with 80 % power. The two-sample t-test method with unequal n's in nQuery Advisor 6.01 was used for the calculation.

Table 7.6: 1 Sample size calculations

| Standardized effect size | 0.45 | 0.50 | 0.55 | 0.6 | 0.65 |
|---|---|---|---|---|---|
| Power | 80% | 80% | 80% | 80% | 80% |
| n for each active treatment arm | 59 | 48 | 40 | 34 | 29 |
| n for placebo arm | 118 | 96 | 80 | 68 | 58 |
| Total | 354 | 288 | 240 | 204 | 174 |

Based on the calculations provided in Table 7.6:1, a sample size of 48 per active treatment arm and 96 for placebo arm was selected as adequate for a phase II proof of concept trial. This sample size would allow us to detect an effect size of 0.5 with 80 % power or an effect size of 0.6 with 92 % power, 2-sided alpha at 0.05.

*Assuming a 10% dropout rate, this sample size would allow us to detect an effect size of 0.53 with 80% power and assuming a 20% dropout rate, this sample size would allow us to detect an effect size of 0.56 with 80% power, 2-sided alpha at 0.05.*

# 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 Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

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/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

According to local requirements the terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

## 8.1 STUDY APPROVAL, PATIENT 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 patient participation in the trial, written informed consent must be obtained from each patient 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 patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient.

The patient 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 patient.

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

In this study each patient needs a dedicated study partner who will accompany the patient throughout the trial. The study partner also will actively contribute to specific neuropsychological assessments, which provide information about the patient's cognitive status and activities of daily living. The study partner will join the informed consent process and read the patient information together with the patient. He/she will sign a separate informed consent form, which explains his role as a study partner and how the personal data he / she provided about themselves and about the patient will be used by Boehringer Ingelheim or the institutions as mentioned above.

## 8.2 DATA QUALITY ASSURANCE

In order to achieve a high level of standardised processes, data collection of efficacy and safety endpoints are coordinated centrally:

- Central rater pre-qualification, training, provisioning and quality review of neuropsychological assessments. Central quality review of assessments; for that purpose assessment procedures will be audio recorded. [redacted] has been selected as service provider to support tasks related to the neuropsychological assessments.
- Central lab analysis of efficacy endpoints, biomarkers and safety lab
- Central ECG collection
- Central IRT for randomisation and kit allocation

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 CTMF.

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

## 8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

### 8.3.1 Source documents

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

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need

to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

### 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/eCRFs and all source documents, including progress notes 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 (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in section 8.3.1.

## 8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

### 8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the BI 409306 this is the current version of the Investigator's Brochure (U11-1079). The current version of this reference document is to be provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

### 8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

## 8.5 STATEMENT OF CONFIDENTIALITY

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

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient'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.

## 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. For all other participating OPU's local regulations will apply.

# 9. REFERENCES

## 9.1 PUBLISHED REFERENCES

R03-0748 Berg L. Clinical dementia rating (CDR). Psychopharmacol Bull 1988. 24(4):637-639.

R10-5092 Cooke SF, Bliss TVP. Plasticity in the human central nervous system. Brain 2006;129:1659-1673.

R10-5095 Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M, Alzheimer's Disease International, . Global prevalence of dementia: a Delphi consensus study. Lancet 2005;366:2112-2117.

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

R10-5105 Strauss E von, Viitanen M, Ronchi D de, Winblad B, Fratiglioni L, . Aging and the occurrence of dementia: findings from a population-based cohort with a large sample of nonagenarians. Arch Neurol 1999;56:587-592.

R10-5106 Wimo A, Winblad B, Aguero-Torres H, Strauss E von, . The magnitude of dementia occurrence in the world. Alzheimer Dis Assoc Disord 2003;17(2):63-67.

R10-5109 Bliss TVP, Collingridge GL, . A synaptic model of memory: long-term potentiation in the hippocampus. Nature 1993;361:31-39.

R13-2645 Harrison J, Minassian SL, Jenkins L, Black RS, Koller M, Grundman M, . A neuropsychological test battery for use in Alzheimer disease clinical trials. Arch Neurol 2007;64(9):1323-1329.

R13-2647 Pedrosa H, Sa A de, Guerreiro M, Maroco J, Simoes MR, Galasko D, Mendonca A de Functional evaluation distinguishes MCI patients from healthy elderly people - the ADCS/MCI/ADL scale. J Nutr Health Aging 14 (8), 703 - 709 (2010)

R14-0163 Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013. 9:63-75.

R14-2556 Dubois B, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 13, 614 - 629 (2014)

R14-4676 C.M. Cullum et al. Normal Aging and Forgetting Rates on the Wechsler Memory Scale-Revised. Arch. Of Neuropsych., Vol. 5, pp.23-30, 1990

R96-2608 Rosen WG, Mohs RC, Davis KL, . A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141(11):1356-1364.

