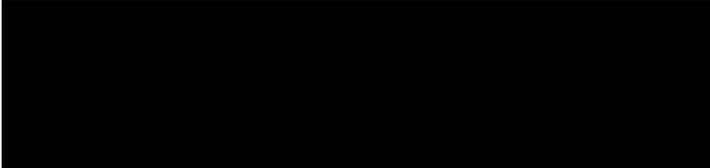
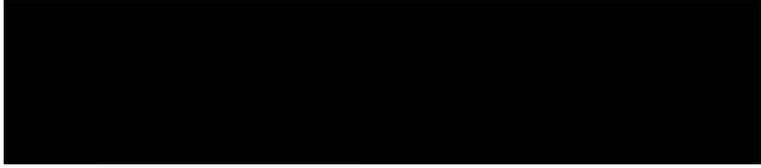
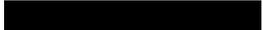


## Clinical Trial Protocol

Doc. No.: c02216748-08

<b>EudraCT No.:</b>	2013-005040-28
<b>BI Trial No.:</b>	1289.7
<b>BI Investigational Product:</b>	BI 409306
<b>Title:</b>	A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease.
<b>Clinical Phase:</b>	II
<b>Trial Clinical Monitor:</b>	 Phone:  Fax: 
<b>Co-ordinating Investigator:</b>	 Phone:  Fax: 
<b>Status:</b>	Final Protocol (Revised Protocol based on global amendment No.4)
<b>Version and Date:</b>	<b>Version: 5.0</b> <b>Date: 23 Feb 2017</b>
<b>Page 1 of 79</b>	
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## CLINICAL TRIAL PROTOCOL SYNOPSIS

<b>Name of company:</b> Boehringer Ingelheim		<b>Tabulated Trial Protocol</b>	
<b>Name of finished product:</b> NA			
<b>Name of active ingredient:</b> BI 409306			
<b>Protocol date:</b> 17 Oct 2014	<b>Trial number:</b> 1289.7		<b>Revision date:</b> 23 Feb 2017
<b>Title of trial:</b>	A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease		
<b>Co-ordinating Investigator:</b>	[REDACTED]		
	Phone: [REDACTED] Fax: [REDACTED]		
<b>Trial site(s):</b>	60		
<b>Clinical phase:</b>	II		
<b>Objective(s):</b>	To assess safety, tolerability and efficacy of different doses of BI 409306 compared to placebo in treatment of cognitive impairment due to AD		
<b>Methodology:</b>	Placebo -controlled, double-blind, randomised parallel-design comparison of 5 groups over 12 weeks of treatment.		
<b>No. of patients:</b>	<b>total entered:</b> 354 <b>each treatment:</b> 118 for placebo group and 59 for each treatment group		
<b>Diagnosis :</b>	Patients with diagnosis of mild Alzheimer's dementia according to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease and ICD10 and DSM V criteria		
<b>Main criteria for inclusion:</b>	The population will include male and female patients at least 55 years old with mild Alzheimer's dementia. A MMSE (Mini-Mental-State-Examination) score between 18-26, an ADAS-cog <sub>11</sub> score higher than 12 at screening, and a global CDR score of 1 or greater are required for inclusion. A caregiver has to be available for study site activities and on call by arrangement with the study site.		
<b>Test product(s):</b>	BI 409306		
<b>dose:</b>	10mg QD, 25mg QD, 50mg QD, 25mg BID		
<b>mode of admin.:</b>	Tablet, Oral		

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<b>Name of company:</b> Boehringer Ingelheim		<b>Tabulated Trial Protocol</b>	
<b>Name of finished product:</b> NA			
<b>Name of active ingredient:</b> BI 409306			
<b>Protocol date:</b> 17 Oct 2014	<b>Trial number:</b> 1289.7		<b>Revision date:</b> 23 Feb 2017
<b>Comparator products:</b>	Donepezil (Aricept®; randomisation to this treatment stopped via amendment 2), Placebo		
<b>dose:</b>	10mg QD (starting with 5 mg for the first 4 weeks)		
<b>mode of admin.:</b>	Tablet, Oral		
<b>Duration of treatment:</b>	12 weeks		
<b>Criteria for efficacy:</b>	<p>Primary endpoint:</p> <ol style="list-style-type: none"> <li>Cognition as measured by change from baseline in Neuropsychological Test Battery (NTB) total z-score after 12-week treatment.</li> </ol> <p>Secondary endpoints include:</p> <ol style="list-style-type: none"> <li>Change from baseline in ADCS-ADL total score after 12-week treatment</li> <li>Change from baseline in CDR-SB (Clinical Dementia Rating Scale Sum of Boxes) total score after 12-week treatment</li> <li>Change from baseline in ADAS-cog<sub>11</sub> (Alzheimer's Disease Assessment Scale-cognitive subscale) total score after 12-week treatment</li> </ol>		
<b>Criteria for safety:</b>	Adverse event reporting, vital signs, ECG (digital) and standard laboratory tests, Columbia-Suicide Severity Rating Scale (C-SSRS).		
<b>Statistical methods:</b>	<p>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, current AChEI use (Yes, No) 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.</p> <p>Descriptive statistics</p>		

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## FLOW CHART

Trial Period	Screening	Placebo Run-in Period	Treatment Period							Follow-up
			3 Baseline	4a <sup>12</sup>	4b <sup>12</sup>	4c <sup>12</sup>	5	6	EOT/ED <sup>11</sup>	
Visit	1	2		1	2	3	4	8	12	16
Studyweeks	-3	-2		1	2	3	4	8	12	16
Study-Day (or duration during screening/ run-in)	Duration 1-7 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 ████████████████████	X									
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 <sup>2</sup>	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 <sup>12</sup>	X <sup>12</sup>	X	X	X	X
Post Dose Heart Rate Procedure <sup>3</sup>			X							
Physical examination	X								X	
Neurological examination	X								X	
Resting ECG (digital)	X		X	X	X <sup>12</sup>	X <sup>12</sup>	X	X	X	X
Adverse events	X	X	X	X	X <sup>12</sup>	X <sup>12</sup>	X	X	X	X
Dispense trial medication <sup>4</sup>		X	X				X	X		
Collect study drug			X				X	X	X	
Medication Compliance Check			X				X	X	X	
Laboratory tests: Chemistry, haematology, urinalysis	X		X				X	X	X	X
Blood Glucose (Onsite) <sup>5</sup>	X		X				X		X	
████████████████████			█					█		
████████████████████			█						█	
Urine drug screen	X								X	
Urine pregnancy test <sup>8</sup>	X		X				X	X	X	
Vitamin B12 and folate	X								X	
RPR (FTA, if RPR positive)	X									
<b>Prospective Suicidality Monitoring</b>										
C-SSRS	X <sup>9</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>

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Trial Period	Screening	Placebo Run-in Period	Treatment Period							Follow-up
			3 Baseline	4a <sup>12</sup>	4b <sup>12</sup>	4c <sup>12</sup>	5	6	EOT/ED <sup>11</sup>	
Visit	1	2								FU
Studyweeks	-3	-2		1	2	3	4	8	12	16
Study-Day (or duration during screening/ run-in)	Duration 1-7 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									
CDR	X									
CDR-SB			X <sup>13</sup>				X		X	
NTB			X <sup>13</sup>				X		X	
ADCS-ADL			X <sup>13</sup>						X	
ADAS-cog <sub>11</sub>	X		X <sup>13</sup>						X	

<sup>1</sup> Prior to any study related procedure

<sup>2</sup> Results of a MRI or CCT-scan have to be available before visit 2. Please refer to exclusion #1 for further details. If a CCT or MRI cannot be obtained within the given visit window the duration of the screening period may be extended to a maximum of 21 days (if needed).

<sup>3</sup> 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. Additional vital signs 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 and section 6.2 for details).

<sup>4</sup> At all visits, the respective kit number has to be allocated to the patient via IRT

<sup>5</sup> Only for patients with antidiabetic therapy (see section 6.2 for details).

[REDACTED]

<sup>8</sup> 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.

<sup>9</sup> Columbia Suicide Severity Rating Scale baseline/screening scale

<sup>10</sup> Columbia Suicide Severity Rating Scale baseline since-last-visit scale

<sup>11</sup> 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).

<sup>12</sup> 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.

<sup>13</sup> 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.

