CLINICAL TRIAL PROTOCOL

	Document Number:	**c03632269-05**
EudraCT No.:	2015-005438-24	
BI Trial No.:	1346.23	
BI Investigational Product(s):	BI 425809	
Title:	A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy and safety of orally administered BI 425809 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease.	
Brief Title:	BI 425809 in patients with cognitive impairment due to Alzheimer's Disease	
Clinical Phase:	II	
Trial Clinical Monitor:	Phone: , Fax:	
Coordinating Investigator:	Phone: Fax:	
Status:	Final Protocol (Revised Protocol (based on global amendment No. 4))	
Version and Date:	**Version: 5.0**	**Date: 12 Jul 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**NA**	
Name of active ingredient:		**BI 425809**	
Protocol date: 14 Apr 2016	**Trial number:** 1346.23		**Revision date:** 12 Jul 2018

Title of trial:	A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy and safety of orally administered BI 425809 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease.
Coordinating Investigator:	Phone:
Trial site(s):	Multi-centre, multi-national trial
Clinical phase:	II
Objective(s):	To assess safety, tolerability and efficacy of different doses of BI 425809 compared to placebo in treatment of cognitive impairment due to Alzheimer's Disease
Methodology:	Placebo-controlled, double-blind, double-dummy, randomized, parallel-group design comparison of 5 treatment groups over 12 weeks of treatment
No. of patients:	~950 enrolled
total entered:	~585
each treatment:	~117
Diagnosis :	Patients with diagnosis of mild-to moderate Alzheimer's Disease Dementia according to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease
Main criteria for inclusion:	The population will include male and female patients at least 55 years old with mild-to-moderate Alzheimer's Disease Dementia. A MMSE (Mini-Mental-State-Examination) score between 15-26 is required for inclusion. A caregiver

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**NA**	
Name of active ingredient:		**BI 425809**	
Protocol date: 14 Apr 2016	**Trial number:** 1346.23		**Revision date:** 12 Jul 2018

	has to be available for study site activities and on call by arrangement with the study site
Test product(s):	BI 425809
dose:	2mg QD, 5mg QD, 10mg QD, 25mg QD
mode of administration:	Tablet, oral
Comparator products:	Placebo matching BI 425809 1mg and 5mg And Placebo matching BI 425809 25 mg
dose:	Not applicable
mode of administration:	Tablet, oral
Duration of treatment:	12 weeks
Endpoints:	Primary endpoint: 1. Change from baseline in ADAS-cog_{11} (Alzheimer's Disease Assessment Scale-cognitive subscale) total score after 12-week treatment Secondary endpoints include: 2. Change from baseline in ADCS-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living) total score after 12-week treatment 3. CIBIC Plus total score after 12-weeks treatment
Safety criteria:	Adverse event reporting, vital signs, ECG (digital) and standard laboratory tests, Columbia-Suicide Severity Rating Scale (C-SSRS).
Statistical methods:	The primary objective is to define a suitable dose for BI 425809 regarding efficacy and safety for further pivotal testing in Phase III. For this purpose, a multiple comparison procedure with modelling (MCPmod) approach is considered. The primary endpoint is mean change from baseline in ADAS-$_{Cog11}$ total score after 12 weeks of treatment. Comparisons between treatment groups will be exploratory in nature and based on the numerical comparison of the respective treatment differences including confidence intervals when appropriate.

FLOW CHART

Trial Period		**Screening**	**Treatment Period**							**Follow-up**	
Visit	**0**[12]	**1**	**2 Baseline**	**3a**[9]	**3b**[9]	**3c**[9]	**4**	**5**	**EOT/ ED**[8]	**FU1**[11]	**FU2**
Study-Day (or duration during screening/ run-in)		Duration 14 days	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**EOT +7**	**EOT +28**
Study Week		**-2**		**1**	**2**	**3**	**4**	**8**	**12**	**13**	**16**
Visit window (in days)		**+7 to - 28**[20]		±2	±2	±2	±5	±5	+5	+2	+5
Patient information & informed consent signed (including informed consent for PGx)[1]	X										
Register Patient in IRT		**X**[17]									
Randomisation (via IRT)			**X**[18]								
Register Patient's End of Study Call in IRT											**X**
Demographics (of patient and study partner)		X									
Medical history / baseline conditions	X										
In-/exclusion criteria	X	X	X								
Imaging of the Brain[2]	X										
Concomitant medications[13]	X	X	X	X	X	X	X	X	X	X	X
Height (screening only)/weight		X							X		X
Vital signs		X	X	X	X[9]	X[9]	X	X	X		X
Physical examination		X							X		
Neurological examination		X							X		
Resting ECG (digital)		X		X[16]	X[9, 16]	X[9, 16]	X[16]		X[16]		X[16]
Adverse events	X	X	X	X	X[9]	X[9]	X	X	X	X	X
Dispense trial medication[3]			X				X	X			
Last dose of trial medication									**X**		
Collect study drug							X	X	X		
Medication Compliance Check							X	X	X		
Laboratory tests: Chemistry, haematology, urine analysis		X[14]	X				X	X	X		X
Urine drug screen		X							X		
Neuropsychological Rating Scales[19]											
MMSE		X									
ADAS-cog$_{11}$		X	X[10]				X[10]		X[10]		
CIBIS			X[10]								
CIBIC+									X[10]		
ADCS-ADL		X	X[10]						X[10]		
Prospective Suicidality Monitoring[19]											
C-SSRS		X[6]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]

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Study Week		**-2**		**1**	**2**	**3**	**4**	**8**	**12**	**13**	**16**
Visit window (in days)		**+7 to - 28**[20]		±2	±2	±2	±5	±5	+5	+2	+5
Completion of patient participation											X
Vital status collection[15]									X		

[1] Prior to any trial related procedures, including any pre-trial washout of medications and / or medication restrictions (for more details on medication restrictions refer to Section 4.2.2.1).

[2] Results of a MRI or CCT-scan have to be available prior to visit 2. Please refer to Exclusion #1 in Section 3.3.3 for further details.

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

[6] Columbia Suicide Severity Rating Scale baseline/screening version

[7] Columbia Suicide Severity Rating Scale since-last-visit version

[8] Also to be completed for permanently withdrawn patients or who have discontinued the trial prematurely not willing to come to remaining trial visits: in case of early termination visit FU1 should preferably be performed no later than 7 days after the last study drug intake (visit FU2 should follow four weeks later).

[9] If the assessments at visit 3a do not show clinically relevant findings compared to baseline and if deemed clinically acceptable by the investigator then visits 3b and 3c may be performed as phone contacts. Attendance of the study partner is not necessarily required during visits 3 a-c. ECG and vital signs are only to be performed at clinic visits. **At any of visit 3 (i.e. visit 3a to 3b) the IMP may be taken at home.**

[10] The neuropsychological assessments may be performed one day before the actual clinic visit 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. Neuropsychological rating scales assessments need to be done in one day and may not be split in two individual days.

[11] This visit can be done as phone or clinic visit

[12] **Visit 0** can be **performed on the same day** with Visit 1 (the Screening Visit) if there is no need to make these visits separate (e.g. medication washouts, CCT or MRI scan **availability**)

[13] Refer to section 4.2.2.1 to check for concomitant medication restrictions, requirements including any pre-trial washout of medications

[14] Laboratory parameters: Haemoglobin, GFR, ALT, AST and alkaline phosphatase found abnormal at visit 1 may be re-tested **twice** prior to Visit 2. If Vitamin B12 and/or folate are found below lower limit normal, please initiate the respective treatment to stabilise the condition. Vitamin B12 and/or folate re-test may be done twice prior to Visit 2. *For possible extensions of screening period refer to Section 6.1.*

[15] Patients who prematurely discontinue from the trial and refuse to attend remaining trial visits will be contacted for vital status collection at week 12.

[16] Perform the 12-lead ECG preferably within 3-5 hours post IMP dosing.

[17] **Patient needs to be registered in the IRT also if becoming a screen failure between V0 and V1.**

[18] **Perform randomization call in the IRT preferably after the neuropsychological assessments are done.**

[19] **All scales should be administered as the first procedure at the clinic visit in the order pre-set in the rater station (the order of the scales in the rater station is consistent with the protocol Flow Chart).**

[20] **The screening period may be shorten to a minimum of 7 days if all screening procedures and results are available. At the same time the screening period may be extended by additional 4 weeks (28 days) for any reasons. *For further details please refer to Section 6.1.***

TABLE OF CONTENTS

ABBREVIATIONS

ABCB1	ATP-binding cassette sub-family B member 1 (gene encoding for P-gp)
AChE-Is	Acetylcholine Esterase Inhibitors
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study/Activities of Daily Living
AE	Adverse Event
AESI	Protocol-specified Adverse Event of Special Interest
AIC	Akaike Information Criterion
AUC	Area under the Curve
CCT	Cranial Computer Tomography
CI	Confidence Interval
CIBIC+	Clinician's Interview-Based Impression of Change
CIBIS	Clinical Interview-Based Impression of Severity
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
DEDP	Drug Exposure During Pregnancy
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ED	Early discontinuation
EDC	Electronic Data Capture
ERG	Electroretinogram
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
GlyT1	Glycin Transporter 1
HEENT	Head-Eyes-Ears-Nose-Throat
HPC	Human Pharmacology Centre
i.v.	Intravenous
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IM	Intermediate metabolizer

IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LC-MS	Liquid Chromatography tandem Mass Spectrometry
LTP	Long Term Potentation
MCPmod	Multiple Comparison Procedures and modelling
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model Repeated Measures
MMSE	Mini-Mental-State-Examination
MRI	Magnetic Resonance Imaging
MST	Medical Subteam
NMDA-R	N-methyl-D-aspartate receptor
NOA	Not analyzed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
OPU	Operative Unit
p.o.	per os (oral)
PDE9	Phosphodiesterase-9
PG(x)	Pharmacogenomic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic
PM	Poor metabolizers
POC	Proof of Concept
PSA	Prostate Specific Antigen
PTM	Placebo to Match
q.d.	quaque die (once a day)
RDC	Remote Data Capture
REP	Residual Effect Period
RNA	Ribonucleic Acid
RPR	Rapid Plasma Reagin
s.c.	Subcutaneous
SAE	Serious Adverse Event
SP(1)	Spatial
SPC	Summary of Product Characteristics
STORM	Storage Conditions for Trial Medications
SUSAR	Suspected Unexpected Serious Adverse Reactions
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

UN	Unstructured

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Alzheimer's Disease Dementia, 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 behavioural 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 used to treat the impairments in memory and function in patients with dementia. 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 N-methyl-D-aspartate (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. GlyT1 inhibition increases post-synaptic NMDA receptor signaling and BI 425809 increases learning and memory in rodent models. By GlyT1 inhibition a cascade of intracellular, post-

synaptic signalling events is triggered through elevation of second messengers such as cAMP and cGMP with subsequent activation of protein kinases and manifestation of long-term potentiation (LTP) and synaptic plasticity. LTP is regarded as a validated physiological model for cellular processes underlying learning and memory formation [R10-5109; R10-5092; R10-5102].

1.2 DRUG PROFILE

BI 425809 is a GLYT1 inhibitor that is being developed for symptomatic treatment of AD and for symptomatic treatment of cognitive impairment in schizophrenia as adjunct to classic antipsychotic therapy.
Schizophrenia and AD are chronic, severe, and disabling brain disorders affecting both men and women.
Both disorders are characterized by abnormalities in glutamatergic pathways related to NMDA receptor hypofunction in cortical and hippocampal brain areas [R13-4518; R13-4521]. These abnormalities are hypothesized to lead to negative symptoms and cognitive impairment in schizophrenia and cognitive impairment in AD.
Inhibition of GLYT1 aims at improving NMDA receptor hypo-activation in patients with schizophrenia and AD by increasing the concentration of the NMDA receptor co-activator glycine in the synaptic cleft, thereby leading to improvement of negative and cognitive symptoms in patients with schizophrenia (as add-on therapy to antipsychotics) as well as to cognitive improvement in AD patients.
Based on in vitro data, at the highest proposed Phase 2 dose of 25 mg, BI 425809 may cause clinically relevant induction of CYP2B6. Based on a Phase I clinical study BI 425809 is a mild CYP3A4 inducer at 25mg. Based on clinical DDI study BI with **itraconazole** and rifampicin BI 425809 is a sensitive **CYP3A4** substrate and should not be given with moderate-to-strong inhibitors or inducers of **CYP3A4**.

Clinical Safety Pharmacology

In healthy volunteers, BI 425809 is generally well tolerated. The most frequent AEs were adverse CNS symptoms, most commonly headaches that showed a trend for dose dependency, were reversible and can be clinically monitored. In addition, BI 425809 may be associated with transient visual disturbances, and somnolence (drowsiness). These effects are understood to be mostly mild to moderate and transient. Decreased haemoglobin is a potential risk based on preclinical data and class effect; however, no clear decrease in haemoglobin was seen in BI 425809-treated subjects compared to placebo in phase I trials so far.

No serious safety concerns have been identified with administration of GLYT1 inhibitors in humans. The most frequent adverse events were CNS effects and visual effects. Visual effects are generally seen at higher doses and are transient in nature. Visual AEs and changes in Hb levels should be anticipated with GLYT1 inhibitors and are of special interest and should be closely monitored. Additionally, CNS effects should be anticipated and are expected to be dose-limiting.

For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB) which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Currently approved AD treatment is used to treat the impairment in memory and function in patients with dementia. Registered treatment mainly consists of 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. However, there is still a high unmet medical need for additional symptomatic therapies able to improve cognition and function in patients with mild-to-moderate dementia of Alzheimer's type.

This study is performed to define a suitable dose of BI 425809 regarding efficacy and safety for further pivotal testing in Phase III. The main rationale for this study is to provide proof of clinical concept and dose ranging data in patients with mild-to-moderate dementia of Alzheimer's type aged at least 55 years at enrolment.

2.2 TRIAL OBJECTIVES

The proof of clinical concept will be achieved through primary endpoint comparison (mean change from baseline in ADAS-Cog_{11} total score at Week 12) of the four BI doses (2mg QD, 5mg QD, 10mg QD and 25mg QD) and placebo. A non-flat dose response relationship between the BI doses and placebo will be tested using the multiple comparison procedures and modelling (MCPmod) approach [R10-1424, R15-1961].

Other objectives of this study are safety of BI 425809.

2.3 BENEFIT - RISK ASSESSMENT

The favorable benefit-risk ratio based on the so far acquired knowledge about BI 425809 is the rationale to conduct further studies with this molecule. Currently available data comprising of six phase 1 trials results involved in total 229 healthy subjects treated with single or multiple doses of orally administered BI 425809 up to 150 mg per day.

Based on non-clinical data, clinical data from other compounds in the same class, and subjects exposed in phase I trials; BI 425809 is assessed to be generally safe and well tolerated [c02155957-07].

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.6.1.

This is newly developed drug at an early stage of testing and therefore an individual benefit cannot be guaranteed.
This is a trial of short duration and the assignment to the placebo arm is not associated with a higher risk for the patient. 1 out of 5 patients will be randomised to the placebo arm. 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.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a 12-week, multi-centre, multi-national, randomised, double-blind, double-dummy, placebo controlled, parallel group comparison in patients with mild-to-moderate Alzheimer's Disease Dementia. In total, 585 patients with mild-to-moderate Alzheimer's Disease Dementia who meet the entry criteria are planned to be randomised in this trial. The randomised treatment will be double blind.
All patients suitable after screening will be randomised into 12-week double-blind treatment period at Visit 2 and will be assigned to one of the 4 treatment groups or placebo, refer to Figure 3.1: 1.

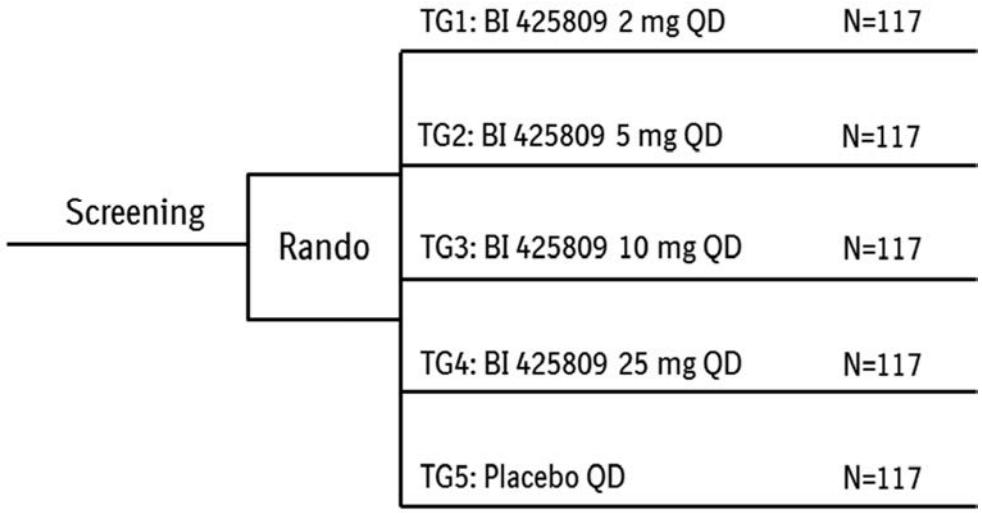

Figure 3.1: 1 Trial Design

After the end of the double-blind treatment period, patients will be followed up for additional 4 weeks without study medication. 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.

3.1.1 Administrative structure of the trial

Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

Bracket Global has been selected as service provider to support tasks related to the neuropsychological assessments: necessary rater prequalification, rater training (online and at investigator meeting), provision of rater materials and central review of neuropsychological assessments (see Section 8.3.1 for details).

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

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

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 has been nominated and will be responsible to coordinate Investigators at different centres participating in this multicentre trial. The Coordinating investigator was selected by the sponsor. will review the trial protocol, any subsequent amendments to the protocol and the (draft) Clinical Trial Report (CTR). Relevant documentation on the participating (Principal) Investigators and other important trial staff shall be filed in the ISF.

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

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.
In order to estimate the relative drug effect on cognition and function, a double-blind comparison against placebo is included in this trial.
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 425809.
The data collected in this double-blind, randomised, and placebo-controlled trial are standard in this indication and will provide important information in terms of efficacy and safety on the use of BI 425809 in patients with mild-to-moderate AD.