P10-10921 Lidstone SC, Schulzer M, Dinelle K, Mak E, Sossi V, Ruth TJ, Fuente-Fernandez R de la, Phillips AG, Stoessl A. Effects of expectation on placebo-induced dopamine release in Parkinson disease. Arch Gen

Psychiatry 2010. 67(8):857-865.

## 9.2 UNPUBLISHED REFERENCES

U10-2286-01 [redacted] Electrophysiological evaluation of the efficacy of a Boehringer Ingelheim compound at native targets using functional parameters: Investigation of the influence of 25004777 on glutamatergic synaptic transmission and synaptic long-term potentiation in hippocampus after strong tetanization.; BI409306-Rosenbrock-1007-H; 17 Jul 2007

U10-2789-01 [redacted] Effects of BI 409306 on behaviour assessed by observation in a modified IRWIN-test and on nocturnal activity in rats after oral administration of 0.3, 1 and 3 mg/kg. GP2009/0096/0097/PH3. 10 Nov 2010.

U10-2801-01 [redacted], BI 409306: Mutagenicity study using micronucleus analysis of rat bone marrow - Part of the 4-week oral (gavage) toxicity study No. 10B040, international number 10B061, 10 Oct 2011

U10-2898-01 [redacted], BI 409306: Modified Irwin test in the rat, including body temperature and short-term locomotor activity by single oral (gavage) administration, 10B054; 7 Oct 2011

U10-2899-01 [redacted] BI 409306: Evaluation of respiratory parameters in the conscious male rat, using whole body bias flow plethysmography after single oral (gavage) administration,10B055, 29 Feb 2012

U11-1079 [redacted], Investigator's Brochure: BI 409306 in Alzheimer's Disease and Cognitive Impairment associated with Schizophrenia, current version

U11-1173-01 [redacted], BI 409306: 4-week oral (gavage) toxicity study in beagle dogs, 10B084, 10 Jan 2012

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

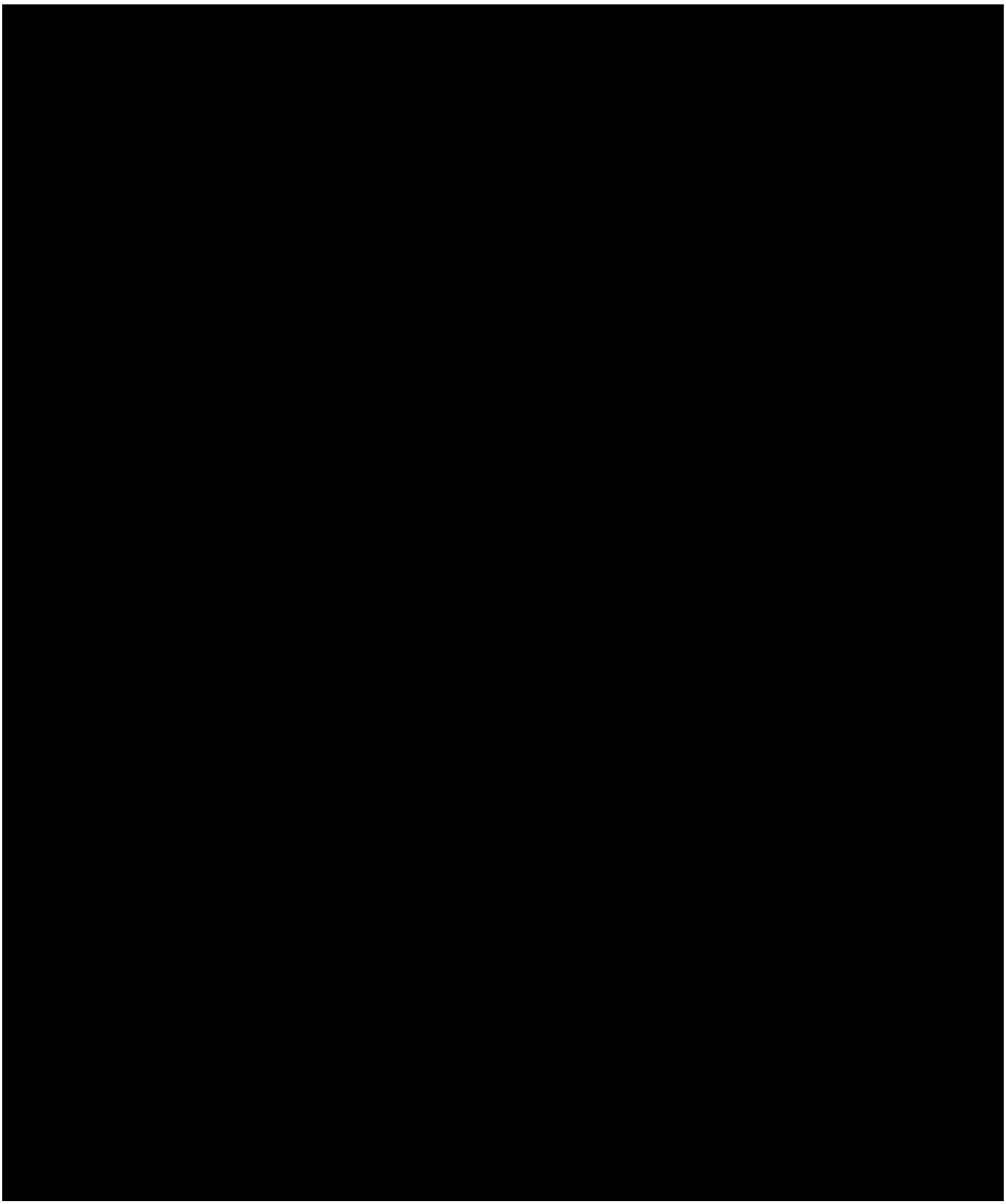
U12-2165-01 [redacted] Randomised, double-blind, placebo-controlled, parallel-group proof of mechanism study to assess the pharmacokinetics and to evaluate the pharmacodynamic effect of different single oral doses of BI 409306 in healthy male volunteers. 1289.3. 17 Sep 2012