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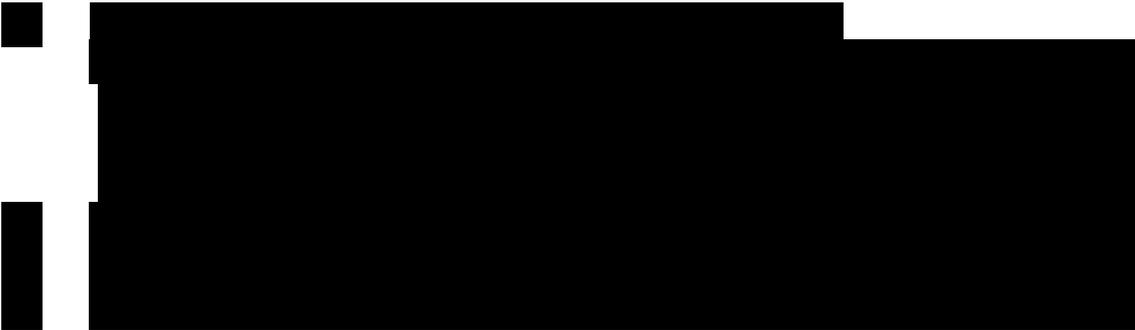
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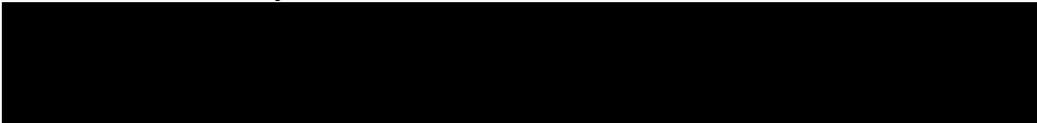
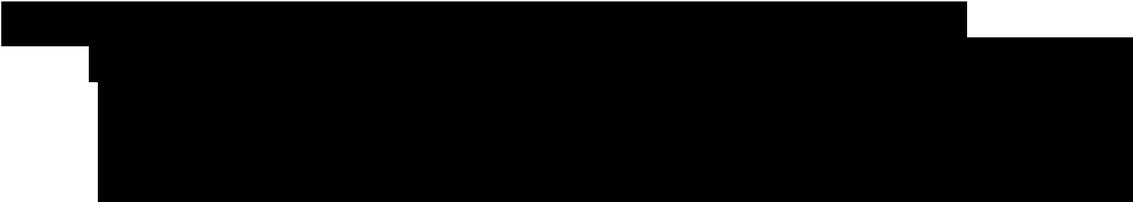
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LTP	Long Term Potentiation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MNDA	Myeloid cell nuclear differentiation antigen
MMSE	Mini-Mental-State-Examination
MST	Medical Subteam
MRI	Magnetic Resonance Imaging
NMDA-R	N-methyl-D-aspartate receptor
NTB	Neuropsychological Test Battery
OPU	Operative Unit
p.o.	per os (oral)
P-gp	P-glycoprotein
PCC	Protocol Challenge Committee
PDE9	Phosphodiesterase-9
█	█
PM	Poor metabolizer
POC	Proof of Concept
RPR	Rapid Plasma Reagin
PTM	Placebo to Match
PK	Pharmacokinetic
PM	Poor metabolizers
RDC	Remote Data Capture
REP	Residual Effect Period
RNA	Ribonucleic Acid
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
$t_{max,ss}$	Time to maximum plasma concentration (at steady state)
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
UM	Ultrarapid metabolizer

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## 1. INTRODUCTION

### 1.1 MEDICAL BACKGROUND

Dementia of Alzheimer's Type (DAT), a chronic progressive mental disorder caused by Alzheimer's Disease (AD), 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 25 million people 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 symptoms and signs [R10-5105].

In the early stage of the clinical disease manifestation cardinal symptoms are characterized by an impairment of episodic memory and other cognitive domains, like executive function, orientation and judgment. This is followed by a 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). With progression of the disease there is an increasing utilization of resources and medical care finally leading to the need of 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.

Currently approved AD treatment is purely symptomatic. Registered symptomatic treatment is possible with acetylcholinesterase inhibitors (AChE-Is) and memantine. Donepezil, galantamine, and rivastigmine are the three widely registered AChE-Is for the treatment of mild to moderate AD. Donepezil is also approved for severe AD in the US and Canada. Memantine, an uncompetitive NMDA-receptor antagonist, is registered in Europe and in the US for the treatment of moderate to severe AD.

Currently, AChE-Is in general and donepezil in particular can be regarded as gold standard for treatment of mild-to-moderate AD.

On cellular level AD is characterized by a progressive loss of synapses and neurons. Affected transmitter systems mainly include cholinergic and glutamatergic neurons. Glutamate as the major excitatory neurotransmitter in the human brain is most prominently associated with functions of memory formation and learning. Glutamatergic transmission is mediated by various receptors with the post-synaptic 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.

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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 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 that are superior to currently available treatment options (if any).

For full details on drug profile, please refer to the latest version of the IB [[c02101303](#)].

[REDACTED]

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### 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 that occurred shortly after dosing and mostly resolved within 1 h. 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  $12.9 \pm 4.4$  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.

### Visual Side Effects

In healthy volunteer trials, 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 resolved within 1 h. These visual side effects are in close connection to maximum BI 409306 plasma concentrations which sharply and steeply peak within the first 1-2 hours and then rapidly decline afterwards.

Two preclinical studies have been conducted to elucidate these phenomena. Since no data were available on PDE9 protein expression in the retina, an immunohistochemical analysis

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was performed in the first preclinical study in order to assess PDE9 expression in retina cells of rat and human tissue. This study demonstrated specific staining of PDE9 expression in rat and human retina tissue, confirmed via both positive tissue control (cerebellum and kidney) and via negative control (absence of primary antibody; isotype control). There was widespread distribution of PDE9 in the rat and human retina except the outer segment of the photoreceptor layer.

It is concluded from these experiments that PDE9 protein is expressed in retina and PDE9-inhibition leads to changes in retina physiology (ERG and ganglion cell activity), providing a likely explanation for the transient visual effects noted in human.

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## 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 AD.

This 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).

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, and its availability and use in the future will not reduce the medical need for symptomatic treatment. 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.

### 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 patients with the following criteria: mild dementia of Alzheimer's type aged at least 55 years, a MMSE between 18 and 26.

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.

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 risk 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 patients' safety.

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This is an experimental drug at an early stage of testing and therefore an individual benefit cannot be guaranteed. This is a trial of short duration. Therefore, the assignment to the placebo arm is not associated with a higher risk for the patient, and the study procedures (e.g. AD assessment, safety and suicidality monitoring etc.) may in fact benefit the patients e.g. intensive medical care, a potentially better knowledge of the underlying disease which may lead to a better handling of this disease. Also, this disease 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 the disease the patient may directly benefit from the drug development based on the results of this trial.

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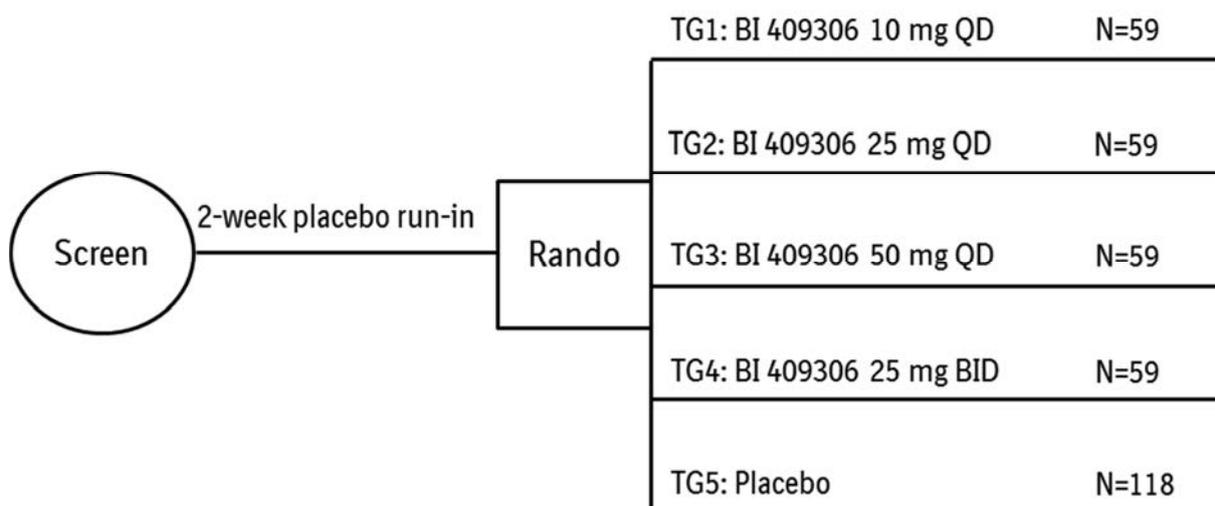
### 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

#### 3.1 OVERALL TRIAL DESIGN AND PLAN

This is a 12-week, multi-centre, randomised, double-blind, placebo controlled, parallel group comparison in patients with mild DAT.

In total, **354** patients with mild DAT who meet the entry criteria are planned to be randomised in this trial. The randomised treatment will be double blind. Each patient will be treated with one of the following forms of treatment: active treatment with BI 409306, or placebos (each patient will receive placebos to match each of the active treatments).