3.3 SELECTION OF TRIAL POPULATION

Recruitment of the 585 patients will be competitive. Patients who discontinue following randomisation will not be replaced and may not be re-enrolled at a later date. A record is kept of all patients failing to complete all trial visits and their reasons for discontinuation.
This trial aims to randomise approximately half of patients with mild Mini-Mental State Examination ((MMSE) 20-26) and half with moderate (MMSE 15-19) AD. The sponsor/study team will monitor recruitment closely and reserves the right to stop further enrollment of either mild or moderate patients in order to meet this goal.
Permission to randomise more than 15 patients per site must be obtained from the TCM at Boehringer Ingelheim. This shall only be allowed after a careful review of the data quality and the performance of the site.
A log of all patients enrolled into the trial (i.e. who have signed 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 trial entry

Patients with the diagnosis of mild-to-moderate Alzheimer's Disease 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 Disease Dementia) will be included.
Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Diagnosis of mild-to-moderate Alzheimer's Disease 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. MMSE score of 15-26 at screening (Visit 1).

3. Concomitant use of AChEIs is allowed but not required. 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 who are not currently taking AChEIs but have taken them in the past are also eligible if AChEIs were stopped at least 3 months prior to screening.

4. All patients must sign and date an Informed Consent Form consistent with ICH-GCP guidelines and local legislation prior to participation in the trial *(i.e. prior to any trial related procedures, including any pre-trial washout of medications/medication restrictions, Section 4.2.2.1.)*

All patients must be able to give informed consent personally and have capacity for such consent. An informed consent given by a legal representative alone will not be accepted.

5. Patients must have a reliable study partner (per investigator judgment, 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 Neuropsychological Rating Scales 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.

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

7. 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

1. Dementia secondary to disorders other than Alzheimer's Disease Dementia (for example: Vitamin B12/Folate deficiency, neurosyphilis, craniocerebral trauma, small vessel disease). Lewy body dementia or vascular or multi-infarct dementia as primary diagnosis is excluded. The above should be assessed based on clinical data, current laboratory findings, and a MRI or CT of the brain.
   If previous cranial imaging is not available or older than 12 months prior to screening then a CT or MRI needs to be performed at screening. Local regulations need to be checked if use of radiation for a cranial CT scan is allowed in the concerned country. If performing of a cranial CT is not allowed (e.g. Germany, France), a MRI must be performed.

2. Any central nervous system disease other than AD which according to the investigator may be associated with worsening of cognition. Patients with epileptic seizure in last 2 years should be excluded.

3. A disease or condition which in the opinion of the investigator are likely to interfere with trial testing procedures or put the patient at risk when participating in this trial.

4. Any documented active or suspected malignancy or history of malignancy with need of concomitant treatment that interfere with the investigational product.

5. Patients with life expectancy of less than 2 years are also excluded.

6. Any other clinical condition that, in the opinion of the investigator, would jeopardize patient safety while participating in this clinical trial.

7. Severe renal impairment defined as a GFR < 30 mL/min/1.73 m2 in the screening central lab report.

8. Haemoglobin less than 120 g/L (12g/dL) in men or 115g/L (11.5g/dL) in women in the screening lab report. History of haemoglobinopathy such as thalassemia major or sickle-cell anaemia.

9. Clinically significant uncompensated hearing loss in the judgment of the investigator. Use of hearing aids is allowed.

10. Any suicidal behaviour in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).

11. 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).

12. Known history of HIV infection.

13. 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.

14. Previous participation in investigational drug studies of dementia of Alzheimer's Type within three months prior to screening. **Patients having received any active treatment in studies targeting disease modification of AD are excluded.** Previous participation in studies with non-prescription medications, vitamins other nutritional formulations or non-pharmacological treatments is allowed.

15. Treatment with restricted medication (refer to Table 4.2.2.1:1) prior to Visit 1 and/or during the screening period.

16. Planned elective surgery requiring general anaesthesia, or hospitalisation for more than 1 day (requiring an overnight stay) during the study period.

17. For females: Women who are of child bearing potential. Women not of childbearing potential are defined as: Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

    For males: 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.

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.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

It is important to distinguish between premature study drug discontinuation and premature study discontinuation.

Patients can stop taking study drug for various reasons as described below; however, they should be encouraged to re-start study medication at the Investigator's discretion when he/she considers it safe to do so.

After premature study drug discontinuation patients should be asked to further attend scheduled trial visits, follow-up visits and assessments until the end of the trial unless they withdraw consent to participate in the study. Should it not be possible to attend all visits, at least phone contacts should occur at the scheduled visit time points. It is vital to explain to these patients the importance to continue trial participation.

Every effort should be made to collect data in all patients randomised. This includes randomised patients who never take study medications and patients that prematurely discontinue study drug.

Procedures to be followed for patients prematurely terminating the study drug and refusing to attend further trial visits are detailed in Section 6.2.3. Patients that withdraw from trial participation or study drug will not be replaced. The data for patients who discontinue trial treatment or completely withdraw from the trial after randomization must be documented and the reason for withdrawal and the date of last dose of study drug must be recorded in the (e)CRF. These data must be included in the trial database and must be reported.

An individual patient is to be discontinued from study drug if the following occurs:

- The patient withdraws consent for study treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication (see Section 4.2.2 for details).
- In the opinion of the Investigator, continuation on the study drug is not in the patient's best interest, or if the patient fails to comply with the protocol (e.g. non-attendance at trial assessments, and reason to be recorded in the electronic eCRF)
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- The patient's disease/s and/or any concomitant condition significantly worsens, in clinical judgement of the Investigator

- The patient exhibits serious suicidality, in the clinical judgment of the investigator or according to the following criteria:
- 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)
- Patient non-compliance with study drug administration (per Section 4.3)
- Patient is unblinded to treatment by site staff
- Decision by Boehringer Ingelheim to discontinue a specific patient (e.g. in case of SAEs).

If a patient becomes pregnant or a pregnancy is suspected during the trial the investigational drug will be stopped, the patient will be discontinued from treatment and the patient will be followed up through the end of the trial and until birth or otherwise termination of the pregnancy. For further information, including the process for follow-up on the outcome of the pregnancy please see Section 5.3.7.
Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3.
For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the (e)CRF. These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:
1. Failure to meet expected enrolment goals overall or at a particular trial site (this may include under-recruitment or risk of over-recruitment towards the end of the recruitment period)
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Table 4.1: 1 Treatment groups

Group	Treatment Regimen	Treatment	tbl./d
1	**BI 425809 2mg QD**	**1mg**	2-0-0
		25mg PTM	1-0-0
2	**BI 425809 5mg QD**	**5mg**	1-0-0
		1 and 5mg PTM	1-0-0
		25mg PTM	1-0-0
3	**BI 425809 10mg QD**	**5mg**	2-0-0
		25mg PTM	1-0-0
4	**BI 425809 25mg QD**	1 and 5mg PTM	2-0-0
		25 mg	1-0-0
5	**Placebo QD**	1 and 5mg PTM	2-0-0
		25 mg PTM	1-0-0

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

Table 4.1.1: 1 BI 425809, 2mg:

Substance:	BI 425809
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co KG Birkendorfer Strasse 65 D-88397 Biberach a.d. Riss
Unit strength:	1 mg
Daily Dose	2 mg QD (2-0-0) in Treatment Group 1
Posology	QD
Route of administration:	Per os

Table 4.1.1: 2 BI 425809, 5mg:

Substance:	BI 425809
Source:	Boehringer Ingelheim Pharma GmbH & Co KG Birkendorfer Strasse 65 D-88397 Biberach a.d. Riss
Unit strength:	5 mg
Daily Dose	5 mg QD (1-0-0) in Treatment Group 2 10 mg QD (2-0-0) in Treatment Group 3
Posology	QD
Route of administration:	Per os

Table 4.1.1: 3 BI 425809, 25mg:

Substance:	BI 425809
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co KG Birkendorfer Strasse 65 D-88397 Biberach a.d. Riss
Daily Dose	25 mg QD (1-0-0) in Treatment Group 4
Unit strength:	25 mg
Posology	QD
Route of administration:	Per os

Table 4.1.1: 4 Placebo matching BI 425809, 1mg and 5mg:

Substance:	Placebo matching BI 425809
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co KG Birkendorfer Strasse 65 D-88397 Biberach a.d. Riss
Unit strength:	n.a.
Daily Dose	n.a.
Posology	QD
Route of administration:	Per os

Table 4.1.1: 5 Placebo matching BI 425809, 25mg:

Substance:	Placebo matching BI 425809
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co KG Birkendorfer Strasse 65 D-88397 Biberach a.d. Riss
Unit strength:	n.a.
Daily Dose	n.a.
Posology	QD
Route of administration:	Per os

4.1.2 Method of assigning patients to treatment groups

Patients are randomised to treatment groups at Visit 2. Note that the medication number is different from the patient number (the latter is assigned at trial entry).
During Visit 2 and after the patient's eligibility has been confirmed, the treatment will be assigned via Interactive Response Technology (IRT). To facilitate the use of the IRT, the Investigator will receive all necessary instructions.

4.1.3 Selection of doses in the trial

Efficacy in animal cognition tests is shown at doses that produce approximately 50% glycine increase in cerebrospinal fluid (CSF). These doses also result in CSF levels of BI 425809 of 1x GLYT1 IC50.

In a clinical phase I study (1346.3) [c03724403-01] a mean 50% glycine increase in CSF was achieved at a dose of 10mg QD.
A mean CSF concentration of BI 425809 of 1xGLTY1 IC50 (5nM) was achieved at a dose of 5 mg QD. Therefore, the target clinical dose is 5-10 mg QD.