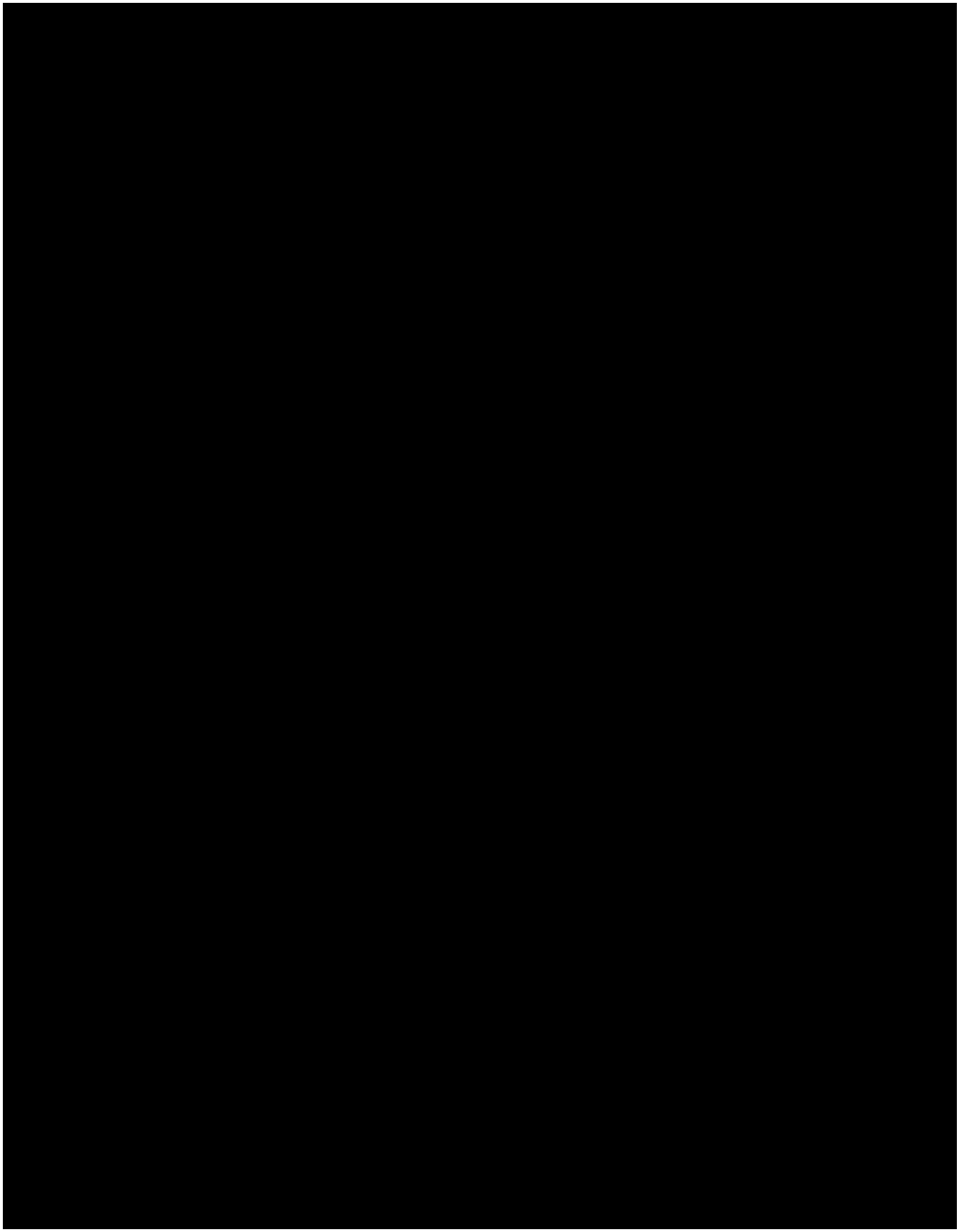
U13-1182-01 [redacted]. Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple-rising doses of BI 409306 film-coated tablets given orally q.d. or bid for 14 days in young healthy and elderly healthy male/female volunteers (randomised, doubleblind, placebo-controlled within dose groups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