After obtaining informed consent, patients enter the screening period. All patients suitable after screening will undergo a 2-week single-blind placebo run-in period before randomisation. Patients who successfully complete the single blinded phase and who still meet the inclusion/exclusion criteria will be randomised to the 12-week double-blind treatment period at Visit 3 and will be assigned to one of the following 5 treatment groups: 10 mg, 25 mg, 50 mg BI 409306, 25 mg BI 409306 twice daily (BID), or placebo.



After the end of the double-blind treatment period, patients will be followed up for 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

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Procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, ordering the materials as needed for the trial, ensuring 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 service provider to support the following tasks related to the neuropsychological assessments: necessary rater prequalification, rater training (online and at investigator meeting), provision of rater materials and central review of assessments (see [section 8.2](#) for details).

Central laboratory and central ECG service vendors 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 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, 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 are screening positive 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 crossover design.

Treatment with BI 409306 will be compared to treatment with placebo.

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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) [[R11-5045](#)].

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 be sufficient to assess the efficacy, tolerability and safety of BI 409306.

The data collected in this double-blind, randomized, placebo-controlled trial are standard in this indication and will provide important information in terms of efficacy and safety on the use of BI 409306 maintenance treatment in patients with mild to moderate AD.

Independent raters for efficiency and AE are strongly recommended because the drug has known side effects which may inadvertently bias the trial team doctors who see the patients for visits. Please refer to section [6.2](#).

### 3.3 SELECTION OF TRIAL POPULATION

Untreated male and female patients, at least 55 years old, with diagnosis of mild Dementia of Alzheimers' Type (DAT) will be randomised. Recruitment will be competitive and participating sites are expected to enter at least **354** 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 [Sections 6.2](#) and [7.3](#) for details). Patients who discontinue following randomisation 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. 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.

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

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 the diagnosis of mild Alzheimer's Dementia (according to the Core Clinical Criteria of the recommendations from the National Institute on Aging-Alzheimer's Association workgroups [[R13-4115](#)] on diagnostic guidelines for Alzheimer's Dementia) will be included.

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### 3.3.2 Inclusion criteria

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

1. Diagnosis of mild Alzheimer's Dementia according to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease (see [section 3.3.1](#)).
2. Mini-Mental State Examination (MMSE) score of 18-26, an Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog<sub>11</sub>) score > 12 and a global CDR score of 1 or greater at screening.
3. 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.
4. Patients must have a reliable study partner (per investigator judgement for instance a family member, partner etc., guardian (must be always the same person)) who is in close contact with the patient, available on call and who is able to contribute to the assessment of the ratings of the functional endpoints including CDR-SB at specific study visits as stated in the [flow chart](#). This person will be able to communicate in the language in which the patient is being assessed and should also serve as a backup contact for the study site. The study partner must sign a separate informed consent form which describes their contributions during the study.
5. 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.
6. Previous use of AD medications (AChEIs, memantine) is allowed up 3 month prior to screening. Patients who are currently taking AChEIs are eligible as long as they have been using a stable dose for at least 3 months prior to screening and no change is foreseen for the duration of the study. This dose must be consistent with the product label in the concerned country. Patients currently taking memantine are excluded. .
7. Male or female patients at least 55 years of age. 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.]) at discretion of the investigator.

### 3.3.3 Exclusion criteria

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

1. Dementia secondary to other disorders (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. 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

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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 haemorrhage 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. History or diagnosis 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 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 (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 manifest hyperthyroidism.
  - f. Unstable/uncontrolled major depression
  - g. Significant pulmonary disease predisposing to hypoxia.
  - h. Immunological disorder such as per investigator judgement clinically significant allergies, Lupus erythematoses, or scleroderma.
  - i. Uncontrolled/Unstable haematological disease (regardless of cause) 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 as a GFR < 30 mL/min/1.73 m<sup>2</sup> in the screening central lab report.
6. Neurological disease (other than DAT such as: Lewy body dementia – primary diagnosis, Huntington's disease, Parkinson's Disease, encephalitis, epilepsy, vascular or multi-infarct dementia, stroke, congenital mental deficiency, multiple sclerosis) and psychiatric disorders such as schizophrenia, or mental retardation.
7. Any suicidal behaviour in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).

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8. Any suicidal ideation of type 4 or 5 in the 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/DAT within three months prior to screening. Having received active treatment in any other study targeting disease modification of AD like A $\beta$  immunization and tau therapies. Previous participation in studies with non-prescription medications, vitamins or other nutritional formulations is allowed.
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. Bodyweight < 50 kg.
13. Planned elective surgery requiring general anaesthesia, or hospitalisation for more than 1 day (requiring an overnight stay) during the study period.
14. Pre-menopausal women (last menstruation  $\leq$  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).
15. 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.
16. Use of any investigational drug or procedure within 3 months or 6 half-lives (whichever is longer) prior to randomisation.
17. The following drugs are prohibited for 3 months prior to randomisation and for the duration of the trial:
  - a. tricyclic antidepressants,
  - b. antidepressants that are monoamine oxidase inhibitors,

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- c. neuroleptics with moderate or greater anticholinergic potency (eg, 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.](#)

18. 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 screening
19. Any other clinical condition that, in the opinion of the investigator, would jeopardize patient safety while participating in this clinical trial
20. Incompliance with study drug intake defined as a compliance <75% during the run-in phase
21. Clinically significant uncompensated hearing loss in the judgement of the investigator. Use of hearing aids is allowed.
22. Known hypersensitivity to the drug product excipients (gelatin, povidone K25, 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).
- 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.
- If the patient experiences sinus tachycardia (defined as resting heart 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. Heart rate is generally to be measured in a supine position after 5 min rest. See also [Section 5.2.5.](#)
- The patient exhibits serious suicidality, in the clinical judgement of the investigator or according to criteria below:

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- 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 are being violated, or if the patient fails to comply with the protocol (e.g. nonattendance at study assessments).

Patients who drop out during screening or during placebo run-in phase prior to randomisation (Visit 3) will be considered as screening failures. Data will be collected for signed IC for the study [REDACTED] demographics, AE, concomitant medications and randomisation and will be recorded in the eCRFs. No further follow-up is required.

Patients who discontinue or withdraw from the study after randomisation (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 drop out during screening or during placebo run-in phase prior to randomisation (Visit 3) will be considered a screening failure. They must be recorded as screening failures in eCRFs and no further follow-up is required.

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

#### 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:

- Failure to meet expected enrolment goals overall or at a particular trial site,
- Emergence of any efficacy/safety information that could significantly affect continuation of the trial and/or invalidate the earlier positive benefit-risk-assessment,
- 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).

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## 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 blind 2-week placebo run-in-period, patients who qualify according to inclusion and exclusion criteria will be randomised to one of the five following treatment groups of investigational drugs:

Table 4.1:1 Treatment groups

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

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Table 4.1:1 Treatment groups (continued)

5	Placebo	BI 10 mg PTM	1-0-0
		BI 25/50 mg PTM	1-0-1
		Donepezil 5/10mg PTM	0-0-1

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

Table 4.1.1: 1 BI 409306, 10mg

Substance:	BI 409306
Pharmaceutical form:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG 
Unit Strength:	10 mg
Daily Dose:	10 mg QD (1-0-0) in Treatment Group 1,
Route of administration:	Per os
Posology:	QD
Duration of use:	12 weeks

Table 4.1.1: 2 BI 409306, 25mg and 50mg

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

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Table 4.1.1: 3 Placebo matching BI 409306, 10mg

Substance:	Placebo matching BI 409306
Pharmaceutical form:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG [REDACTED]
Unit Strength:	n.a.
Daily Dose:	n.a.
Route of administration:	Per os
Posology:	QD
Duration of use:	12 weeks

Table 4.1.1: 4 Placebo matching BI 409306, 25mg and 50mg

Substance:	Placebo matching BI 409306
Pharmaceutical form:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG [REDACTED]
Unit Strength:	n.a.
Daily Dose:	n.a.
Route of administration:	Per os
Posology:	QD or BID
Duration of use:	12 weeks

Table 4.1.1: 5 Placebo matching Donepezil 5mg and 10mg

Substance:	Placebo matching Donepezil HCl (Aricept <sup>®</sup> )
Pharmaceutical form:	Overcapsuled Tablet(s)
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG [REDACTED]
Unit Strength:	5 mg, 10 mg
Daily Dose:	5 mg (week 1-4), 10 mg (week 5-12) in Treatment Group 6
Route of administration:	Per os
Posology:	QD (0-0-1)
Duration of use:	12 weeks

Patients that have been randomised into the study prior to this protocol version being implemented, have a chance of being randomised to treatment with the formerly used active

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comparator donepezil. These patients will continue in the study. Please refer to table 4.1.1:6 for further details on Donepezil.