4.1.4 Drug assignment and administration of doses for each patient

IRT will allocate medication kit numbers at Visit 2, 4, and 5. The amount of trial medication dispensed and returned will be recorded on drug accountability forms.
For blinding reasons all treatments will consist of three tablets verum or placebo to be taken in the morning depending on the treatment arm. This will not be changed during the entire study period (V2-EOT).
For days without site visits, patients should be instructed to take the tablets orally with water in the morning at approximately the same time every day with or without food. If a dose is missed by more than **12**hrs, 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. The first dose of study medication will be taken in the end of visit 2 under supervision of the investigator or site staff. At all site visits the morning dose of the investigational drug will be taken during the visit under supervision of the investigator or relevant site staff after (if applicable) the blood samples were taken**, the only exceptions are visits 3 a-c at which the IMP may also be taken at home. The last dose of study medication will be taken at EOT/ED visit (i.e. end of randomized treatment visit).**
The actual visit date and time of study drug administration at the trial visit will be recorded in the eCRF at each visit. 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 a visit with scheduled PK samples should have the visit rescheduled as soon as possible, ideally on the following day.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock.
The randomization code will be kept secret by Clinical Trial Support up to database lock.

The randomization codes will be provided to bioanalytics prior to last patient out to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients. Bioanalytics will not disclose the randomization code or the results of their measurements until the trial is officially unblinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / Pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

For Japan only: In this blinded trial, an emergency code break will be available to the Investigator / the sub-Investigators via the IRT system. This code break may only be accessed in emergency situations when the identity of the trial drug must be known to the Investigator /the sub-Investigators in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the Sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case third party needs to break the code, however, when the Investigator cannot be reached, the code can be opened by calling emergency code manager.

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

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

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 trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,

- 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
- Availability of the proof of a medical license for the principal Investigator
- for USA availability of 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 disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product 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 products received from the Sponsor. At the time of return to the Sponsor / appointed CRO, the Investigator / Pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

For any chronic concomitant treatments stable dose and treatment regime should be maintained whenever possible during patient's participation in the trial. In particular this would apply for antihypertensive drugs, lipid-lowering drugs, antidiabetic drugs and proton pump inhibitors.

Refer to Table 4.2.2.1:1 for relevant washout periods prior to cognitive testing during the study.

Table 4.2.2.1:1 Provides an overview of required, permitted and restricted medication.

			Study Period		
Drug class	**Sub-class**	**Prior to Visit 1**	**Visit 1 and Screening Period**	**Treatment Period**	**Follow-up Period**
AD treatments	Cholinesterase inhibitors: eg Donepezil, rivastigmin, galantamine, tacrine, phenserine	Permitted if initiated and stable for at least 3 months prior to Visit 1 and no change is foreseen during the study	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
	memantine	NOT permitted for at least 3 months prior to Visit 1	NOT permitted	NOT permitted	NOT permitted
Hypnotics/Sedatives	Benzodiazepines and Miscellaneous (eg H_1 inhibitors, melatonine, herbal products etc.)[1]	Permitted if stable 8 weeks prior to V1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
	Barbiturates	NOT permitted for at least 3 months prior to Visit 1	NOT permitted	NOT permitted	NOT permitted

Table 4.2.2.1:1 Provides an overview of required, permitted and restricted medication. (cont.)

			Study Period		
Drug class	**Sub-class**	**Prior to Visit 1**	**Visit 1 and Screening Period**	**Treatment Period**	**Follow-up Period**
Antipsychotics (Neuroleptics)	Typical (1st generation) and Atypical (2nd generation) Antipsychotics[1]	Permitted if stable at least 8 weeks prior to Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
Antidepressants	Tricyclic, Tetracyclic, MAO inhibitors, SSRI, SNRI, SMSs, SARIS, NaSSA, NRIs and other mechanisms of action including herbal products[1]	Permitted if stable at least 8 weeks prior to Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
Nootropics/ Cognitive enhancers including Gingko and peripheral vasodilators	Miscellaneous[1]	Permitted if initiated at least at Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
Psychostimulants and Psychodyslectics	Miscellaneous[1]	Permitted if stable at least 3 months prior to Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
Antiepileptics	Miscellaneous	Permitted if stable at least 3 months prior to Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change

Table 4.2.2.1:1 Provides an overview of required, permitted and restricted medication. (cont.)

			Study Period		
Drug class	**Sub-class**	**Prior to Visit 1**	**Visit 1 and Screening Period**	**Treatment Period**	**Follow-up Period**
Antiparkinsonics	Any Dopaminergics and/or MAO-B inhibitors and/or COMT Inhibitors and/or Anticholinergics including Antihistaminines with anticholinergic effect	Permitted if stable at least 3 months prior to Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
Muscle relaxants	Central[1]	Permitted if stable at least 8 weeks prior to Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
Antiemetics	Antihistamines, Benzamides, 5-HT_3 inhibitors[1]	Permitted if stable at least 8 weeks prior to Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
Antimuscarinic drugs used for urinary incontinence treatment[1]		Permitted if stable at least 4 weeks prior to Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change
Central Analgesics	Opioid agonists[1]	**Permitted if stable** at least 4 weeks prior to Visit 1	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change	Permitted if no dose and/or treatment regime change

Table 4.2.2.1:1 Provides an overview of required, permitted and restricted medication. (cont.)

			Study Period		
Drug class	**Sub-class**	**Prior to Visit 1**	**Visit 1 and Screening Period**	**Treatment Period**	**Follow-up Period**
Strong and Moderate CYP3A4 inhibitors and inducers[2,3]		NOT permitted for at least 8 weeks prior to Visit 1	NOT permitted	NOT permitted	NOT permitted
CYP3A4 sensitive drugs with narrow therapeutic index (e.g. cyclosporine, fentanyl)[2,3]		NOT permitted for at least 8 weeks prior to Visit 1	NOT permitted	NOT permitted	NOT permitted
Grapefruit juice and St. John's wort preparations		**NOT permitted for at least 7 days prior to Visit 2**	**NOT permitted**	**NOT permitted**	**NOT permitted**
Vitamin B12/Folate		Permitted **in case of stable treatment prior to V1 or even** if initiated either at Visit 1 or during screening period	Permitted	Permitted	Permitted
Nutritional Support of AD		**Permitted in case of stable treatment prior to V1 or even if initiated either at Visit 1 or during screening period**	**Permitted if no dose and/or treatment regime change**	**Permitted if no dose and/or treatment regime change**	**Permitted if no dose and/or treatment regime change**
Investigational Drugs		NOT permitted for at least 3 months or 6 half-lives (whatever comes longer) prior to Visit 1	NOT permitted	NOT permitted	NOT permitted

[1]If these drugs are taken occasionally, i.e. on as needed bases, or if such treatment needs to be added and/or dose changed then dosing on the night prior to cognitive testing is not allowed.

[2]For medication list, refer to the ISF

[3]If any of the listed drugs need to be added, then the IMP should be discontinued for at least the period of needed concurrent use. Once the use of either strong/moderate CYP3A4 inhibitors and inducers or CYP3A4 sensitive drugs with narrow therapeutic index is stopped, the re-introduction of the trial drug is possible as per investigator clinical judgement. The re-introduction details may be consulted with the clinical monitor local.

Please note: CYP3A4 ***and CYP2B6*** *sensitive drugs may have decreased levels of exposure when given concomitantly with BI 425809. Investigators should assess if dose adjustments and/or monitoring of the underlying disease is clinically required for patients who are taking such drugs. For a list of CYP3A4* ***and CYP2B6*** *sensitive drugs please refer to the* ***list in the*** *ISF.*
BI 425809 may cause clinically relevant induction of CYP2B6. CYP2B6 sensitive drugs are not excluded but are to be given with caution.

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. **The use of grapefruit juice (strong CYP3A4 inhibitor) and St. John's wort preparations (strong CYP3A4 inducer) are restricted (see list of CYP3A4 inhibitors in the ISF) starting 7 days before the first IMP administration until the end of treatment.**

Considering the visual disturbances reported after drug administration and as a general precaution for CNS-active drugs, it is recommended that subjects should exercise caution when driving or operating machinery after drug administration.

Dietary supplements and herbal remedies may impact the assessment of cognitive tests **and therefore may be used only in line with Table 4.2.2.1:1**.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on counts, treatment compliance will be calculated as the number of capsules taken, divided by the number of capsules which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the Sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}}$$

If the number of doses taken is not between 80-120%, site staff will explain the patient the importance of treatment compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

The following efficacy measures are completed at the times shown in Section 6.2 and the Flow Chart:

5.1.1 Primary Endpoint(s)

- The change from baseline in ADAS-Cog_{11} (Alzheimer's Disease Assessment Scale-Cognitive subscale 11 item) total score after 12 weeks of treatment

5.1.2 Secondary Endpoint(s)

- Change from baseline in the ADCS-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living) score after 12weeks of treatment
- CIBIC+ (Clinician's Interview-Based Impression of Change) score after 12 weeks of treatment

5.2 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.

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, with lower scores indicating less severe impairment. A negative change indicates an improvement from baseline [R96-2608].

ADCS-ADL 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, with higher scores indicating less severe impairment. A positive change indicates an improvement from baseline [R97-3207].