U13-1303-01 [redacted]. Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of BI 409306 film-coated tablets given orally q.d. for 14 days in young and elderly healthy male/female volunteers (randomized, double-blind, placebo controlled within dose groups Phase I study). 1289.17. 22 Feb 2013

c02098989-02 [redacted], Safety, tolerability and pharmacokinetics of single oral doses of BI 409306 (tablet) in healthy Chinese and Japanese male volunteers and multiple oral doses of BI 409306 (tablet) in healthy Japanese male volunteers (randomised, double-blind, placebo-controlled within dose groups); BI409306; 6 June 2014

# 10. APPENDICES





## 10.2 LUMBAR PUNCTURE PROCEDURE AND CEREBROSPINAL FLUID (CSF) COLLECTION AND PROCESSING

Evaluation of CSF amyloid is considered a gold standard to support a diagnosis of Alzheimer's disease; it is highly likely that many potential patients would initially undergo CSF sampling before being considered for participation in this study. For the study it is necessary that the CSF sampling procedure is standardized and the evaluation of CSF amyloid as diagnostic inclusion criteria is performed at a central lab to ensure consistency of results.

CSF sampling is an invasive procedure. To avoid repeated lumbar puncture for diagnosis and confirmation of eligibility, patients who initially underwent CSF sampling for diagnostic workup of cognitive impairment can be considered for inclusion if CSF was collected within the last 4 months prior to Informed Consent and if the sampling and storage was done according to the specifications set out in this protocol. The sampling of the CSF should be performed under the current medically accepted standards in the referring country (for instance: separate informed consent and considering potential contraindications like raised intracranial pressure, thrombocytopenia and other bleeding diathesis (including ongoing anticoagulant therapy) or suspected spinal epidural abscess. Aliquoting of samples as specified in the protocol is not necessary and it would be considered acceptable if the sites are able to provide at least 6ml of CSF as a single bulk sample or multiple aliquots. Multiple thawing of the samples once frozen is not allowed.

In the event the CSF sample provided is considered unacceptable for evaluation by the central lab, it is at the discretion of the investigator to consider taking an additional CSF sample for inclusion in the 1289.5 study or such patients would need to be screen failed or undergo PET for demonstration of amyloid pathology.

### 10.2.1 Positioning

The subject should assume a sitting position and arching "like a cat" with his or her back flexed to widen the gap between the spinous processes. The lumbar spine should be perpendicular to the bed. The point of insertion of the needle will be determined by palpation at the intersection of the midline and a line connecting the superior aspects of the iliac crests. Deviations should be recorded in the source data as well as in the eCRF.

The needle will be inserted in the interspace between L3 and L4 or L4 and L5. The proper position will be indicated with a skin-marking pen.

### 10.2.2 Preparation

The site should follow its local standard procedures for preparation of lumbar puncture. The further procedure will be performed in a sterile manner.

### 10.2.3 Analgesia

Maximal 5 mL local anaesthetic (e.g. Xylocaïne® 2% with epinephrine) will be infiltrated subcutaneously.

### 10.2.4 Lumbar puncture and CSF collection

An (preferentially 25G) atraumatic needle with stylet in place will be inserted at the superior aspect of the inferior spinous process in the midline and approximately 15° cephalad. Advance the needle into the spinous ligament (increased resistance). Continue to advance the needle within the ligament until there is a fall in resistance. Remove the stylet. Collect the first 2 ml of CSF in collection tube 1 and further 6 ml in collection tube 2 (collection tubes to be used: Sarstedt, cat nr: 62.554.502).

### 10.2.5 End of Procedure

After all CSF has been collected, the needle will be removed, the site cleaned and a bandage applied.

### 10.2.6 CSF processing and shipment

Freshly collected CSF must be kept at room temperature (RT) but should be centrifuged within 1 hour of collection at 2000 xg, 10 min, RT. Immediately after centrifugation the respective supernatants should be transferred to fresh tubes (Sarstedt, cat nr: 62.554.502) and tubes inverted once. The CSF should then be divided into 500 µl aliquots (Sarstedt; tubes cat nr: 72.703, lids cat nr: 65.716) and immediately stored at approximately -80°C.

Coding of aliquots from collection tube 1: CT1_1, CT1_2, …

Coding of aliquots from collection tube 2: CT2_1, CT2_2, …

The reason for splitting up the CSF at collection into 2 separate tubes is to ensure that the actual CSF sample to be analysed is not contaminated with tissue, blood, etc. So all analyses should be performed from the 2nd collection tube. Nevertheless, CSF from the 1st collection tube will still be kept as this might proof valuable for additional analyses.

All aliquots (from collection tube 1 and 2) will be shipped on dry ice to the central laboratory, from where they will be shipped in batches to the biobank.