Table 4.1.1: 6 Donepezil 5mg and 10mg

Substance:	Donepezil HCl (Aricept <sup>®</sup> )
Pharmaceutical form:	Overcapsulated Tablet(s)
Source:	ESAI UK/EISAI
Unit Strength:	5 mg, 10 mg
Daily Dose:	5 mg (week 1-4), 10 mg (week 5-12)
Route of administration:	Per os
Posology:	QD (0-0-1)
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 randomisation 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 randomise 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 treatment 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-CSF 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 approximately 0.5 to 1 hour later than in plasma and decline monoexponentially 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

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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.

Following the run-in period patients will be randomised (Visit 3) to one of the 5 treatment arms.

Patients who qualify will be randomised to one of five treatment groups as follows:

- 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)

Patients that have been randomised into the study prior to this protocol version being implemented, have a chance of being randomised to treatment with the formerly used active comparator donepezil. Donepezil belongs to the class of AChEIs and represents the current standard of care for mild Alzheimer's Dementia. Therefore, we consider it to be safe and justifiable that these patients will stay on this treatment until end of the planned treatment duration. The double-blind treatment used in this trial will contain placebo for donepezil to keep the blind.

Medication will be dispensed in a double-blind manner. All patients will take 2 tablets in the morning and 1 tablet and 1 capsule in the evening.

Patients should be instructed not to take their trial medication on the morning of visits because they will receive trial medication during the visits. Patients who, by mistake, took medication on the morning of the visit should have the visit rescheduled as soon as possible, ideally on the following day.

Visits should preferentially be scheduled in the morning, at approximately the same time of the day. The actual visit date and time of study drug administration at the trial visit will be recorded in the eCRF.

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

At Visit 2, 3, 5 and 6 study medication will be provided to the patient. At each of these visits, 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.

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All patients who meet inclusion criteria will be assigned a placebo run-in kit at the beginning of the run-in period (Visit 2), and dispensing will occur just once. During the run-in period patients will take 4 placebo tablets/capsules daily (2 tablets in the morning and 1 tablet and 1 capsule in the evening) to mimic the dosing schedule during treatment period. At beginning of the run-in period (V2), patients should be instructed to take their trial medication twice daily with water. The first dose of study medication will be taken at the end of visit 2 under supervision of the investigator or site staff. At all following visits the investigational drug will be taken during the visit under supervision of the investigator or relevant site staff always after the blood samples were taken as described in [Section 5.2.3](#), [5.2.5](#).

Medication should be taken with or without food in the morning (except for visit days with neuropsychological assessments) and in the evening at approximately the same time every day. 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. Run-in medication assignment will be done through IRT.

Following the run-in period patients will be randomised (Visit 3) to one of the 5 treatment arms. IRT will allocate medication kit numbers at Visit 3, 5 and 6. The amount of trial medication dispensed and returned will be recorded on drug accountability forms.

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

The actual visit date and time of study drug administration at the trial visit will be recorded in the eCRF at each visit.

Patients should be instructed to take the tablets orally with water at approximately the same time every day in the morning 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 scheduled trial visits. 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 (██████████). The actual date and time of administration of the medication at the trial visit will be recorded in the eCRF.

The oral basic treatment with donepezil will be similar to the other treatments but will start with 5 mg once daily for the first 4 weeks of the trial. After then the dose will change to 10 mg once daily. Once this protocol version is implemented, no additional patients will be randomized to the Donepezil arm but patients already randomised to Donepezil will continue in the study.

Enrolment of patients currently on AChEIs can only be initiated after the IRT system has been re-programmed and activated accordingly. Sites will be notified by the CMLs.

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## 4.1.5 Blinding and procedures for unblinding

### 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.

Study medications will be administered double blinded. In order to maintain blinding in regard to each treatment, each dose will contain 3 tablets and 1 capsule daily in a double-dummy design, as shown in [Table 4.1:1](#). Placebo tablets / capsules are identical in the size and appearance to the corresponding active tablet / capsule and are combined with active drug tablets as needed in each treatment group to maintain the blinding.

After randomisation at Visit 3, patients, investigators and everyone involved in analysing or with an interest in this double-blind trial will remain blinded with regard to the randomised 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 randomisation 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 randomisation 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 prespecified group of users who are not involved into 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. Please refer to Section 4.1.5.2 for the rules regarding breaking the code for an individual or for all patients in emergency situations. The random code will be transferred to the trial data manager only after the Blinded Report Planning Meeting, and after locking of the trial database.

The randomisation codes will be provided to bioanalytics prior to last patient out to allow them to perform appropriate pharmacokinetic analytical determination. Bioanalytics will not disclose the randomisation 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

For blinded trials an emergency code break will be available to the investigator / pharmacist / investigational drug storage manager. This code break may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or if required to assure safety of trial participants. If the code break for a patient is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope and appropriate CRF page along with the date and the initials of the person who broke the code.

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

For details of packaging and the description of the label, refer to the ISF.

#### 4.1.7 Storage conditions

Study medication (BI 409306, Donepezil 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, <in exceptional cases, medication could already be sent to the site, before its activation via IVRS>
- 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.

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## 4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

There are no special emergency procedures to be followed.

### 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 are allowed as needed. Olanzapine or risperidone are allowed as needed for occasional intake in case of psychotic symptoms. If these above substances 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, methyl dopa, antiemetic's etc. However, the serotonin and combined serotonin/norepinephrine Re-Uptake Inhibitors (SSRIs/SNRIs) like fluoxetine, escitalopram, citalopram, sertalin, venlafaxin, duloxetine are allowed, but paroxetine is excluded. Other antidepressant drugs without anticholinergic 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 phosphodiesterase inhibitors (for example theophylline, 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. 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").

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 and of other prescribed treatment for AD after visit 1 is prohibited.

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#### 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.

### 4.3 TREATMENT COMPLIANCE

Patients will be asked to bring all trial medication containers (with or without any remaining tablets/capsules) with them to each trial visit. The tablets /capsules 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%. If compliance is outside this range, the patient should be carefully interviewed and, if necessary, re-informed about the purpose and the conduct of the trial. Unreliable patients should not be randomised at the discretion of the investigator.

Compliance during the randomised 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.

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## 5. VARIABLES AND THEIR ASSESSMENT

### 5.1 EFFICACY – PHARMACODYNAMICS

#### 5.1.1 Endpoint 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-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living) 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.

#### **Neuropsychological Test Battery (NTB)**

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)

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- 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-ADL**

This is a rating scale used to assess basic and instrumental activities of daily living. In the full version of the scale, 23 items are rated by the investigator using information supplied by the caregiver. Each item has a score range varying from 0-3 to 0-5. The sum score could range from 0 to 78. Higher scores indicate better function [[R97-3207](#)].

**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

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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.

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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 underlying disease or other pre-existing conditions

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

#### 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 eCRF, 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 following alterations of liver parameters:

- For patients with normal liver function at baseline:  
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 [section 10.2](#) 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 chapter [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 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](#).

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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. Therefore, all events reported within 7 days after the last trial medication will be considered on drug. 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) 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

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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

All safety parameters that will be determined during the trial conduct are listed in [Table 5.2.3: 1](#). All analyses will be performed by a central laboratory. Patients don't have to be fasted for the blood sampling for the safety laboratory. The respective reference ranges and details about sample handling and shipment will be provided in the ISF (Lab Manual).

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

Table 5.2.3: 1 Safety laboratory parameters – whole blood, serum or plasma

---

**Haematology**

- Haematocrit
- Haemoglobin
  - Reticulocyte Count (reflex test if Hb outside normal range)
- Red Blood Cells (RBC) / Erythrocytes
- WBC / Leukocytes
- Platelet Count / Thrombocytes
- Differential Automatic (relative and absolute count):  
Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes

---

**Clinical chemistry**

- Albumin
- Alkaline phosphatase
  - $\gamma$ -GT (gamma-glutamyl transferase) reflex test triggered by elevated alkaline phosphatase on two sequential measures
- ALT (alanine aminotransaminase, SGPT)
- AST (aspartate aminotransaminase, SGOT)
- Bicarbonate
- Bilirubin total, fractionated if increased
- Calcium
- Chloride
- Creatinine
- Vitamin B12
- Creatine kinase (CK)
- CK-MB, troponin (reflex tests if CK is elevated)
- Lactate dehydrogenase (LDH)
- Lipase
- Magnesium
- Phosphate
- Potassium
- Protein total
- Sodium
- Urea (BUN)
- TSH
- Folate

---

**Serology**

- HIV-antibody and Syphilis testing (Rapid plasma reagin (RPR), if RPR positive, then performing Fluorescent Treponemal Antibody test (FTA))
-

Table 5.2.3: 2 Safety laboratory parameters – urine

---

### Urinalysis

#### Semi quantitative

- Nitrite
- Protein
- Glucose
- Ketone
- Urine pH
- Leukocyte esterase (for WBC)\*

#### Urine Drug Screen

- Cannabis
- Cocaine
- Benzodiazepine
- Amphetamines
- Barbiturates
- Methadone
- Opiates
- Phencyclidine (PCP)

#### Human urine chorionic gonadotropin (HCG)

---

- Pregnancy testing (HCG, urine) will be performed in female patients of child bearing potential only according to the time points indicated in the [Flow Chart](#) or if required by local regulations more frequently or in plasma instead of urine

### 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 a 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. In this case the repeated ECG recordings will be used if quality was better.