CIBIS and CIBIC+ (Clinician's Interview-Based Impression of Change) scales are based on semi- structured interview covering domains of function and cognition. They additionally require the assessment of psychiatric signs and symptoms. The patient and their caregiver are interviewed and questioned by the clinician [R17-3992].

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A full physical examination will be performed at the visits indicated in the Flow Chart. This should be performed according to medical standards and usually includes (but is not necessarily limited to) a review of the following organ systems: General appearance (including Skin), Head-Eyes-Ears-Nose-Throat (HEENT), Chest (including Pulmonary and Heart), Abdomen, Extremities, Urogenital and neurological assessment (basic mental status, cranial nerves, motor system, sensation, cerebellum/coordination). **Clinically relevant abnormal findings documented after inclusion will be reported as (S)AEs.**

5.3.2 Vital Signs

Systolic and diastolic blood pressure (BP) and pulse rate (PR) will be measured after the patient has rested for at least 5 min in the sitting position. The measured vital signs will be documented in the source documents and recorded in the eCRF.

5.3.3 Safety laboratory parameters

Parameters that will be determined during the trial conduct are listed in Table 5.3.3: 1 and Table 5.3.3: 2. 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). **Haemoglobin, GFR, ALT, AST and alkaline phosphatase found abnormal at Visit 1 may be re-tested twice prior to Visit 2.**

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

- TSH at screening only
- Vitamin B12 and folate at screening and EOT only; if at Screening visit (Visit 1) Vitamin B12 and folate lab results are found abnormal (below lower limit normal) an appropriate treatment may be initiated. Two re-tests can be done prior to Visit 2. The patient can be randomised only if Vitamin B12 and folate lab results are within normal reference ranges. Refer to section 6.1 for further information on visit scheduling.

Table 5.3.3: 1 Safety laboratory parameters – whole blood, serum or plasma

Hematology

- Haematocrit
- Haemoglobin
- MCV, MCH, RDW, MCHC
- Reticulocyte Count and Index (reflex test if Hb outside normal range or decreased >2g/dL compared to baseline)
- 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
  - γ-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
- Ferritin, serum iron, transferrin and TIBC as reflex if Hb outside normal range or decreased >2g/dL compared to baseline
- Creatine kinase (CK)
- CK-MB, troponin (reflex tests if CK is elevated)
- Lactate dehydrogenase (LDH)
- Lipase
- Magnesium
- Phosphate
- Potassium
- Protein total
- Sodium
- Urea (BUN)
- LDL/HDL and total cholesterol
- Triglycerides
- TSH
- Folate

Table 5.3.3: 2 Safety laboratory parameters – urine

Urinalysis

Semi quantitative

- Nitrite
- Protein
- Glucose
- Hemoglobin
- 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 only be performed if required by local regulations. It may also be done more frequently or in plasma instead of urine if required (please note: this trial will include no patients of child-bearing potential)

5.3.4 Electrocardiogram

A12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 – V6) will be performed as scheduled in the Flow Chart using the equipment provided by the central ECG vendor. The ECGs will be recorded for at least 10 second duration after the subjects have rested for at least 5 minutes in a supine position. Electrode placement will be performed according to the method of Einthoven/Goldberger (ankles and wrists). Single ECGs will be recorded at the time points indicated in the Flow Chart. At visits 3, 4 **and** EOT the ECGs will be performed preferably within 3-5 hours post IMP dosing to correlate with the c_{max} of the BI 425809. 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.

The investigator or a designee should evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal. The electronic version of the ECG is regarded

as source data. Dated and signed printouts will be stored in the patient's medical file if there is no validated and certified e-medical record for ECG data.

Additional ECGs may be collected by the investigator for safety reasons. Clinically relevant findings noticed at baseline assessment should be reported as baseline condition. Clinically relevant abnormal findings noticed after baseline assessment will be reported as adverse events and followed up and/or treated locally until normal or stable condition.

All ECGs will be transmitted electronically to the central ECG vendor to perform a centralized and independent analysis. Abnormalities detected during this centralized ECG evaluation will not necessarily qualify as AEs.
Central evaluation on individual ECGs will be performed by the vendor and a report will be provided to the site. Decisions on patient's eligibility, treatment or further follow-up of any ECG related findings are the responsibility of the investigator.

5.3.5 Other safety parameters

5.3.5.1 Suicidal risk assessed by the C-SSRS

Consistent with the FDA draft guidance entitled "Suicidal Ideation and Behaviour: Prospective Assessment of Occurrence in Clinical Trials", prospective assessment of suicidal ideation and behaviour is included in this study using the C-SSRS **(paper version; shall be administered via Bracket rater-station).**
The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behaviour and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behaviour and ideation.
The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behaviour, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report.
The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the 'screening / baseline' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening or baseline visit. The life time history of suicidal ideation and behaviour will also be recorded.
After the baseline visit the assessment 'since last visit' will be performed at each clinic or phone visit ('since last visit' version). The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behaviour or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behaviour must be reported as separate SAEs by the investigator.
For 'Self-injurious behaviour, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied.
For each negative report (suicidal ideation type 1, 2 or 3) after start of the trial, the investigator is to decide based on clinical judgment whether it represents an adverse event (AE) as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

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

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

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- 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 judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe. All reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior

from prospective monitoring in C-SSRS (see Section 5.3.5.1 for details) are also considered to be life-threatening and must be reported as SAEs by the investigator.

For Japan only: The following events will be handled as "deemed serious for any other reason". An AE which possibly leads to disability will be reported as an SAE.

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

The latest list of "Always Serious AEs" can be found in the RDC. These events should always be reported as SAEs as described in Section 5.3.7.

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

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

The following are considered as AESIs:

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

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

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

No further AESIs have been defined for this trial.

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

Mild:	Awareness of sign(s) or symptom(s) that 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 AEs
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).

Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

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

For Japan only: the reason for the decision on causal relationship for unlisted AEs needs to be provided in the CRF.

5.3.7 Adverse event collection and reporting

AE Collection
The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual patient's end of trial:
  - all AEs (serious and non-serious) and all AESIs.

- After the individual patient's end of trial:
  - the investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.

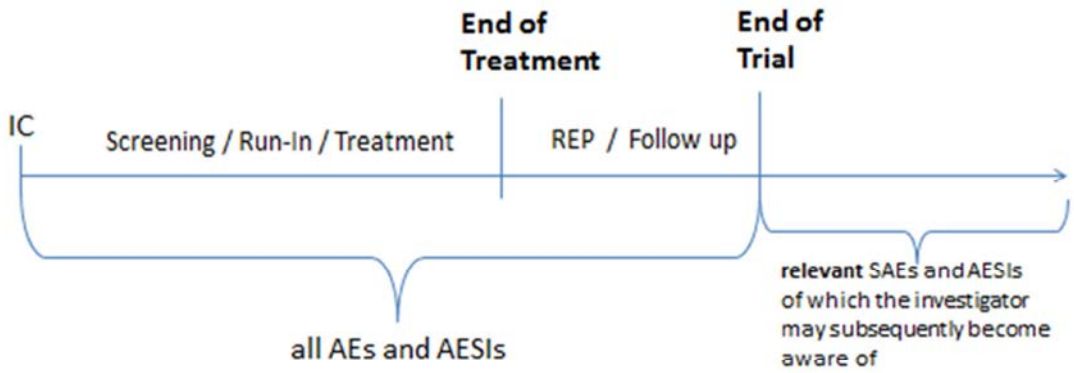

Figure 5.3.7: 1 Collection and reporting of AEs/SAEs during the study

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 and SAE form, if applicable. A local ophthalmology assessment will be required for 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 REP is defined as 11 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

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

For Japan only : All SAEs and AESIs must be reported immediately to the head of the trial site.

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

Information required
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication.

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

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

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

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) **any** potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits should be initiated preferentially in the morning starting before 9:00 AM **and as consistently as possible throughout the entire trial.** Patients should be instructed to avoid intake of the morning dose of the study medication at home at scheduled visit days as they will be dosed whilst at the study site **under site staff supervision.**
All patient visits should be scheduled according to the Flow Chart. All visit procedures should preferably be completed on one day. If necessary (preferred), all planned neuropsychological rating scales (as per Flow Chart) from Visit 1 (screening) to Visit 6 (end of treatment) can be performed one day prior to the planned clinic visit. Sites should make every attempt to adhere to the protocol time windows as close as possible. **The screening period may be shorten to a minimum of 7 days if all screening procedures and results are available. At the same time** the screening period (i.e. period between Visit 1 and Visit 2) may be extended by additional 4 weeks (i.e. 42 days in total) for any reason (e.g. administrative reasons, lab re-tests, concomitant medication adherence, adverse event, etc.). If screening period needs to be extended any further, the clinical monitor should be contacted to discuss further steps. If any visit after the randomisation has to be rescheduled, subsequent visits should follow the original visit schedule with the goal to reach 85+5 days treatment period. The trial medication packs contain sufficient medication to allow for these time windows.
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

The following requirements for the conduct of the neuropsychological assessments need to be followed:

- 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.
- CIBIS/CIBIC+ rater should not perform other ratings and further procedures such as laboratory procedures, dispensing of IMP, or monitoring of AEs and ASEs. 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 members of the site staff performing the assessment have to be properly trained (either at the investigator training or individually) and training documentation has to be filed in the ISF. The training standards and standards for the conduct of the assessments will be defined for each assessment individually and can be found in the ISF. It is the responsibility of the

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

6.2.1 Screening and run-in period(s)

Screening Period

Informed Consent prior to trial participation
All patients must sign an Informed Consent consistent with ICH-GCP guidelines prior to any study specific procedures. Please refer to Section 8.1 for details.