[redacted]

## 10.4 CLINICAL EVALUATION OF LIVER INJURY

### 10.4.1 Introduction

Alterations of liver laboratory parameters, as described in section 5.2.2.1 (Adverse Events of Special Interest), are to be further evaluated using the following procedures:

### 10.4.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient´s repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, and bilirubin (total and direct) will be evaluated by local laboratory and results are made available to the investigator and to BI as soon as possible. If in such a case ALT and/or AST ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to BI as soon as possible.

In addition,

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the "DILI checklist" provided in the ISF
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the "DILI checklist" provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the "DILI checklist" provided in the ISF;

and report these via the CRF.

Assessment of additional lab parameters:

*Clinical chemistry*
alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, triglycerides

*Serology*
Hepatitis A (Anti-IgM, Total), Hepatitis B (HbsAg, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Total), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)

*Hormones, tumormarker*
TSH

*Haematology*
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.

- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and / or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

| | | |
|---|---|---|
| **Number of global amendment** | | 1 |
| **Date of CTP revision** | | 14 Oct 2014 |
| **EudraCT number** | | 2013-005031-24 |
| **BI Trial number** | | 1289.5 |
| **BI Investigational Product(s)** | | BI 409306 |
| **Title of protocol** | | A multi-centre, double-blind, parallel-group, randomized controlled study to investigate the efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with Alzheimer's Disease |
| | | |
| **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** | | Synopsis |
| **Description of change** | | Clarification of main criteria for inclusion |
| **Rationale for change** | | To make synopsis consistent with changes and clarifications throughout the protocol. |
| **Section to be changed** | | Flow Chart |
| **Description of change** | | Flow Chart replaced for clarification and to include changes throughout the protocol. The neuropsychological assessment schedule was adapted. |
| **Rationale for change** | | Clarifications and additional testing as well as changes in Visit Schedule as recommended by authority feedback. |
| **Section to be changed** | | Abbreviations |

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|---|---|---|
| **Number of global amendment** | | 1 |
| **Description of change** | | Missing abbreviations were added |
| **Rationale for change** | | To make section consistent the protocol |
| **Section to be changed** | | 2.3 |
| **Description of change** | | Rationale for suicidal monitoring was clarified |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 2.3 |
| **Description of change** | | “of short duration” was added |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.1 and 6.2.3 |
| **Description of change** | | Follow-up period was extended to 4 weeks |
| **Rationale for change** | | To be aligned with project standards |
| **Section to be changed** | | 3.2 |
| **Description of change** | | The rationale for the choice of a placebo group was added |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.3 |
| **Description of change** | | Re-screening was limited to exceptional cases on a case by case basis |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.3 |
| **Description of change** | | The wording was adapted due to changes of MMSE and CDR cut-offs |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.1.1 |
| **Description of change** | | Time frame for safety evaluation was specified |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.3.1 |
| **Description of change** | | The reference to the IWG criteria was changed to the newest available version, the reference to DSM(V) was removed, “and/or informant” was added |
| **Rationale for change** | | Update and clarification |
| **Section to be changed** | | 3.3.2 |
| **Description of change** | | The cut-off for the MMSE was changed and a cut-off for the global CDR-score was introduced |
| **Rationale for change** | | Based on scientific advice from external experts the new cut-offs describe the target population (see section 3.3.1) more appropriately |
| **Section to be changed** | | 3.3.2 |
| **Description of change** | | The time period for confirmation of abnormal AD biomarker was added to the wording of the criterion. |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.3.2 and 8.1 |

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| **Number of global amendment** | | 1 |
| **Description of change** | | Inclusion Criterion #7 and #8 were changed. The option of consent by a legal representative was deleted throughout the CTP |
| **Rationale for change** | | To be in accordance with ICH-GCP |
| **Section to be changed** | | 3.3.3 |
| **Description of change** | | The medical conditions listed in exclusion #4 were clarified |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.3.3 |
| **Description of change** | | The unit of GFR was changed from<br>ml/min to<br>ml/min/1.73m$^2$ |
| **Rationale for change** | | A typographical error was corrected |
| **Section to be changed** | | 3.3.3 |
| **Description of change** | | Ex# 10 now includes DSM-V |
| **Rationale for change** | | Clarification to meet project standards |
| **Section to be changed** | | 3.3.3 |
| **Description of change** | | Exclusion criterion #11 was reworded from<br>HIV infection confirmed by a central lab test<br>to<br>Known history of HIV infection. |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.3.3 |
| **Description of change** | | Exclusion criterion #12 was removed |
| **Rationale for change** | | Already covered by Exclusion criterion #1 |
| **Section to be changed** | | 3.3.3 |
| **Description of change** | | Exclusion criterion #13: The acceptable methods for birth control for female patients of child-bearing potential were changed |
| **Rationale for change** | | Clarification based on authority feedback |
| **Section to be changed** | | 3.3.3. |
| **Description of change** | | An additional exclusion criterion “For male patients. Men who are able to father a child, unwilling to be abstinent or to use an adequate form of effective contraception for the duration of study participation and for at least 28 days after treatment has ended” was added. |
| **Rationale for change** | | Based on authority feedback |
| **Section to be changed** | | 3.3.3 |
| **Description of change** | | “or dementia” was deleted from Exclusion #1 |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.3.3 |
| **Description of change** | | Exclusion #16: The list of medications prohibited 3 months prior to randomisation was reworded |