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. Clinically relevant abnormal findings will be reported as baseline conditions or adverse events. Any ECG abnormalities will be carefully monitored and if necessary the subject will be removed from the trial and medically treated.

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All ECGs will be transmitted electronically to the central ECG vendor in order to enable a centralized and independent re-evaluation of all 12-lead ECGs (This will only be done if requested by the sponsor. Abnormalities detected during this centralised ECG evaluation will not necessarily qualify as AE.).

## 5.2.5 Assessment of other safety parameters

### 5.2.5.1 Physical examination (PE)

A 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, extremities, and nervous system will be performed. The physical examination will include examination of known and suspected sites of disease.

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

### 5.2.5.2 Vital signs

Vital signs (systolic/diastolic blood pressure (including orthostatic measurement as outlined below), supine pulse rate after 5 minutes rest) 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.
4. Repeat blood pressure and pulse rate measurements after standing 1 and 3 minutes.

Only at visit 3 the following additional vital signs 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 minutes post-dose. Pulse rate should be taken before the respective blood for PK sampling is drawn.
- Systolic/diastolic blood pressure (including orthostatic measurement) is to be done at baseline 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.

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If there is a finding which meets any withdrawal criterion (See Section [3.3.4.1](#)), the subject should be removed from study participation. The investigator may repeat the additional post-dose pulse rate assessment at any other visit at the timepoints described for Visit 3 if deemed clinically necessary for any reason.

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 behaviour 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 behaviour and five questions related to suicidal ideation, evaluated as either present or not. Patients presenting with any suicidal behaviour 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 Screen 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 the [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.

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[REDACTED]

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## 6. INVESTIGATIONAL PLAN

### 6.1 VISIT SCHEDULE

All trial visits should preferentially take place in the morning starting before 9:00 AM. Patients should be instructed not take trial medication on the morning of a clinic visit before attending the clinic.

All patients are to adhere to the visit schedule as specified in the [Flow Chart](#) (with time window for rescheduling).

If any visit has to be rescheduled, subsequent visits should follow the original visit date 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 adequate by the Investigator and BI Clinical Monitor.

### 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, , ADCS-ADL and ADAS-cog<sub>11</sub>) 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

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

This trial (1289.7) investigates patients with mild Alzheimer's dementia. In parallel BI is investigating the effect of BI 409306 in patients with cognitive impairment caused by the Alzheimer's disease in study 1289.5. It is expected that both trials share a high percentage of trial sites. One of the medically well-established non-invasive neurological assessments is the Mini Mental Stage Examination (MMSE) which evaluates the severity of cognitive impairment. This assessment is used in both trials as part of the eligibility assessments.

Patients who do not reach the required scores of  $<27$  in MMSE or CDR total score of greater than 1 are not eligible for this study and must be registered as screen failure in IRT. If the result of the MMSE and CDR would fulfill the requirements of the parallel trial 1289.5 and the patient and his study partner agree to alternatively participate in 1289.5 after giving a new consent then the results of the MMSE and CDR can be transferred into the database of 1289.5 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 1289.5 is no later than 7 days after the MMSE for 1289.7 was performed. The patient will then be registered as a new patient in the IRT of 1289.5. This does not apply to sites participating in only one of the 1289.5/1289.7 studies.

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

#### Visit 1 (screening)

- Patients must sign Informed Consent ( [REDACTED] ) before any study related procedures are performed.
- The patient should be recorded on the enrolment log and be registered in the IRT as a screened patient.
- Study procedures have to be completed according to the [Flow Chart](#).
- Demographics include age, educational level, current or past professional experience
- ECG and vital sign measurement will be performed.
- For diabetic patients with antidiabetic therapy: exclusion of hypoglycemia for the period of the neuropsychological assessment (documented plasma glucose concentration  $\geq 90$  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
- Blood pressure must always be measured before taking any blood sample.
- A complete physical examination and neurological examination.
- Laboratory samples will be collected as described in the flow chart.
- Assessment for MRI (if no pre-existing MRI or CT of the brain is already available (please refer to [inclusion criteria](#) for details)) must be scheduled in order that results are available prior to Visit 2
- Administer the following neuropsychological assessments in the following order:

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- MMSE
- CDR
- ADAS-cog<sub>11</sub>
- Administration of C-SSRS (baseline/screening scale)
- Once Visit 1 procedures are complete and laboratory results are received, inclusion/exclusion criteria must be reviewed again. If the patient is still eligible according to inclusion/exclusion criteria, the patient should be contacted to schedule next visit.
- If a patient does not meet inclusion/exclusion criteria the patient must be recorded in CRFs as a screen failure. Patient must be registered as screen failure in IRT.

### Visit 2 (Run-in period)

- Study procedures have to be completed according to the [Flow Chart](#).
- Blood pressure must always be measured before taking any blood sample.
- Contact IRT to obtain run-in medication kit number and dispense the medication to the patient
- Administration of C-SSRS (baseline since last visit scale)
- The intake of trial medication and handling of medication blisters should be discussed and trained with the patient and the caregiver. The first dose of trial medication should be taken by the patient after the neuropsychological assessments have been administered. **The first dose of the study medication should be taken under the supervision of the study staff.**
- Patients who fail the run-in period following Visit 2 procedures should be registered as a screen failure in the IRT.

## 6.2.2 Treatment period(s)

### Visit 3

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.

- Study procedures have to be completed according to the [Flow Chart](#).
- Collect returned run-in medication.
- Re-assessment of in/exclusion criteria including assessment of compliance of study drug intake.
- Neuropsychological assessments and collection of urine and blood for laboratory testing must be performed prior to administration of study medication.
- Blood pressure must always be measured before taking any blood sample.
- ECG will be performed
- Laboratory samples will be collected as described in [Flow Chart](#).

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- For diabetic patients with anti-diabetic therapy: exclusion of hypoglycemia for the period of the neuropsychological assessment (documented plasma glucose concentration  $\geq 90$  mg/dl (5mmol/l) at the beginning and directly after the assessment).
- Administer the following neuropsychological assessments in the following order:
  - CDR-SB
  - NTB
  - ADCS-ADL
  - ADAS-cog<sub>11</sub>
- Administration of C-SSRS (baseline since last visit scale)
- The intake of trial medication and handling of medication blisters should be discussed and (if deemed necessary) re-trained with the patient and the caregiver. The dose of trial medication should be taken by the patient after the neuropsychological assessments have been administered.
- Contact IRT to randomise patient and obtain medication kit numbers and dispense the medication to the patient (if neuropsychological testing was not performed according to the protocol patients should not be randomized, please refer to [inclusion criteria](#), #6).
- 
- Post dose vital signs assessment: 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 110 mins post-dose (15-25 mins, 25-35 mins, 35-55 mins, 70-110 mins post-dose). Pulse rate should be taken before the respective blood for PK sampling is drawn. Systolic/diastolic blood pressure (including orthostatic measurement) is to be done at baseline and at 70-110 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.
- Instruct patient NOT to take study medication on the morning of trial visits.

#### Visits 4, 5, 6 and EOT/ED

Visits 4, 5, 6 and EOT/ED are part of the treatment period.

#### 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.
- Administration of C-SSRS (baseline since last visit scale)
- The attendance of the study partner is not necessarily required during the visits 4a-c.
- Instruct patient NOT to take study medication on the morning of trial visits 5 and 6.

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### Visits 5, 6 and EOT/ED

- Study procedures have to be completed according to the [Flow Chart](#).
- Collect returned medication at every visit prior to dispensing new medication
- Neuropsychological assessments and collection of urine and blood for laboratory testing [REDACTED] 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  $\geq 90$  mg/dl (5mmol/l) at the beginning and directly after the assessment).
- Administer the following neuropsychological assessments in the following order:
  - CDR-SB (V5 and EOT)
  - NTB (V5 and EOT)
  - ADCS-ADL (EOT)
  - ADAS-cog<sub>11</sub> (EOT)
- Administration of C-SSRS (baseline since last visit scale)
- The intake of trial medication and handling of medication blisters should be discussed and (if deemed necessary) re-trained with the patient and the caregiver. The dose of trial medication should be taken by the patient after the neuropsychological assessments have been administered.
- [REDACTED]
- Blood pressure must always be measured before taking any blood sample
- Laboratory samples will be collected as described in [Flow chart](#).
- New medication kit must be dispensed at Visits 5 and Visit 6 and IRT must be contacted at those visits to obtain medication kit numbers to be dispensed.
- Instruct patient NOT to take study medication on the morning of next trial visits.
- Visit EOT/ED is the end of treatment visit. Study medication will not be taken at Visit EOT/ED.