Particular procedures
The screening visit (see Flow Chart for full details) will include the following procedures/assessments: check of signed Informed Consent, demographics, review of relevant medical history/baseline conditions at the discretion of the Investigator, relevant medication history and review of concomitant therapy, inclusion/exclusion criteria, physical exam, body weight and height, vital signs (blood pressure and pulse rate), ECG, safety laboratory tests. Neuropsychological assessments and suicidality monitoring will be done.

6.2.2 Treatment period(s)

The procedures of the visits in the treatment phase will be performed as outlined in the Flow Chart.

Visit 2 (Baseline)
As soon as eligibility of a screened patient is confirmed, the patient may enter the study and Visit 2 can be conducted. This visit includes the assessment of the endpoints and randomisation via IRT. IRT should **preferably be called after** the patient has completed the assessments of the neuropsychological endpoints.
At the start of Visit 2 it should be ensured that all Visit 1 procedures have been successfully completed and eligibility has been confirmed (including results of the neuropsychological rating scales performed at Visit 1).
Neuropsychological assessments will be done. Similarly suicidality monitoring shall be performed and eligibility criteria shall be re-assessed.
Study medication should be taken at the end of the visit at the site and study drug kits will be dispensed for home administration. Intake of study drug and handling of the blisters needs to be trained with the patient and the study partner.

Visit 3a
This visit will be a mandatory clinic visit. Study procedures have to be completed according to the Flow Chart.

Visit 3b and 3c:
These visits may be phone contacts with the patient if (in discretion of the investigator) no clinically relevant changes in vital signs are observed at Visit 3a. Study procedures have to be completed according to the Flow Chart.

The attendance of the study partner is not required for Visits 3a-c. **The IMP may be taken at home at visits 3 a-c.**

Visits 4, 5 and EOT
These visits are part of the treatment period. Procedures are to be performed according to the flowchart. The recommendations for the performance of the neuropsychological assessments should be noted and followed.

Unscheduled visits will be possible at the discretion of the investigator at any time in order to check the safety of the patient.

6.2.3 Follow Up Period and Trial Completion

All randomised patients should be followed up until the end of study at week 16.

End of Treatment (EOT) Visit:
If the regular end of the treatment period at week 12 is reached or if the patient withdraws consent for further participation in the trial the EOT Visit will be completed. The overall duration of the treatment period (randomisation to EOT) should not be less than 85 days.
It is important to distinguish between premature study drug discontinuation and complete withdrawal of consent to participate in further study procedures. Patients not willing to continue study drug intake should be asked to further attend scheduled trial visits, follow-up visits and assessments until the end of the trial unless they withdraw consent to participate in the study. Should it not be possible to attend all visits, at least phone contacts should occur at the scheduled visits time points. For patients not attending remaining trial visits or not being available for phone contacts replacing the remaining clinic visits any attempt will be made to get information on vital status at Week 12 (refer to Flow Chart). Patients will be asked to agree to be contacted by the site personnel, which could be by telephone calls (in person visit would be preferred), to allow collection of this information. If death occurs, the investigator will review the circumstances, including the relevant medical records to ascertain the most likely primary and secondary causes of death. Collection of vital status will be performed in accordance with national ethical and regulatory guidelines. The need for vital status information will be explained to patients prior to their participation in the trial.
It is vital to explain to these patients the importance to continue trial participation (please see Section 3.3.4 for further details).

All unused study medication will be collected and study drug diary will be checked.
Procedures are to be performed according to the Flow Chart.

Follow-up (FU) 1:
This follow-up visit will preferentially be performed as a phone contact one week after EOT for all patients who had at least one dose of trial medication (see Flow Chart for procedures to be performed).

Follow-up (FU2) 2:

This visit is a clinic visit and need to performed 28±3 day after EOT (see Flow Chart for procedures to be performed).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

See Section 3.1 for details on the design of the study.

See Section 2.2 for details on the objective of the study.

A multiple comparison procedure with modelling (MCPMod) approach is considered for proof-of-concept. Further details are included in Section 7.3.1.1.

The treatment comparisons for the primary continuous endpoint will be conducted using a restricted maximum likelihood estimation based on mixed model repeated measures analysis. Further details are included in Section 7.3.1.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary endpoint is mean change from baseline in ADAS-Cog_{11} total score after 12 weeks of treatment. Baseline refers to the last observed measurement prior to administration of any randomised study medication.

The null hypothesis is that there is a flat dose response pattern across placebo and any dose of BI 425809 within the tested dose range (0-25mg) on mean change in ADAS-Cog_{11} total score from baseline to treatment week 12.
The alternative hypothesis is that there is a non-flat dose response pattern indicating a benefit of BI 425809 compared to placebo.
The MCPmod procedure allows for the simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of type I error (one-sided alpha of 0.05). The pre-specified models and their parameters used for this test are outlined in Section 7.3.1 and Section 7.7.

7.3 PLANNED ANALYSES

Analysis set
The statistical analyses will be based on the following patient populations:

- Treated Set

The treated set (TS) is defined as all patients treated with at least one dose of study medication. Patients in the treated set will be analyzed based on the actual treatment received at the randomization. The TS will be used for safety analyses.

- Full Analysis Set

The full analysis set (FAS) will consist of all randomised patients who were treated with at least one dose of study drug and had a baseline and at least one post-baseline on treatment efficacy assessment. Patients in the FAS will be analyzed based on the intent-to-treat

principle (i.e., patients in the FAS will be analyzed based on the planned treatment assigned at randomization). The FAS will be used for efficacy analyses.

Data from subjects who are screened but not randomised will be listed but not included in any summary statistics or inferential statistics. Specifications of important protocol violations will be provided in the TSAP.

7.3.1 Primary endpoint analyses

7.3.1.1 Primary analysis of the primary endpoint

The analyses for PoC and dose-finding will be done using multiple comparison procedures and modelling (MCPmod) techniques [R10-1424] for mixed model repeated measures (MMRM) [R15-4293], whereby several possible dose response models (patterns) will be evaluated (while keeping full control of the type I error of 5%, 1-sided) to identify the best-fitting model or subset of models. The MMRM model as described in Section 7.3.1.2 will be fitted for MCPmod.

For the PoC testing and for the sample size calculation, the basic shape of each of the models to be tested must be pre-defined. Six different models will be tested in the analysis: betamod, emax, sigEmax, linear, linear logistic and logistic. Except in the model 'betamod', the maximum effect is assumed to be achieved at the maximum dose being tested. For the sample size calculation, the maximum standardized effect size is assumed to be 0.35. Further details are given in Section 7.7.

The active BI 425809 doses are 2 mg, 5 mg, 10 mg, and 25 mg daily. The following model assumptions and resulting graphs (Figure 7.3.1.1: 1) have been selected to cover both plausible and a diverse range of dose response patterns:

- Betamod: 75% of the maximum effect is achieved at 2 mg
  87.5% of the maximum effect is achieved at 5 mg
  25% of the maximum effect is achieved at 25 mg
  Maximum effect achieved at 10 mg
  Scalar parameter = 26
- Emax1: 20% of the maximum effect is achieved at 2 mg
- sigEmax: 25% of the maximum effect is achieved at 5 mg
  75% of the maximum effect is achieved at 10 mg
- Linear: no assumptions needed
- Linear logistic no assumptions needed
- Logistic: 10% of the maximum effect is achieved at 5 mg
  50% of the maximum effect is achieved at 10 mg

PoC is established if at least one model is significant, rejecting the null hypothesis of a flat dose-response relation over 12 weeks for the primary endpoint (mean change from baseline in ADAS-Cog_{11} total score) jointly for each of the candidate dose-response models with a contrast test controlled for the family-wise error rate ($\alpha = 0.05$ 1-sided).

If PoC is established, the best-fitting model from the above set of six models can be refitted to the data without any parameter assumptions to generate new estimates of the model parameters from the data. The target dose will be obtained via model averaging across the significant models based on Akaike Information Criterion (AIC) (the smaller the AIC value the better the model fit). The target dose(s) can then be determined from that model by incorporating information on the minimum clinically relevant effect as well as safety information. The target dose to be chosen should show a delta of at least 2 points in the mean change from baseline ADAS-Cog_{11} total score at week 12 compared to placebo. This will be measured on the modelled efficacy and only doses within the dose range investigated (0mg-25mg) will be considered although the actual modelling will be performed on a broader range of doses including extrapolation.