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| **Number of global amendment** | | 1 |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 3.3.3 |
| **Description of change** | | Known hypersensitivity to drug product excipients was added |
| **Rationale for change** | | Based on authority feedback |
| **Section to be changed** | | 3.3.4.1 |
| **Description of change** | | "if" was added |
| **Rationale for change** | | A typographical error was corrected |
| **Section to be changed** | | 3.3.4.1 |
| **Description of change** | | ", for pre-specified PGx sampling" was deleted |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | Table 4.1:1 |
| **Description of change** | | Run-in group was removed because it is not a treatment group |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | Table 4.1.1:1 |
| **Description of change** | | Reference to run-in was removed |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 4.1.4 |
| **Description of change** | | "at approximately the same time every day" was added and "because they will receive new medication kits during the visits" was removed |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 4.1.7 |
| **Description of change** | | Storage conditions were updated to better match the STORM document |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 4.2.2.1 |
| **Description of change** | | "Agonist"<br>Was changed to<br>"Antagonist" |
| **Rationale for change** | | A typographical error was corrected |
| **Section to be changed** | | 4.2.2.1 |
| **Description of change** | | St. Johns wort, Carbamazepine, extracts from Ginko, artemisinin, enzalutamide, efavirenz, lopinavir, ritonavir, tipranavir, rifampicin were added to the list of prohibited medications |
| **Rationale for change** | | Relevant CYP2C19 inducers where excluded |
| **Section to be changed** | | 5.1.1 and 7.3.1 |
| **Description of change** | | NTB total score<br>Was replaced by<br>NTB total z-score |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 5.1.1 |

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| **Number of global amendment** | | 1 |
| **Description of change** | | Total CDR score was replaced by CDR-SB |
| **Rationale for change** | | Clarification, a typo was corrected |
| **Section to be changed** | | 5.2.2.1 |
| **Description of change** | | The paragraph “Worsening of suicidal ideation and behaviour” was deleted |
| **Rationale for change** | | Paragraph was included by error and contained misleading information |
| **Section to be changed** | | 5.2.2.2 |
| **Description of change** | | Wording on reporting of visual AEs moved from section 6.2.2 and changed to match project standards |
| **Rationale for change** | | To be aligned with project standards |
| **Section to be changed** | | 5.2.5.2 |
| **Description of change** | | Section 10.1.1 was updated to project wording |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 5.2.3 |
| **Description of change** | | Instructions for assessment of safety laboratory parameters were reworded to match project standards; Vitamin B12 and Folate were added to table 5.2.3: 1 |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 5.2.4 |
| **Description of change** | | ECGs will be transmitted to the vendor instead of being electronically stored at site only |
| **Rationale for change** | | Changed to be aligned with project standards |
| **Section to be changed** | | 5.2.5.3 |
| **Description of change** | | Assessment of C-SSRS by paper was added |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 5.3.1.1 |
| **Description of change** | | Sample handling instructions included in the lab manual were deleted |
| **Rationale for change** | | Clarification to avoid contradicting statements |
| **Section to be changed** | | 5.6 |
| **Description of change** | | Instructions for handling/destruction of CSF and biomarker samples were updated |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 5.6.1 |
| **Description of change** | | Duplicate text (instructions can be found in section 10.2) was deleted |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 6.2 |
| **Description of change** | | Instructions for neuropsychological assessments were reworded to match project standards. |
| **Rationale for change** | | Update of project standards |

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| **Number of global amendment** | | 1 |
| **Section to be changed** | | 6.2.1 |
| **Description of change** | | CDR, ADAScog$_{11}$, was added to the screening procedures |
| **Rationale for change** | | Reflection of changes made to procedures |
| **Section to be changed** | | 6.2.1. and 6.2.2 |
| **Description of change** | | Recommendations for patients with antidiabetic therapy were added to visits with neurocognitive assessments |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 6.2.2 |
| **Description of change** | | The option of doing the neuropsychological assessments on the last day of the screening period was added to the CTP |
| **Rationale for change** | | To increase feasibility, change based on investigator feedback received |
| **Section to be changed** | | 6.2.2 |
| **Description of change** | | Visit 4 was changed to be a clinic visit |
| **Rationale for change** | | Based on authority feedback |
| **Section to be changed** | | 6.2.2 |
| **Description of change** | | Wording on visual adverse events was moved to section 5.2.2.2 |
| **Rationale for change** | | Update according to project standards |
| **Section to be changed** | | 6.2.2 |
| **Description of change** | | Various changes were made to reflect the changes made throughout the protocol |
| **Rationale for change** | | Reflection of changes made to other sections of the protocol |
| **Section to be changed** | | 7.3 |
| **Description of change** | | The statement “No Per Protocol Set (PPS) analysis will be performed” was deleted. |
| **Rationale for change** | | Changed to be aligned with project standards |
| **Section to be changed** | | 7.5 |
| **Description of change** | | Randomisation ratio was corrected |
| **Rationale for change** | | Correction of a typographical error |
| **Section to be changed** | | 7.6 |
| **Description of change** | | !"# $%&'()*+#',-. /$)"0,'/-1 *2 )"# 1)30. &*/#, /'1 '00#0 |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 8.7 |
| **Description of change** | | Section was removed |
| **Rationale for change** | | Section only to be included if trial is run in Japan according to CTP template |
| **Section to be changed** | | 10.2 |
| **Description of change** | | The instructions for CSF puncture and handling |