### End of Treatment

End Of Treatment Visit will need to be performed for any patients who discontinue study medication, i.e. both for patients who complete the full 12-week treatment period and for patients who discontinue study medication early.

Patients who discontinue study medication early should be registered as withdrawn in the IRT, and patients who complete the full 12-week treatment period should be registered as completed in the IRT.

Assessments should be performed as mentioned in [Flow Chart](#) and the respective protocol sections.

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

For all patients completing the study according to protocol, a follow-up contact (Visit 8) with the patient should be done by the investigator at the end of the follow-up phase of 28 days. The attendance of the study partner is not necessarily required during the FU visit.

In case of premature discontinuation from the 12-week treatment period however, a Visit 7 / End of Treatment Visit should be performed within 7 days of last intake of study drug (if this visit occurs within the time window of a scheduled visit, the Visit 7 / End Of Treatment Visit will replace the scheduled visit) and the patient should return to Visit 8 (28 days after End Of Treatment Visit).

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## 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

### 7.1 STATISTICAL DESIGN – MODEL

#### 7.1.1 Design

This phase II trial is a multi-centre, double-blind, parallel-group, randomised, placebo- and active- 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 mild Alzheimer's Dementia. The primary endpoint is Neuropsychological Test Battery (NTB) response, defined as change from baseline in total z-score after 12-week treatment. Further analysis details are provided in Section 7.3 (Planned Analyses).

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).

The randomisation allocation ratio is 1:1:1:1: 2 of 10 mg, 25mg, 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 randomisation allocation ratio is modified from a traditional equal ratio where only about 14% 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 (Visit3) 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:

$H_{1-0}$ : 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

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

If the null hypothesis  $H_{1-0}$  is rejected in favor of  $H_{1-a}$ , 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.

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

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where  $\mu(d_i)$  denotes the mean response of NTB of the dose level  $i$  group,  $d_i$  denotes for dose levels  $i$ , for  $i = 1, 2, \dots, 4$  and  $\beta$ 's are the coefficients. The dose  $d_i$  will be treated as continuous variable.

Testing for linear dose response curve

H<sub>2-0</sub>:  $\beta_1 = 0, \beta_2 = 0$

H<sub>2-a</sub>:  $\beta_1 \neq 0, \beta_2 = 0$

If the null hypothesis H<sub>2-0</sub> is rejected in favor of H<sub>2-a</sub>, then the following test will be tested for quadratic dose response curve.

H<sub>3-0</sub>:  $\beta_2 = 0$

H<sub>3-a</sub>:  $\beta_2 \neq 0$

- 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<sub>4-0</sub>: The dose group with the peak response in respective model Mean NTB response = Mean NTB response of placebo

H<sub>4-a</sub>: The dose group with the peak response in respective model Mean NTB response  $\neq$  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

The data for patients on donepezil will be analysed using descriptive statistics.

All calculated p-values should be considered descriptive for the analysis. Therefore, no alpha correction will be carried out.

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

## 7.3 PLANNED ANALYSES

### Analysis set

#### **Treated Set**

The treated set (TS) will consist of all patients who were randomised and treated with at least one dose of study drug.

#### **Full Analysis Set**

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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 (Visit 3) 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 randomised 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 [[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 z-score after 12 weeks of treatment. The model will include fixed, categorical effects of treatment, visit, current AChEI use (Yes, No) 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<sub>11</sub> and ADCS-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.

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*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 the residual effect period after last treatment administration will be considered 'treatment-emergent'.*

*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.

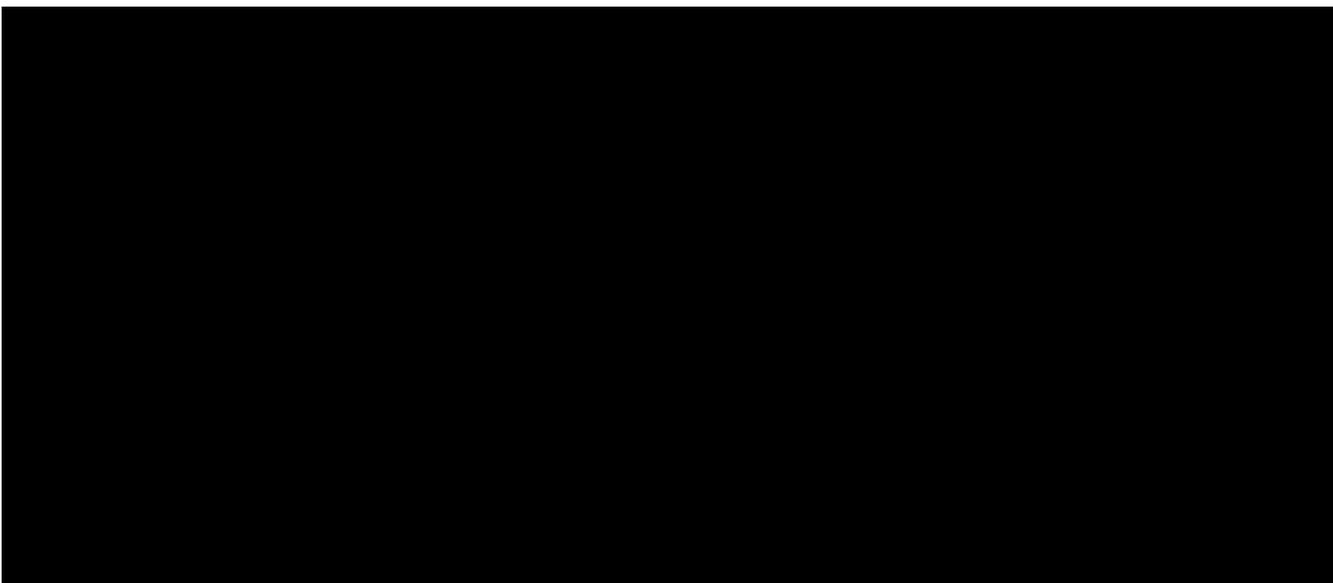
*Vital signs, ECG and other safety parameters at screening/run-in/baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.*

*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**

There is no interim analysis planned for this study.




#### 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 z-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 unblinding.

#### 7.5 RANDOMISATION

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

The randomisation will be stratified by current AChEI use (Yes,No).

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

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## 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 (Visit 3) in NTB total z-score after 12-week treatment. (See [section 7.2](#) for the details of hypothesis testing.) As previously mentioned, the randomisation allocation ratio of 1:1:1:1: 2 of 10 mg, 25mg, 50 mg, 25 mg BID of BI 409306 and placebo is used so that 33% of patients will be randomised 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 sizes 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	<b>0.475</b>	0.50	0.55	0.6	0.65
Power	80%	<b>80%</b>	80%	80%	80%	80%
n for each active treatment arm	59	<b>53</b>	48	40	34	29
n for placebo arm	118	<b>106</b>	96	80	68	58
Total	<b>354</b>	<b>318</b>	<b>288</b>	<b>240</b>	<b>204</b>	<b>174</b>

**Based on the calculations provided in Table 7.6:1 and recent data for trials using adjunct therapy, a sample size of 59 per active treatment arm and 118 for placebo arm was selected as adequate for this phase II proof of concept trial. This sample size would allow us to detect an effect size of 0.45 with 80% power, 2 sided alpha .05. Assuming a 10% dropout rate, this sample size would allow us to detect an effect size of 0.475 with 80% power and assuming a 20% dropout rate, this sample size would allow us to detect an effect size of 0.5 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 and if located in Japan the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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.

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## 8.2 DATA QUALITY ASSURANCE

In order to achieve a high level of standardized processes, data collection of efficacy and safety endpoints is coordinated centrally: [REDACTED]

[REDACTED] has been selected as service provider to support tasks related to the neuropsychological assessments. A detailed description of services can be found in the vendor contract. 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; for that purpose assessment procedures will be audio recorded

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.

Central lab analysis of safety lab

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.

For eCRFs all data must be derived from source documents.

### 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.

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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 [[c02101303](#)]. The current versions 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, *i.e. the CA*.