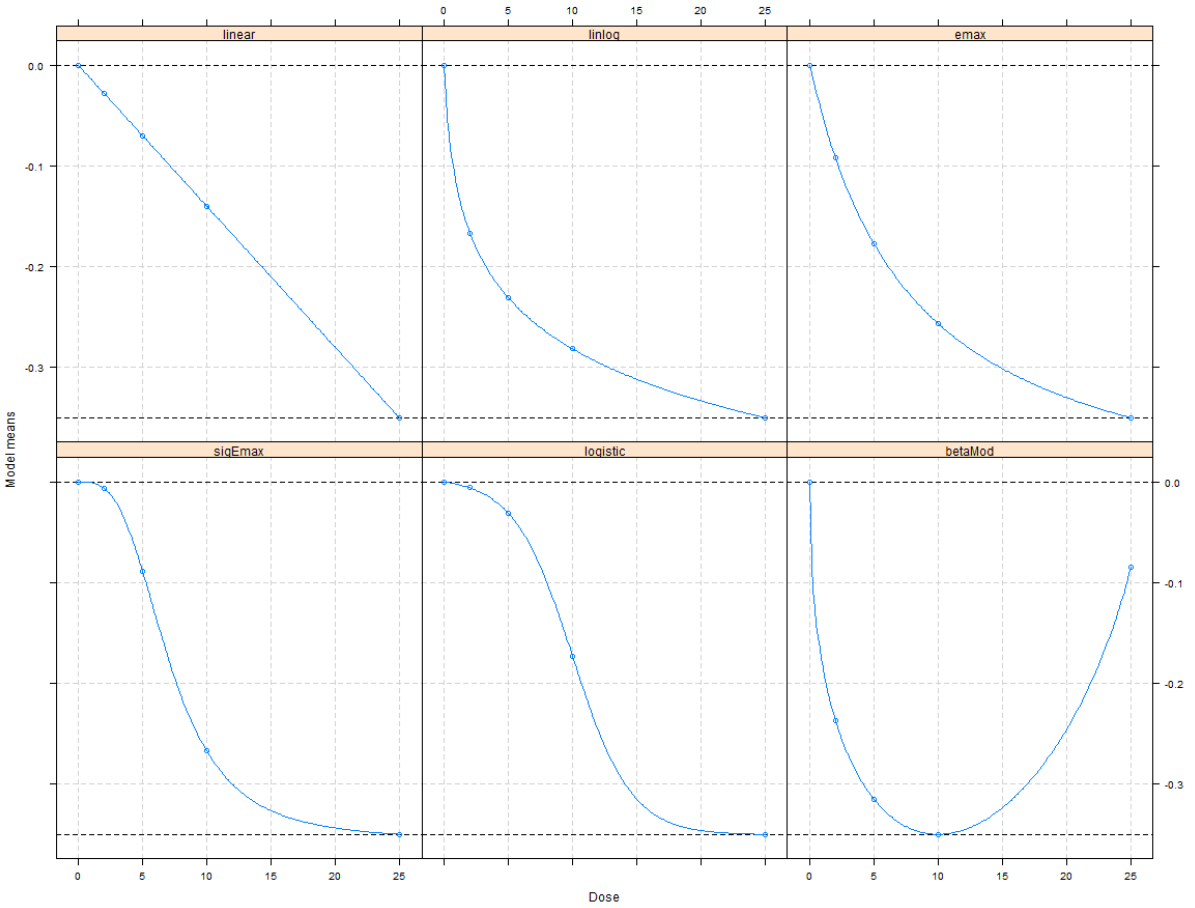

Figure 7.3.1.1: 1: Shape of the models within the candidate set

7.3.1.2 Secondary analyses of the primary endpoint

If considered necessary and for the purpose of further model refinement MCPmod might be repeated on the primary endpoint but with an extended set of shapes including the original candidates. Additionally to that covariates may be taken into account in a sensitivity analysis.

The primary endpoint will also be analysed using a restricted maximum likelihood estimation based on MMRM for the change from baseline in ADAS-Cog_{11} total score after 12 weeks of

treatment. The model will include fixed, categorical covariates of treatment, visit, baseline MMSE ($\geq$ 20, < 20) 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 measurements.

The first model to converge will be used as the primary analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).). Analyses will be implemented using SAS (version 9.4) PROC MIXED. Procedures to follow if the analysis fails to converge will be described in the TSAP.

The primary treatment comparisons will be between the placebo and the different doses of BI 425809 with respect to the mean change from baseline in the ADAS-Cog_{11} total score after 12 weeks of treatment. Adjusted mean change from baseline as well as treatment contrasts will be presented together with the 95% confidence intervals. The primary treatment comparisons will be the contrast between treatments at the endpoint visit.

Comparisons between treatment groups will be exploratory in nature and based on the numerical comparison of the respective treatment means.

7.3.2 Secondary endpoint analyses

If considered necessary a MCPmod approach will also be applied to the secondary endpoints.

Comparisons between treatment groups will be exploratory in nature and based on the numerical comparison of the respective treatment means.

More details on the analyses of the secondary endpoints will be included in the TSAP.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 11 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.

All treated patients will be included in the safety analysis and will be summarized under the actual trial medication received at randomization. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 11 days after the last drug intake.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). Frequency tables for all adverse events, protocol-specified AESI, serious adverse event (SAE), adverse event leading to death, adverse event leading to discontinuation, investigator assessed drug-related adverse event and serious adverse event will be generated for treatment-emergent adverse events. In addition, summary statistics and descriptive analyses will be conducted for other safety parameters including suicidality as assessed by C-SSRS.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at the specified time points.
If a patient misses a visit, the missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption.

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

7.6 RANDOMISATION

Eligible patients will be randomly assigned to one of the 5 treatment groups, with an allocation of 1:1:1:1:1 respectively for BI 425809 2 mg once daily: BI 425809 5 mg once daily: BI 425809 10 mg once daily: BI 425809 25 mg once daily: placebo once daily.

The randomisation will be stratified by baseline MMSE ($\geq$ 20, < 20). The randomisation will be done in blocks to achieve balanced allocation.

The randomisation of patients to the treatment groups will be performed via an interactive response technology (IRT). BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on an assumed maximum effect size of BI 425809 vs. placebo of 0.35 for the primary endpoint, as well as on the pre-specified model parameters listed in Section 7.3.1.1. The assumed standardized effect size of 0.35 is based on the expectation that BI 425809 has somewhat better efficacy than AChEIs, for which results are summarized in Table 7.7:1.

Table 7.7: 1 Effect sizes for Acetyl Cholinesterase Inhibitors (AChEI)

K Rockwood (2004) [R15-5201]	AChEI Effect size (ES): Median (range)
Donepezil	Low Dose ES = 0.15 (0.03-0.22)
Galantamine	Medium Dose ES = 0.23 (0.12-0.29)
Rivastigmine	High Dose ES = 0.28 (0.01-0.31)

For the PoC analysis of the four BI 425809 dose groups vs. placebo using the MCPmod approach with the parameters as listed in Section 7.3.1, a sample size of 95 evaluable patients per group is needed to establish PoC with 80% average power (one-sided 5% alpha level). An additional 10% of Japanese patients will be added, bringing the total to 105 evaluable patients. The primary analysis will be conducted on all patients, while an internal decision making analysis will be conducted excluding the Japanese patients.

Assuming that 10% of the randomised patients withdraw early without providing useful information, then 117 randomised patients per group are required. With 5 treatment groups, a total of 585 patients are required. Table 7.7: 2 below gives the sample size calculations under different standardized effect sizes using 1-sided type I error rate of 0.05 and 80% power. The calculations for the PoC step have been performed using Dose Finding in the R-package [R15-2001] released on 28 SEP 2014 (depends on R version ≥ 2.15.0). The R codes for the sample size calculations as well as the analyses using the MCPmod approach will be provided in the TSAP.

Table 7.7: 2 Sample size calculation under different standardized effect sizes for the ADAS-Cog$_{11}$ total score change from baseline with 80% power and one-sided alpha of 0.05

Standardized Effect size	0.3	0.325	**0.35**	0.375	0.4
Power = 80%					
N for each active treatment arm	126	107	**95**	81	71
N including 10% Japanese patients[1]	139	119	**105**	90	78
Total	695	595	**525**	450	390
Adjusting for 10% dropout					
N for each treatment arm[2]	154	132	**117**	100	87
Total	772	660	**585**	500	433

[1] Power = 85%
[2] Power = 88%

The sample size calculations in Table 7.7: 3 consider a range of standardized effect sizes and power for a direct comparison between BI 425809 doses and the placebo. Two-sample t-test is used for these exploratory treatment comparisons without adjustment for multiplicity.

Table 7.7: 3 Sample size calculations under different standardized effect sizes and power for the ADAS-Cog$_{11}$ total score change from baseline with one-sided alpha of 0.05

Standardized Effect size	0.3	0.325	0.35	0.375	0.4
Power = 85%					
N for each active treatment arm	161	137	119	103	91
Power = 80%					
N for each active treatment arm	139	118	102	89	78
Power = 75%					
N for each treatment arm	121	103	89	78	68

The two-sample t-test method with equal n's in nQuery Advisor 6.01 was used for the calculation.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), and relevant regulations.

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

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. 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 rule, no trial results should be published prior to finalization of the Clinical Trial Report.

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

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File).

8.1 TRIAL 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 (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional 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 or the patient's legally accepted representative.

The Investigator must give a full explanation to trial patients by using the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB / IEC 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 (CRF) / (e)CRF for individual patients will be provided by the Sponsor. 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 reported on the CRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

Neuropsychological rating scales data entered into the Rater Station will be regarded as source data. These will be centrally reviewed and may be further analysed by the delegated third party vendor.

For eCRFs all data must be derived from source documents.
For the paper CRF, the following data need to be derived from source documents:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))

- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The Investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRF/eCRF 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 CRF / eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and trial site's contract with the sponsor.

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

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 425809 this is the current version of the IB [c02155957-07].