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| **Number of global amendment** | | 1 |
| | | were clarified |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 10.4.2 |
| **Description of change** | | Serology was added and is to be done in case of reported liver injury and typos were corrected. |
| **Rationale for change** | | To meet SOP requirements |

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| **Number of global amendment** | | 2 |
| **Date of CTP revision** | | **22 Dec 2014** |
| **EudraCT number** | | 2013-005031-24 |
| **BI Trial number** | | 1289.5 |
| **BI Investigational Product(s)** | | BI 409306 |
| **Title of protocol** | | A multi-centre, double-blind, parallel-group, randomized controlled study to investigate the efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with Alzheimer's Disease |
| | | |
| **To be implemented only after approval of the IRB/IEC/Competent Authorities** | | ☐ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only** | | ☒ |
| | | |
| **Section to be changed** | | 3.3.2 |
| **Description of change** | | Reference added |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | Table 4.1.1: 1 |
| **Description of change** | | Source of IMP was corrected |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 4.1.4, 6.2.1 - 6.2.3, 10.4.2 |
| **Description of change** | | Requirements to take study drug fasted were removed. Now drug can be taken with or without food. |
| **Rationale for change** | | Data from food interaction study (trial 1289.22) show no clinically relevant food interaction with BI 409306 |
| **Section to be changed** | | 4.2.2.1 |
| **Description of change** | | Use of strong or moderate CYP3A4 inhibitors are |

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| **Number of global amendment** | | 2 |
| | | also prohibited |
| **Rationale for change** | | Clarification that the use of strong or moderate CYP3A4 inhibitors is prohibited. While the contribution of CYP3A4 to the metabolism of BI 409306 is minor, there is no data available regarding the potential effect of CYP3A4 inhibitors on exposure of BI 409306. Therefore such medications could interfere with the investigational product as described in Section 3.3.4.1. |
| **Section to be changed** | | 5.2.2.2 |
| **Description of change** | | Follow-up period changed to 28 days |
| **Rationale for change** | | Correct a typo |
| **Section to be changed** | | Table 5.2.3: 1 |
| **Description of change** | | Additional routine safety lab parameters added |
| **Rationale for change** | | Completeness of safety lab panel |
| **Section to be changed** | | 6.2.1 |
| **Description of change** | | Removed: Recommendation to perform study procedures in the order as listed in the FC removed |
| **Rationale for change** | | This applies only to the neuropsychological assessments and not in general to all procedures. |
| **Section to be changed** | | 6.2.3 |
| **Description of change** | | Follow-up visit is a mandatory clinic visit |
| **Rationale for change** | | Correct typo |
| **Section to be changed** | | 7.2 |
| **Description of change** | | Specification of baseline visit added |
| **Rationale for change** | | Clarification |
| **Section to be changed** | | 7.3.3 |
| **Description of change** | | Residual effect period is 7 days |
| **Rationale for change** | | Correct typo |
| **Section to be changed** | | 10.2.6 |
| **Description of change** | | Samples will be shipped to the central lab and not directly to the analytical lab |
| **Rationale for change** | | Clarification - sample logistics adjusted |
| **Section to be changed** | | Section 11, description of change for 3.3.3 |
| **Description of change** | | Adjust section with contraception of male patients |
| **Rationale for change** | | Correct typo |

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| **Number of global amendment** | | 3 |
| **Date of CTP revision** | | **03-Aug-2015** |
| **EudraCT number** | | 2013-005031-24 |
| **BI Trial number** | | 1289.5 |
| **BI Investigational Product(s)** | | BI 409306 |
| **Title of protocol** | | A multi-centre, double-blind, parallel-group, randomized controlled study to investigate the efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with Alzheimer's Disease |
| | | |
| **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** | | Synopsis; Sections 2.2; Section 2.3; Section 3.3.2. |
| **Description of change** | | Specifying the definition of eligible patients |
| **Rationale for change** | | According to feedback from the investigators prodromal patients usually ask for treatment and sometimes take available AD medication despite the fact that there are no treatments registered for prodromal AD. In order to avoid unnecessary limitation to the recruitment we allow patients who previously took AD treatment to enter the trial. |
| **Section to be changed** | | Synopsis; Flowchart; Section 5.1; Section 6.2, Section 9.1 |
| **Description of change** | | Removal of the following neuropsychological assessments<br>- MMSE at Visit 3, 5 and EOT/ED<br>- MCI-ADSC-ADL at visit 5 |

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| **Number of global amendment** | | 3 |
| | | - ADCS-ADL completely<br>- ADAS-cog$_{11}$ at Visit 5 |
| **Rationale for change** | | The number of neuropsychological scales was reduced to reduce patient burden during the visits. As many of the items of the removed scales are part of the remaining assessment, the clinical validity of the primary and secondary analyses of the trial is not impacted. |
| **Section to be changed** | | Synopsis |
| **Description of change** | | "disposition" replaced by "deposition" |
| **Rationale for change** | | typo |
| **Section to be changed** | | Flowchart; Section 3.3.3 (ex. #1); Section 5.3.2.2.; Section 6.2.1 |
| **Description of change** | | The use of a CCT to exclude other disorders causing prodromal AD is now allowed if not prohibited by local regulations |
| **Rationale for change** | | To allow patients with a contraindication for MRI (for instance pacemaker) to enter the study. |
| **Section to be changed** | | Section 3.3.3 Exclusion criteria #9 |
| **Description of change** | | Amending the definition of previous participation in studies of mild cognitive impairment and studies targeting Aß and tau therapies |
| **Rationale for change** | | Clarification; |
| **Section to be changed** | | Section 4.2.2.1 |
| **Description of change** | | The use of strong or moderate CYP3A4 inhibitors is now allowed. |
| **Rationale for change** | | Clinical data (trial 1289.23) did not show evidence for clinical significant changes in exposure to BI 409306 after CYP3A4 inhibition. |
| **Section to be changed** | | Section 4.2.2.1 |
| **Description of change** | | Restrictions added for intake of drugs for treatment of AD during trial participation |
| **Rationale for change** | | To clarify that patients with previous treatment with AD drugs are not allowed to intake this drugs during this trial |
| **Section to be changed** | | Table 5.2.3:1 |
| **Description of change** | | Deletion of "(Stix)" |
| **Rationale for change** | | Typo |
| **Section to be changed** | | Section 7.3.2 |
| **Description of change** | | ANCOVA analysis added. Reference to TSAP. |
| **Rationale for change** | | Clarification of analysis models for secondary endpoints with different number of data collection visits. |
| **Section to be changed** | | Section 10.4.2 |

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| **Number of global amendment** | | 3 |
| **Description of change** | | Clinical chemistry: “fasting” glucose added |
| **Rationale for change** | | Typo |

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| **Number of global amendment** | | 4 |
| **Date of CTP revision** | | **17-February 2017** |
| **EudraCT number** | | 2013-005031-24 |
| **BI Trial number** | | 1289.5 |
| **BI Investigational Product(s)** | | BI 409306 |
| **Title of protocol** | | A multi-centre, double-blind, parallel-group, randomized controlled study to investigate the efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with Alzheimer's Disease |
| | | |
| **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** | | ☒ |
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| **Section to be changed** | | Section 1.2. |
| **Description of change** | | Adding information that fluvoxamine, a strong inhibitor of CYP2C19 and CYP1A2 increased plasma exposure of BI 409306. |
| **Rationale for change** | | Include results from clinical DDI study 1289.35 |
| **Section to be changed** | | Section 3.3.3 Exclusion criteria #13 |
| **Description of change** | | Removal of hormonal contraception, which are moderate to strong CYP1A2 inhibitors, from the samples of acceptable methods of contraception. |
| **Rationale for change** | | Hormonal contraception may be a moderate CYP1A2 inhibitor which can lead to a multifold increased plasma exposure of BI409306 in poor metabolizer and therefore is excluded from concomitant use |
| **Section to be changed** | | Section 4.2.2.1 |
| **Description of change** | | Moderate or strong CYP1A2 inhibitors added to |

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| **Number of global amendment** | | 4 |
| | | the list of restricted medications |
| **Rationale for change** | | Moderate or strong CYP1A2 inhibitors may significantly increase plasma exposure of BI 409306 in poor metabolizers |
| **Section to be changed** | | 6.2.2 |
| **Description of change** | | Description of post dose Pk sampling added |
| **Rationale for change** | | Clarification; Visit 3 description to be consistent with the descriptions at Visit 6 |

**APPROVAL / SIGNATURE PAGE**

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**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Trial Statistician | [redacted] | 23 Feb 2017 16:52 CET |
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| Author-Clinical Pharmacokineticist | [redacted] | 23 Feb 2017 16:56 CET |
| Approval-Therapeutic Area [redacted] | [redacted] | 24 Feb 2017 00:21 CET |
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| Meaning of Signature | Signed by | Date Signed |
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