## **8.6 COMPLETION OF TRIAL**

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

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## 9.2 UNPUBLISHED REFERENCES

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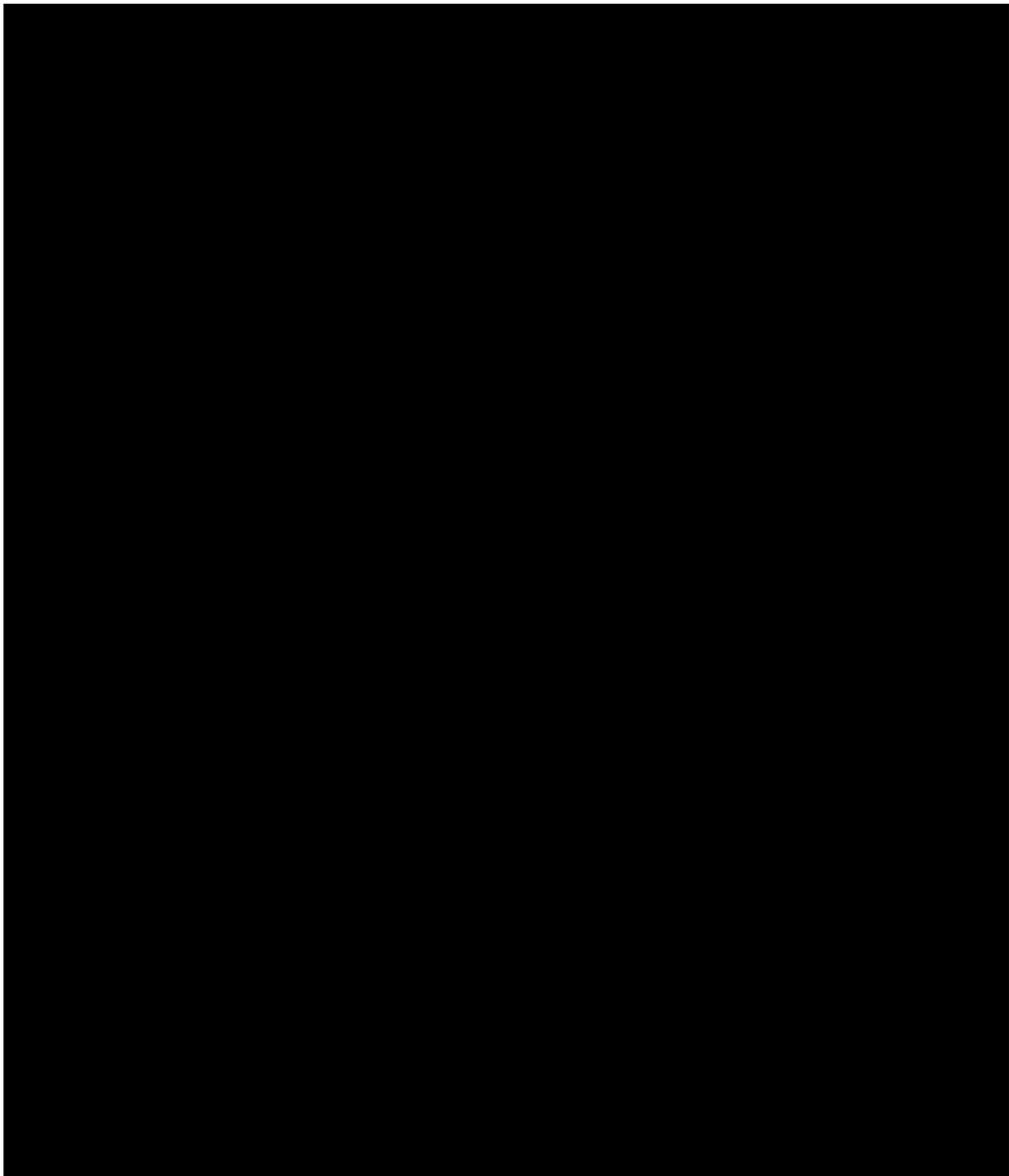
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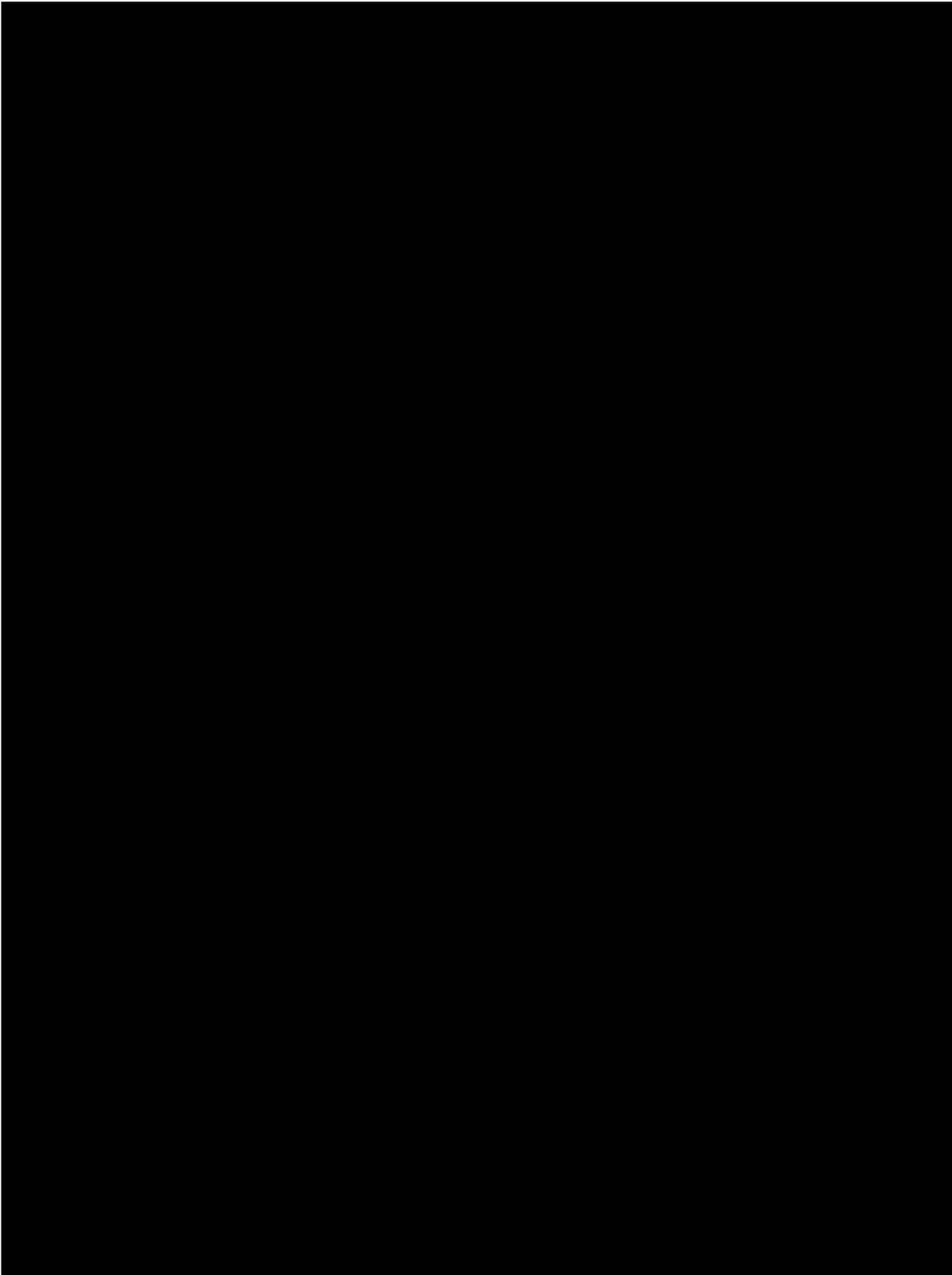
## 10. APPENDICES



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## 10.2 CLINICAL EVALUATION OF LIVER INJURY

### 10.2.1 Introduction

Alterations of liver laboratory parameters, as described in [Section 5.2.2.1](#) (Protocol-Specified Significant Events), are to be further evaluated using the following procedures:

### 10.2.2 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  $\geq 3$  fold ULN combined with an elevation of total bilirubin  $\geq 2$  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.

#### *Clinical chemistry*

alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin,  $\alpha$ -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,

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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).

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## 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

<b>Number of global amendment</b>		1
<b>Date of CTP revision</b>		22 Dec 2014
<b>EudraCT number</b>		2013-005040-28
<b>BI Trial number</b>		1289.7
<b>BI Investigational Product(s)</b>		BI 409306
<b>Title of protocol</b>		A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to donepezil and placebo in patients with cognitive impairment due to Alzheimer's Disease
<b>To be implemented only after approval of the IRB/IEC/Competent Authorities</b>		<input type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input checked="" type="checkbox"/>
<b>Section to be changed</b>		4.1.1
<b>Description of change</b>		The source of IMP was corrected
<b>Rationale for change</b>		Correction
<b>Section to be changed</b>		4.1.4, 6.1, 6.2.1, 6.2.2, 6.2.3
<b>Description of change</b>		Requirements to take study drug fasted were removed. Now drug can be taken with or without food.
<b>Rationale for change</b>		Data from food interaction study (trial 1289.22) show no clinically relevant food interaction with BI 409306

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<b>Number of global amendment</b>		1
<b>Section to be changed</b>		4.2.2.1
<b>Description of change</b>		Use of strong or moderate CYP3A4 inhibitors are now mentioned to be prohibited
<b>Rationale for change</b>		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.
<b>Section to be changed</b>		5.2.2
<b>Description of change</b>		Follow-up period changed to 28 days
<b>Rationale for change</b>		A typographical error was corrected
<b>Section to be changed</b>		6.2.1.
<b>Description of change</b>		The need for determination of blood glucose was removed from V2 description because no neuropsychological assessments will be done at V2
<b>Rationale for change</b>		Correction to align text with flowchart
<b>Section to be changed</b>		6.2.2.
<b>Description of change</b>		V5 was changed to V6
<b>Rationale for change</b>		A typographical error was corrected
<b>Section to be changed</b>		7.2
<b>Description of change</b>		The “highest dose group” was replaced by “the dose group with the peak response”
<b>Rationale for change</b>		A typo was corrected

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<b>Number of global amendment</b>		2
<b>Date of CTP revision</b>		27 Jul 2015
<b>EudraCT number</b>		2013-005040-28
<b>BI Trial number</b>		1289.7
<b>BI Investigational Product(s)</b>		BI 409306
<b>Title of protocol</b>		A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to donepezil and placebo in patients with cognitive impairment due to Alzheimer's Disease
<b>To be implemented only after approval of the IRB/IEC/Competent Authorities</b>		<input checked="" type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input type="checkbox"/>
<b>Section to be changed</b>		Title, Clinical Trial Protocol Synopsis, Sections 1.1, 2.1, 2.2, 3.1, 3.2, 3.3, 3.3.2, 3.3.3, 4.1, 4.1.1, 4.1.2, 4.1.3, 4.1.4, 4.1.7, 5.1.1, 5.1.2, 7.1, 7.5, 7.6
<b>Description of change</b>		The donepezil arm was dropped from the study and therefore reference to donepezil was removed. Patient number and treatment groups, inclusion criteria, trial objectives and description of IRT and IMP were adapted accordingly.
<b>Rationale for change</b>		AChEIs (including donepezil) are the standard treatment in the indication under study. Therefore, the study design was changed to allow both treatment-naïve patients and patients on standard of care to enter the study. With this change it will

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<b>Number of global amendment</b>		2
		be possible to analyse the treatment effect in the expected target population for the compound under study.
<b>Section to be changed</b>		Clinical Trial Protocol Synopsis, Flowchart, sections 6.2, 6.2.2
<b>Description of change</b>		ADCS-MCI-ADL was removed from the study, MMSE was removed from V3, V5 and V7, ADAS-cog <sub>11</sub> and ADCS-ADL were removed from V5
<b>Rationale for change</b>		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 are not impacted.
<b>Section to be changed</b>		Clinical Trial Protocol Synopsis, Section 7.3.1, 7.5
<b>Description of change</b>		Stratification factor current AChEI use (Yes, No) added to primary analysis model and randomisation.
<b>Rationale for change</b>		The study design was changed to allow treatment naïve and patients on the current standard of care to enter the study. This stratification factor was added to the randomization to ensure balance across treatment groups and added to the model to adjust for any potential treatment difference.
<b>Section to be changed</b>		Inclusion #8
<b>Description of change</b>		The criterion was deleted.
<b>Rationale for change</b>		The criterion contained only redundant information also mentioned in Exclusion criterion #1 (see below).
<b>Section to be changed</b>		Flowchart, 3.3.3, Exclusion criterion 1
<b>Description of change</b>		The use a CCT to exclude other disorders causing dementia is now allowed if not prohibited by local regulations
<b>Rationale for change</b>		To allow patients with a contraindication for MRI to enter the study
<b>Section to be changed</b>		3.3.3, Exclusion criterion 9
<b>Description of change</b>		Clarifying the definition of previous participation in studies of mild cognitive impairment and studies targeting Aβ and tau therapies
<b>Rationale for change</b>		Clarification
<b>Section to be changed</b>		4.2.2.1
<b>Description of change</b>		The use of strong or moderate CYP3A4 inhibitors is now allowed.

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<b>Number of global amendment</b>		2
<b>Rationale for change</b>		Clinical data (trial 1289.23) did not show evidence for clinical significant changes in exposure to BI 409306 after CYP3A4 inhibition.
<b>Section to be changed</b>		Section 7.2
<b>Description of change</b>		10 mg QD arm added to step 1, Spelling of NTB fixed
<b>Rationale for change</b>		Typos corrected
<b>Section to be changed</b>		Section 7.3.2
<b>Description of change</b>		ANCOVA analysis added. Reference to TSAP.
<b>Rationale for change</b>		Clarification of analysis models for secondary endpoints with different number of data collection visits.
<b>Section to be changed</b>		10.2.2
<b>Description of change</b>		“fasting” was added to glucose
<b>Rationale for change</b>		A typo was corrected.

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<b>Number of global amendment</b>		3
<b>Date of CTP revision</b>		01 Sep 2016
<b>EudraCT number</b>		2013-005040-28
<b>BI Trial number</b>		1289.7
<b>BI Investigational Product(s)</b>		BI 409306
<b>Title of protocol</b>		A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to donepezil and placebo in patients with cognitive impairment due to Alzheimer's Disease
<b>To be implemented only after approval of the IRB/IEC/Competent Authorities</b>		<input checked="" type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input type="checkbox"/>

<b>Section to be changed</b>		Synopsis, 3.1, 3.3, 7.6
<b>Description of change</b>		Sample size was changed to a total of N=354 allow to detect an effect size of 0.45 with 80% power, 2 sided alpha .05
<b>Rationale for change</b>		To power the study for a smaller effect size.

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<b>Number of global amendment</b>		4
<b>Date of CTP revision</b>		23 Feb 2017
<b>EudraCT number</b>		2013-005040-28
<b>BI Trial number</b>		1289.7
<b>BI Investigational Product(s)</b>		BI 409306
<b>Title of protocol</b>		A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to donepezil and placebo in patients with cognitive impairment due to Alzheimer's Disease
<b>To be implemented only after approval of the IRB/IEC/Competent Authorities</b>		<input type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input checked="" type="checkbox"/>

<b>Section to be changed</b>		Title Page
<b>Description of change</b>		██████████ replaced by ██████████
<b>Rationale for change</b>		Change of responsibilities
<b>Section to be changed</b>		Section 1.2.
<b>Description of change</b>		Adding information that fluvoxamine, a strong inhibitor of CYP2C19 and CYP1A2 increased plasma exposure of BI 409306.
<b>Rationale for change</b>		Include results from clinical DDI study 1289.35
<b>Section to be changed</b>		Section 3.3.3 Exclusion criteria #14
<b>Description of change</b>		Removal of hormonal contraception, which are moderate to strong CYP1A2 inhibitor, from the samples of acceptable methods of contraception.
<b>Rationale for change</b>		Hormonal contraception may be a moderate CYP1A2 inhibitor which can lead to a multifold increased plasma exposure of BI409306 in poor

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<b>Number of global amendment</b>		4
		metabolizer and therefore is excluded from concomitant use.
<b>Section to be changed</b>		Section 4.2.2.1
<b>Description of change</b>		Moderate or strong CYP1A2 inhibitors added to the list of restricted medications
<b>Rationale for change</b>		Moderate or strong CYP1A2 inhibitors may significantly increase plasma exposure of BI 409306 in poor metabolizers

**Proprietary confidential information.**

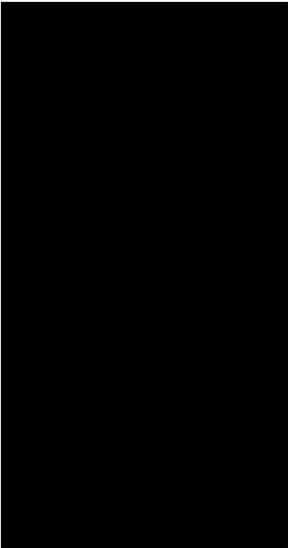
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**APPROVAL / SIGNATURE PAGE**
**Document Number: c02216748**
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**Document Name: clinical-trial-protocol-revision-04**

**Title:** A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy, safety and tolerability of orally administered BI 409306 during a 12-weeks treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease.

**Signatures (obtained electronically)**

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		23 Feb 2017 17:01 CET
Author-Trial Statistician		23 Feb 2017 17:02 CET
Approval-Clinical Pharmacokinetics		23 Feb 2017 17:09 CET
Approval-Therapeutic Area 		24 Feb 2017 00:18 CET
Approval-Team Member Medicine		24 Feb 2017 18:29 CET
Verification-Paper Signature Completion		03 Mar 2017 09:15 CET

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

<b>Meaning of Signature</b>	<b>Signed by</b>	<b>Date Signed</b>
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