8.4.2 Expedited reporting of adverse events

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment pf the first patient in the whole trial.
The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").
The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.
Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.
The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

For Japan only: when the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

For Japan only: The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

For Japan only: In the event of health injury associated with this trial, the Sponsor is responsible for compensation based on the contract signed by the trial site.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		14 Mar 2016
EudraCT number		2015-005438-24
BI Trial number		1346.23
BI Investigational Product(s)		BI 425809
Title of protocol		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.
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		Flowchart, 5.3.5.1
Description of change		The eC-SSRS (electronic version) was replaced by the C-SSRS (paper version).
Rationale for change		The eC-SSRS is an always self-administered questionnaire and not available in a rater-completed version. In the mild-to-moderate dementia population studied in this protocol the rater-completed C-SSRS is the appropriate tool to monitor suicidality.

Number of global amendment		2
Date of CTP revision		14 Apr 2016
EudraCT number		2015-005438-24
BI Trial number		1346.23
BI Investigational Product(s)		BI 425809
Title of protocol		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.
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1.2
Description of change		A typo was corrected and information on CYP2b6 induction was added.
Rationale for change		New information was added.
Section to be changed		2.1
Description of change		
Rationale for change		New information was added.
Section to be changed		3.3.3, 4.2.2.1, and 4.2.2.2
Description of change		A new exclusion and restrictions on herbal medications were added.
Rationale for change		Herbal medications that may potentially interfere with efficacy assessments were excluded
Section to be changed		5.4.1
Description of change		Recording of food intake with study drug was added
Rationale for change		Information will be required to study impact of food intake on exposure
Section to be changed		7.3.3
Description of change		Genes related to PDE9 pathways were removed

		from the planned pharmacogenomic analysis.
Rationale for change		A typo was corrected

Number of global amendment		3
Date of CTP revision		12 Dec 2017
EudraCT number		2015-005438-24
BI Trial number		1346.23
BI Investigational Product(s)		BI 425809
Title of protocol		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.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Title page
Description of change		Update in Trial Clinical Monitor
Rationale for change		Updated information.
Section to be changed		Synopsis
Description of change		• Deletion of CDR from Main criteria inclusion • Primary Endpoint ADAS-cog_{13} (Alzheimer's Disease Assessment Scale-cognitive subscale) was changed to ADAS-cog_{11} (Alzheimer's Disease Assessment Scale-cognitive subscale) • CDR SB (Clinical Dementia Rating Sum of Boxes) was deleted from Secondary Endpoints • CIBIS and CIBIC+ were added among Secondary Endpoints

		• Further editorial changes
Rationale for change		New concept to detect efficacy signal in executive function and memory of the heterogenous AD patient population which will be included in this trial.
Section to be changed		Flow Chart
Description of change		• Visit 0 was added to allow comfortable time window for imaging, review of In/Ex Criteria and concomitant medications • Changes to the structure of Neuropsychological Rating Scales (ADAS-cog_{13} (Alzheimer's Disease Assessment Scale-cognitive subscale) changed to ADAS-$cog_{11,}$ CDR SB (Clinical Dementia Rating Sum of Boxes) was deleted, CIBIS, CIBIC+ were added • Further editorial changes
Rationale for change		• New concept to detect efficacy signal in executive function and memory of the heterogenous AD patient population which will be included in this trial. • Increase clarity on performance of trial related procedures
Section to be changed		1.2
Description of change		Sentences Updated "Based on in vitro data, at the highest proposed Phase 2 dose of 25 mg, BI 425809 may cause clinically relevant induction of CYP2B6. Based on Phase I clinical studies BI 425809 is a mild CYP3A4 inducer at 25mg"
Rationale for change		Section updated to be in line with current version of the IB dated 04 Dec 2017
Section to be changed		2.3
Description of change		Information on further completed phase 1 trials added
Rationale for change		New information added
Section to be changed		3.3.2
Description of change		CDR deleted from inclusion criteria
Rationale for change		CDR shall not be used as an endpoint therefore this complicated and long scale was deleted from Inclusion Criteria
Section to be changed		3.3.3
Description of change		• Change in haemoglobin cut-off value, less

		strict requirement • Editorial changes
Rationale for change		• Reflect negligible Hb lowering effect of drug on Hb levels therefore allow lower HB levels for inclusion • Changes to ease reading and understanding
Section to be changed		3.3.4
Description of change		Editorial changes
Rationale for change		Increase clarity of the text
Section to be changed		4.2.2
Description of change		• Added sentence • Previous text information on concomitant treatments converted into table and elaborated further
Rationale for change		Increase clarity on concomitant treatments, emphasize necessity of stable background treatments throughout the trial participation as any changes may have direct or indirect impact on cognition and the diagnosis under scrutiny
Section to be changed		5.1
Description of change		Changes aligned with protocol synopsis and Flow Chart, description of newly added neuropsychological tests added, pharmacokinetic endpoint previously not mentioned were added
Rationale for change		New concept to detect efficacy signal in executive function and memory of the heterogenous AD patient population which will be included in this trial.
Section to be changed		5.3.3
Description of change		Possibility to introduce Vitamin B12 and folate treatments if values are found abnormal (below lower limit normal) at Visit 1.
Rationale for change		To allow such patient to participate in the trial, to reduce SF rate
Section to be changed		5.3.4
Description of change		Text on central and independent analysis of ECGs added
Rationale for change		To increase objective assessment of ECGs in the trial
Section to be changed		5.4.
Description of change		Editorial changes
Rationale for change		Simplification of the section
Section to be changed		6.1

Description of change		Editorial and operational changes, more explanation on trial conduct and visit planning
Rationale for change		Increase understanding and allow more flexibility for patient and the site staff in the trial
Section to be changed		6.2.3
Description of change		Procedure for Vital status collection and management of patient withdrawn from the trial added
Rationale for change		Increase understanding and add more guidance how to proceed with above mentioned patient
Section to be changed		7
Description of change		Small editorial changes
Rationale for change		To be aligned with the rest of the protocol text
Section to be changed		8.3.1
Description of change		Explanatory text added
Rationale for change		Increase clarity of the text
Section to be changed		Appendix 10.1
Description of change		Editorial changes
Rationale for change		Text simplified, redundant sections deleted

Number of global amendment		4
Date of CTP revision		12 Jul 2018
EudraCT number		2015-005438-24
BI Trial number		1346.23
BI Investigational Product(s)		BI 425809
Title of protocol		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.
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒

Section to be changed		Flow Chart
Description of change		• Correction of typo in visit window of screening period and IRT registration call in thus aligning this information with section 6.1 • Added End of Study IRT call abnd last dose of trial medication information to the Flow Chart (previously if different sections of the protocol) • Correction of typo in IRT patient registration call (must be at V1 as only at V1 we may enter the MMSE score to the IRT) • Putting the order of neuropsychological rating scales in line with the rater station device the sites are using • Enable 2 laboratory re-tests (if needed) in screening period to ease operational conduct • Added footnotes 17-20 • Correction of further minor typos
Rationale for change		Editorial changes to increase clarity of the text and align with further sections of the protocol
Section to be changed		1.2
Description of change		Correction of typos (Cyp → CYP; itroconazole → itraconazole)
Rationale for change		Corrections of typos
Section to be changed		3.3.2
Description of change		Deletion of duplicated sentence in In. Crit. #4
Rationale for change		Editorial change
Section to be changed		3.3.3
Description of change		Rewording of Ex. Crit. #14
Rationale for change		Increase clarity due to too many questions being raised for this Ex. Crit.
Section to be changed		4.1.4
Description of change		• Dose missed by more than 12 hours should be skipped, original text 4 hours *(this was a typo from previous bid posology)* • Added information on drug administration during visits 3a-c and the last trial drug administration.
Rationale for change		Typo correction and added information to increase clarity of the text and align with further sections of the protocol

Section to be changed		4.2.2.1
Description of change		Correction of typos in table 4.2.2.1.1 Central Analgesics and Vitamin B12/Folate Addition text on Nutritional Support in AD and grapefruit juice and St. John's Wort preparations
Rationale for change		Added text to increase clarity and editorial changes
Section to be changed		4.2.2
Description of change		Rewording of dietary supplements restrictions to be aligned with section 4.2.2.1
Rationale for change		Editorial changes to increase clarity of the protocol
Section to be changed		5.2
Description of change		Deletion of inconsistent sentence (coding administration time 90 seconds was deleted)
Rationale for change		Inconsistent sentence deleted
Section to be changed		5.3.1
Description of change		Added text to enable proper reporting of abnormal findings resulting from physical examinations.
Rationale for change		Added text to increase clarity and top be in line with section 5.3.7 of the protocol
Section to be changed		5.3.3; 5.3.4; 5.3.5.1 and 5.3.7
Description of change		Added text to align with Protocol Flow Chart and editorial changes
Rationale for change		Added text and editorial changes to increase clarity
Section to be changed		6.1 and 6.2.2
Description of change		Modified text to increase clarity and ease operational conduct of the trial
Rationale for change		Editorial changes
Section to be changed		7.3.5
Description of change		Typo corrections
Rationale for change		Editorial changes

APPROVAL / SIGNATURE PAGE

Document Number: c03632269 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-05

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

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		13 Jul 2018 11:01 CEST
Author-Trial Clinical Pharmacokineticist		13 Jul 2018 11:38 CEST
Author-Trial Statistician		16 Jul 2018 22:00 CEST
Approval-Therapeutic Area		17 Jul 2018 08:40 CEST
Approval-Team Member Medicine		17 Jul 2018 18:23 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed