Clinical Trial Protocol

Doc. No.: c02218444-07

BI Trial No.:	1289.27
BI Investigational Product:	BI 409306
Title:	Randomised, parallel-group, double-blind study of systemic and ocular safety and pharmacokinetics of BI 409306 in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers
Clinical Phase:	1c
Trial Clinical Monitor:	Phone: Fax:
Coordinating Investigator:	Phone: Fax: E-mail:
Status:	Final Protocol (Revised Protocol based on global amendment No. 3)
Version and Date:	**Version: 4.0** **Date: 22 February 2017**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: N/A			
Name of active ingredient: BI 409306			
Protocol date: 05-Mar-2015	**Trial number:** 1289.27		**Revision date:** **22 February 2017**
Title of trial:	Randomised, parallel-group, double-blind study of systemic and ocular safety and pharmacokinetics of BI 409306 in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers		
Coordinating Investigator:	Phone: Fax:		
Trial site:	Multi-center		
Clinical phase:	Ic		
Objectives:	To evaluate the ocular and systemic safety and pharmacokinetics during 14 day treatment period in patients with schizophrenia, Alzheimer's disease, or age-comparable healthy volunteers treated with oral film-coated tablet of BI 409306 25 or 100 mg		
Methodology:	Multi-center, parallel-group, double-blind trial of two doses of study medication in three groups treated for 14 days		
No. of patients:			
total entered:	60 planned		
each treatment:	30 planned for each treatment group (10 AD/10 CIAS/10 HV per group)		
Diagnosis:	Patients with schizophrenia in stable clinical status and on stable antipsychotic treatment **OR** patients with diagnosis of mild Alzheimer's disease currently treatment-naïve or on stable treatment(s) **OR** age-comparable healthy volunteers.		

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Main criteria for inclusion:	Schizophrenia patients age 18-55 years with established diagnoses of schizophrenia (per Diagnostic and Statistical Manual of Mental Disorders version V (DSM-V)) with the following clinical features: i. Clinically stable and are in the residual (non-acute) phase of their illness for at least 8 weeks prior to randomisation ii. Current antipsychotic and concomitant psychotropic medications must meet the criteria below: ii)-1. Maintained on current atypical (second generation) antipsychotic medications (in any approved dosage form) other than Clozapine and on current dose for at least 8 weeks prior to randomisation, and/or ii)-2. Maintained on current typical (first generation) antipsychotic medications and on current dose for at least 6 months, optionally combined with anticholinergics if treated with a stable dose for at least 6 months prior to randomisation, and/or ii)-3. Maintained on current concomitant psychotropic medications other than anticholinergics, antiepileptics and lithium, and on current dose for at least 8 weeks prior to randomisation. Antiepileptics and lithium are allowed if initiated at least 6 months prior to randomisation. iii. Have no more than a ‘‘moderate’’ severity rating on hallucinations and delusions (Positive and Negative Syndrome Scale (PANSS)–positive syndrome Hallucinatory Behavior item score ≤ 4 and Delusions item score ≤ 4) iv. Have no more than a ‘‘moderate’’ severity rating on positive formal thought disorder (PANSS–positive syndrome Conceptual Disorganization item score ≤ 4) v. Have a minimal level of extrapyramidal symptoms (Simpson-Angus Scale total score < 6) and depressive symptoms (PANSS–general psychopathology syndrome Depression item score ≤ 4) OR Patients with diagnosis of mild Alzheimer’s Dementia according to the recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease, who are currently treatment-naïve or on stable treatment of acetyl cholinesterase inhibitors and/or memantine for at least 3 months before randomization. A MMSE (Mini-Mental-State-Examination) score between 18-26, and age 55 - 85 years with availability of pre-existing brain CCT or MRI compatible with diagnosis of Alzheimer’s disease.		

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Main criteria for inclusion:	Patients older than 85 years may be included based on an acceptable general health status, (e.g. concomitant diseases, physical capability to follow the required study procedures [visits etc.]) per investigators judgement. OR Age-comparable healthy volunteers age 18 to 85 years. Healthy volunteers older than 85 years may be included based on an acceptable general health status, (e.g. concomitant diseases, physical capability to follow the required study procedures [visits etc.]) per investigators judgement.		
Test products:	BI 409306		
dose:	25 mg q.d. or 100 mg q.d.		
mode of admin.:	Tablet, Oral		
Comparator products:	N/A		
dose:			
mode of admin.:			
Duration of treatment:	14 days		
Criteria for Pharmacokinetics:	Secondary: $C_{max,ss}$, $t_{max,ss}$ of BI 409306		
Criteria for safety:	Primary endpoint: • The number (%) of subjects with AEs, coded to the MedDRA-SOC 'Eye disorders', as determined by the investigator at End of Trial Secondary endpoint: • The number (%) of subjects with drug-related AEs as determined by the investigator at End of Trial		
Statistical methods:	Analyses of adverse events will be performed in accordance with BI statistical standards, essentially, tabulations of frequencies/proportions will be displayed. Descriptive statistics will be provided for PK endpoints.		

FLOW CHART

	Screen-ing[1]	Base-line[2]	Treatment														End of Trial[10]
Visit	1	2	3	4**	5**	6**	7	8**	9	10**	11**	12**	13**	14**	15	16	EOT
Day	-28 to -3	-2 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21 to 28
Informed Consent	X																
Demographics	X																
Medical History	X																
Physical Examination	X	X							X								X
Vital Signs[3,4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[4]	X		X						X							X	X
Eligibility Criteria	X[1]																
Randomization		X															
	X[1]																
Laboratory	X	X							X							X	X
Urinalysis	X	X															X
Drug Screen	X																
Pregnancy Test[5]	X	X							X							X	
PK Blood Sample[4*]			X[7*]													X[7*]	
			X														
Drug Administration			X[7]	X	X	X	X	X	X	X	X	X	X	X	X	X[7]	
AEs/CTs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Termination																	X

* Refer to table below for timing of intensive PK sampling for Days 1 and 14.
**Home visits may be conducted for these visits in lieu of study center visits (cf. Section 6.1).

Treatment Day 1 and 14: Blood Sampling for Pharmacokinetic and Vital Signs

Planned Time (h:min)	-2:00	0:00	0:20	0:30	0:45	1:00	1:30	2:00	4:00	6:00
Clock Time (h:min)	Pre-dose	8:00 (dosing)	8:20	8:30	8:45	9:00	9:30	10:00	12:00	14:00
PK Sample	X		X	X	X	X	X	X	X	X
Vital Signs[13] (Day 1 only)	X[13]		X[13]	X[13]	X[13]		X[13]			

Footnotes:

1. Screening to be performed within 3-28 days before drug administration, including body weight, height, smoking and alcohol history, and also an abbreviated visual exam per exclusion criteria (cf. Section 3.3.3).

2. In-patient stay is optional. If feasible for in-patient stay, the following procedures would apply: eligible study participants will be admitted to the study center in-patient facility for overnight stays. All CIAS subjects will remain in-patient for the duration of the treatment period, starting on Day -2 and will be allowed to leave after the last study procedure and after their fitness has been confirmed by the investigator on Day 14. AD subjects and healthy volunteers will check into clinic on Day -2 and remain in-patient till Day 1, return for daily visits till Day 12, and check into clinic again on Day 13 to Day 14. If there is a need that required AD subjects to remain in-patient, then the CIAS schedule plan may be utilized, per investigator discretion.
3. Vital signs will be collected via orthostatic measurements of systolic/diastolic blood pressure and pulse rate supine after 5 minutes rest, immediately after standing up and again after 3 minutes standing (cf. Section 5.2.6).
4. Vital signs and ECGs should be completed before dosing (pre-dose) and PK blood draws. Pre-dose is within 2 hours before the dose is given.
5. Serum pregnancy tests will be performed at specified study visits on female subjects of child-bearing potential – except for CIAS subjects staying in-patient. In addition, urine (dipstick) pregnancy tests will be performed at Visit 2. Only those female subjects with a negative urine pregnancy test will receive study medication at Visit 3 (Day 1).
6.

7. Time of last meal before drug administration will be recorded on PK blood draw Days 1 and 14.
8.

9.

10. End-of-Trial examination (EOT) to be performed 7 to 14 days after last drug administration. Subjects who discontinue treatment early due to any reason (cf. Section 3.3.4.1) must complete an early EOT visit within 7 days of last drug administration, with all the procedures performed.
11.

12.

13. Only on Day 1 PK, pulse rate is to be measured in a supine position after at least 5 minutes of rest pre-dose and at the time points of post-dose PK sampling until 110 mins post-dose (20 ±5 min, 30 ±5 min, 45 ±10 min and 90 ±20 min). Pulse rate should be taken before the respective blood for PK sampling is drawn. Orthostatic measurements of systolic/diastolic blood pressure and pulse rate are to be done at pre-dose and at 70~110 minutes post dose.

TABLE OF CONTENTS

ABBREVIATIONS

AChE-Is	Acetylcholinesterase Inhibitors
AD	Alzheimer's Disease / Alzheimer's Dementia
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic-Pyruvic Transaminase)
AST (SGOP)	Aspartate Aminotransferase (Serum Glutamic-Oxaloacetic Transaminase)
BI	Boehringer Ingelheim
BP	Blood Pressure
BLQ	Below the Limit of Quantification
bpm	beats per minute
BRPM	Blinded Report Planning Meeting
cf.	Consult
CA	Competent Authority
CI	Confidence Interval
CIAS	Cognitive Impairment Associated with Schizophrenia
C_{max}	Maximum concentration of the analyte in plasma
CLCR	Creatine Clearance (calculation)
CML	Local Clinical Monitor
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Concomitant Therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DEDP	Drug Exposure During Pregnancy
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic Acid

DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Version V
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EM	Extensive Metabolizers
EOT	End of Trial
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
gCV	Geometric coefficient of variation
gMean	Geometric Mean
GCP	Good Clinical Practice
h	hour
HV	Healthy Volunteers
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
IUDs/IUSs	Intra Uterine Devices/Systems
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
NC	Not Calculated
NCE	New Chemical Entity
NOA	Not Analyzed
NIMP	Non-Investigational Medicinal Product
NOAEL	No Observed Adverse Effect Level
NOP	No Peak Detectable
NOR	Novel Object Recognition
NOS	No Sample available
PBO	Placebo
PCP	Phencyclidine
p.o.	per os (oral)

PK	Pharmacokinetics
PM	Poor Metabolizers
PR	Pulse Rate
q.d.	quaque die (once a day)
RBC	Red Blood Cell
RDC	Remote Data Capture
REP	Residual Effect Period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SSRIs/SNRIs	Serotonin/Norepihnephrine Re-Uptake Inhibitors
SUSARs	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TDM	Trial Data Management
TDMAP	Trial Data Management and Analysis Plan
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
TSTAT	Trial Statistician
$t_{max,ss}$	Time from (last) dosing to the maximum measured concentration of the analyte in plasma at steady state
ULN	Upper Limit of Normal
V_z/F	Apparent volume of distribution following an extravascular administration
WBC	White Blood Cell

1. INTRODUCTION

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

1.1 MEDICAL BACKGROUND

Alzheimer's disease (AD), a chronic progressive mental disorder, is the most common cause of dementia and accounts for 50 to 70 % of all cases. AD is mainly a disorder of the elderly; however it can also affect patients below the age of 60. More than 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).

AD is characterized, in the early stage, by an impairment of episodic memory and other cognitive domains, like executive function, orientation and judgment. 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. This is followed by a progressive decline in the ability to perform activities of daily living and the appearance of behavioral changes and/or psychiatric symptoms (mood disturbances, hallucinations, personality changes).

Schizophrenia is a chronic, severe, and disabling brain disorder affecting about one percent of the world´s general population. The symptoms of schizophrenia fall into three broad categories:

- Positive symptoms, such as delusions, hallucinations, and disordered thoughts.
- Negative symptoms, such as restricted affect and drive.
- Cognitive symptoms, such as poor executive functioning, trouble focusing or paying attention, impairment of working memory, verbal and visual learning and memory.

Cognitive impairment is a core feature of schizophrenia. There is substantial evidence that cognitive deficits are a major determinant of functional recovery in schizophrenia. Around 20-60% of the variance in functional outcome in schizophrenia is explained by cognitive performance.

On cellular level, AD is characterized by a progressive loss of synapses and neurons. Affected transmitter systems mainly include cholinergic and glutamatergic neurons. Cognitive dysfunction in schizophrenia is caused by an impaired functioning of glutamatergic pathways in (pre-) frontal cortical but also limbic areas of the brain (R10-5098; R10-5113; R10-5103). Glutamate as the major excitatory neurotransmitter in the human brain is most prominently associated with functions of memory formation and learning. Glutamatergic transmission is mediated by various receptors with the post-synaptic NMDA receptor playing an essential role. Upon activation, a cascade of intracellular, post-synaptic signaling events is

triggered through elevation of second messengers such as cAMP and cGMP with subsequent activation of protein kinases and manifestation of long-term potentiation (LTP) and synaptic plasticity. LTP is regarded as a validated physiological model for cellular processes underlying learning and memory formation (R10-5109; R10-5092; R10-5102). Impaired NMDA receptor signalling and reduced levels of cGMP (R10-5110, P10-10289; R10-5097) have been shown in animal models of schizophrenia and in patients suffering from AD. Phosphodiesterase 9A (PDE9A) hydrolyses cGMP with the highest affinity of all PDEs and is highly expressed in the neocortex and hippocampus; therefore it is likely to be a significant determinant of intracellular basal cGMP levels in these brain regions.

PDE9A inhibitors should restore cGMP levels to physiological levels and give rise to memory improvement in patients via enhancing glutamatergic signalling, manifestation of long-term potentiation and strengthening of synaptic plasticity. BI 409306 showed convincing efficacy in two animal models of cognition enhancement addressing cognitive domains and brain regions known to be affected in AD and CIAS.

The pathophysiological mechanisms leading to deficits in cognition in schizophrenia and Alzheimer´s disease are largely unknown. Some of the deficits concern functions, such as working memory, attention, and perceptual organization, that have been proposed to involve synchronization of oscillatory activity in the high-frequency band (β and γ) (R14-3532).

A substantial body of EEG studies supports the hypothesis that schizophrenia and AD are related to impaired neural synchrony and there is growing evidence that impaired sensory-processing significantly contributes to the cognitive deficits in these disorders (R14-3419; R14-3418; R14-3420). Sensory event-related potentials (ERPs) have also been widely used to examine basic neuronal activity in both normal brain function and in schizophrenia and Alzheimer´s disease, and have revealed abnormalities in the basic processing of both repeated and novel environmental stimuli (R14-3433) and may be used as biomarkers of the diseases (R14-3416; R14-3417).

Furthermore, visual acuity disturbances were the most common BI 409306 drug related adverse events, based on the phase I studies data. Since the visual disturbances of the PDE5-inhibitor sildenafil are known to be caused by its PDE6 off-target activity and PDE6 enzyme is expressed in photoreceptor cells of the retina, BI 409306 was evaluated for potential activity against recombinant human PDE6 isoforms revealing no relevant activity (i.e. IC50 > 100 µM). Additionally, BI 409306 was tested for potential affinity to 95 off-target receptors at 10 µM using binding assays showing no relevant activity.

In summary, based on preclinical in vitro data, visual disturbances do not seem to be linked to PDE6 or other off-target activity of BI 409306. Two preclinical studies have been conducted to elucidate an explanation for these phenomena.

Since no data are available on PDE9 protein expression in the retina, an immunhistochemical analysis was performed in the first preclinical study in order to assess PDE9 expression in retina cells of rat and human tissue. This study demonstrated specific staining of PDE9 expression in rat and human retina tissue, confirmed via both positive tissue control (cerebellum and kidney) and via negative control (absence of primary antibody; isotype

control). There was widespread distribution of PDE9 in the rat and human retina except the outer segment of the photoreceptor layer.

Subsequently, BI investigated in a second preclinical study the effects of PDE9- inhibitor BI 409306 on rat retina in-vitro by measuring electro-retinogram (ERG) and ganglion cell activity using different concentrations and sildenafil, a PDE5-inhibitor with PDE6 off-target activity as an active control. Results show that the PDE9-inhibitor increased the amplitude of A-wave and B-wave of ERG, like the experimental control sildenafil. Field action potential analysis revealed that BI 409306, comparable to the experimental control sildenafil, enhanced spike activity of the retinal ganglion cells. The effects of BI 409306 and sildenafil on retinal activity (ERG and ganglion cell activity) were shown to be reversible.

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

This study will utilize targeted ophthalmological assessments to further explain and characterize the effect of BI 409306 on ocular physiology.

1.2 DRUG PROFILE

1.2.1 Drug substance

BI 409306 is a new chemical entity (NCE) intended for oral administration. Film coated immediate release tablets of 25 mg and 100 mg will be applied in this trial.

Pharmacology

BI 409306 is a potent and selective PDE9A inhibitor. In vitro, BI 409306 inhibits the full-length rat PDE9A with an IC50 of 168 nM and shows a long-lasting potentiation of hippocampal LTP in acute slices of rat brain (U10-2281; U10-2282; U10-2283; U10-2286).

In vivo, a dose-dependent increase of cGMP in brain and cerebrospinal fluid (CSF) was seen (U10-2288; U10-2287). In addition, BI 409306 reversed the memory impairment induced by the NMDA receptor antagonist MK-801 in T-maze spontaneous alternation test (T-maze) and novel object recognition test (U10-2472; U10-2284).

The results obtained with BI 409306 are well in line with the mode of action hypothesis of PDE9A inhibition, i e. targeting glutamatergic signalling pathway via increase of cGMP to strengthen LTP and synaptic plasticity leading to memory enhancement.

Preclinical Pharmacokinetics and Metabolism

The pharmacokinetics of BI 409306 in rats and dogs were characterized by rapid absorption and fast distribution into tissues. The volume of distribution was 0.8 l/kg in the rat and 1.4 l/kg in the dog. Total plasma clearance was low in the rat (12.7 mL/min·kg) and in the dog (7.4 mL/min·kg). The absolute bioavailability accounted for 74% in rats and for 100% in dogs (C02101303).

After oral administration of [14C] labeled BI 409306 to rats, 26.2% of the administered dose was recovered in feces and 64.5% was recovered in urine until 48 h post dose (C02101303).

BI 409306 is extensively metabolized, and two major Phase I metabolites are likely formed in humans (U10-2959; U10-2646). In vitro investigations with human hepatocytes and human liver microsomes demonstrated that BI 409306 oxidative metabolism is mainly dependent on cytochrome P450 (CYP) isoenzyme 2C19 (U10-2646). In human liver microsomes of CYP2C19 poor metabolisers, BI 409306 metabolism was low and mediated by CYP 3A4/5, though a contribution of further enzymes cannot be excluded (U11-2807).

The in vitro plasma protein binding of BI 409306 in humans is low (27%) and consistent over other species with no observed gender difference. BI 409306 showed a high intrinsic passive permeability in investigations with Caco-2 cells. BI 409306 was not a substrate of P-gp, BCRP and SLC. The drug was identified as weak inhibitor of P-gp, BCRP, OAT3 and other SLC-transporters with IC_{50}'s of >500 µM, 100 - 500 µM, 26 µM and >200 µM, respectively.

An affinity to melanin containing tissues, i.e. skin and eye was observed; however, as BI 409306 does not significantly absorb light in the relevant wavelength of 290 – 700 nm, no phototoxic potential is expected. After single intravenous and oral administration to rats, BI 409306 was extensively metabolised.

Drug-drug interactions based on inhibition or induction of cytochrome P450 enzymes by BI 409306 are unlikely to occur. In vitro investigations with human hepatocytes and human liver microsomes demonstrated that BI 409306 metabolism is mainly CYP 2C19 dependent.

Safety Pharmacology (other than ocular)

Central nervous system

There was no effect of BI 409306 in the Irwin test in rats and on nocturnal motility in rats up to dose of 45 mg/kg. Reduced body weight gain (24 h post dose but reversible until Day 7), slight to moderate decrease in body temperature (15 min post dose) and slight decrease in locomotor activity (15 min post dose) were limited to the maximum dose tested (750 mg/kg) (C02101303).

Cardiovascular function

BI 409306 did not induce any effects on ECG and blood pressure in dogs (telemetry) up to the dose of 5 mg/kg. Dose dependent increase of contractility, heart rate with cases of sinus tachycardia and systolic ventricular pressure in the dose levels of 9 and 20 mg/kg were observed. Additionally, decrease in systolic pressure and reduction of RR/ PR/ QT intervals were limited to the highest dose level of 20 mg/kg (C02101303).

Respiratory function

No physiologically relevant findings up to the maximum dose tested (750 mg/kg).

Gastrointestinal

BI 409306 had no effects on Gastrointestinal function in rats up to the maximum tested dose

1.2.2 Toxicology

Target organs identified after repeat-dose toxicity testing were liver (rats), adrenal glands (rats), ovaries (rats), spleen (rats) and the cardiovascular system (rats and dogs) (R05-2282; U10-2597; U10-4089; U11-1173). Adverse effects in rats were mainly limited to the highest doses tested. Cardiovascular effects in dogs occurred also at lower dosages but were considered monitorable.

The No Observed Effect Levels (NOEL) after oral administration of BI 409306 for 13 weeks was 9 mg/kg (corresponding to C_{max}) of 9090/7880 nmol/L, and AUC_{0-24h} of 24600/13500 nmol·h/L in males/females) in the rat. After oral administration of BI 409306 for 4 weeks the No Observed Adverse Effect Level (NOAEL) was 9 mg/kg (corresponding to C(max) of 11900/13000 nmol/L, and AUC_{0-24h} of 26900/30800 nmol·h/L in males/females) in the dog.

The overall assessment of genotoxicity testing in vitro and in vivo revealed that BI 409306 is not genotoxic.

Data from the dose range finding studies in mice and rats indicate a low potential of BI 409306 for acute toxic effects (estimated LD50: > 750 mg/kg in mice; around 1000 mg/kg in rats; > 50 mg/kg in dogs).

Assessment of female reprotoxicity has not been conducted yet.

Specific toxicological aspects

The liver and the heart were identified as target organs for adverse histopathological changes, restricted to the highest tested dose of 750 mg/kg in rats (C02101303).

In the liver, adaptive hypertrophy of the hepatocytes (corresponding to reversibly elevated organ weight), mild exacerbation of apoptotic hepatocytes and postnecrotic microgranulomas in males were observed.

Cardiac changes had also been noted in the 2-week oral dose range finding study, including multifocal fibrosis/fibroplasia in the septum and the papillary muscle. A nephropathy in the kidney was ascribed to the male rat-specific nephropathy due to accumulation of α2u-globulin and therefore to be of no relevance for humans.

In the dog, the main finding was increased heart rate, ranging from moderate elevation to tachycardia. Whereas cardiac histopathological changes (slight hemorrhages, inflammatory infiltration with focal necrosis) were noted in the escalating dose study with oral doses ranging from 10-50 mg/kg administered for 3 or 4 days each, no comparable morphological alterations were observed in the pivotal 4-week study up to 40 mg/kg. A slight cellular depletion of hematopoietic cells in the bone marrow was only observed in the escalating dose

study, was neither confirmed in the 2-week dose range finding study nor the pivotal 4-week study and thus may represent an incidental finding.

In summary, the non-clinical safety data of BI 409306 supported a clinical Phase I trial with oral administration in patients with Alzheimer Disease and schizophrenia. The toxicological profile of BI 409306 was characterized by cardiac effects which seem to be consistent with those described for phosphodiesterase inhibitors in general. All adverse effects generally were restricted to high dose levels and were reversible. Visual side effects occurred shortly after dosing because there was widespread distribution of PDE9 in the retina but the side effects will mostly be resolved within 1 h. Based on the available non-clinical data, BI 409306 was associated with an acceptable safety profile for phase I studies with oral administration under close monitoring of the toxicities identified, in particular careful monitoring of cardiac function and serum liver enzymes.

1.2.3 Clinical Study

Safety data from five phase I studies are available (U12-1034; U13-1182; U12-2165; U13-1303; c02098989) in healthy young and healthy elderly volunteers. In all five healthy volunteer trials, the most frequent drug related adverse events were visual side effects that occurred shortly after dosing and mostly resolved within 1 hour. Therefore they are in close connection to maximum BI 409306 plasma concentrations as the concentration-time profile sharply and steeply peak within the first 1-2 hours and then rapidly decline afterwards.

In vitro data on BI 409306 evaluating potential activity against recombinant human PDE6 isoforms in the retina revealed no relevant activity, indicating that visual disturbances do not seem to be linked to PDE6 or other off-target activity of BI 409306 (cf. Section 1.1). Two preclinical studies were then conducted to further explore this phenomenon. The first study confirmed that there was a widespread distribution of PDE9 in the rat and human retina; and the second revealed enhanced spike activity of the retinal ganglion cells and that these activities were shown to be reversible. It was concluded that PDE9 protein is expressed in retina and PDE9- inhibition leads to changes in retina physiology that likely result in the transient visual effects noted in human.

Overall, there were no relevant changes observed for laboratory, ECG recordings, and vital signs following treatment with BI 409306 when compared to placebo. Only a rapid and short lasting increase in supine pulse rate of 12.9 ± 4.4 bpm was detected in Chinese CYP2C19 poor metabolizers subjects treated with BI 409306 (100 mg single dose) in Study 1289.4 (c02098989). Following this observation, pharmacometric analysis of all available human data revealed a BI 409306 plasma concentration dependent increase in supine pulse reaching a maximum of 7-13 bpm (median) at high exposure end in CYP2C19 poor metabolizers treated with BI 409306 at 100 mg. The maximum effects of BI 409306 on pulse rate were generally achieved at maximum BI 409306 plasma concentrations (20-30 minutes post dose) and disappeared rapidly with declining concentrations.

None of the safety data presented a safety issue for further clinical trials.

1.2.4 Pharmacokinetic profile in humans

BI 409306 is rapidly absorbed and distributed with maximum plasma concentrations occurring within the first hour after oral administration to humans. Drug elimination occurs rapidly afterwards in an at least biphasic manner. Less than 2 % of the oral dose is recovered unchanged in urine. Plasma protein binding was determined at 27 % in humans.

BI 409306 is extensively metabolized. Compared to CYP2C19 extensive metabolizers (EM), poor metabolizers (PM) had about 2.2 - 2.3 and 4.1 - 5.0-fold higher peak and total exposure.

However, the C_{max} and $AUC_{0-\infty}$ values observed in the PM group on the 10 mg and 100 mg dose level were still fully contained within the exposure-range observed in the EM group up to a dose of 350 mg.

In the multiple rising dose trials 1289.2 (U13-1182) and 1289.17 (U13-1303), only minor accumulation was seen, regardless of the predicted phenotype of CYP2C19, with mean accumulation ratios for C_{max} and AUC of 1.02 to 1.41 among the once daily treatment groups evaluated. In both multiple dose trials, also elderly male and female volunteers (65 years or older) were included, who showed slightly higher exposure compared to the young volunteers at the highest tested dose of 100 mg q.d.

While plasma exposure increased slightly more than dose proportional over the dose range of 0.5 mg to 350 mg tested in the single rising dose trial, no deviation from dose proportionality was noted in the multiple dose trial over the dose range from 25 mg to 100 mg given once daily.

A drug-drug interaction with fluvoxamine, a strong inhibitor of CYP2C19 and CYP1A2 induced a 30-fold increase of the total plasma exposure (AUC_{0-24}) and a 6-fold increase in Cmax of BI 409306. Mainly non-PMs (10 out of 13 subjects) and only 1 PM were included in the study. These results suggest that in non-PM, CYP1A2 is involved in BI 409306 metabolism, in addition but to a lesser extent to CYP2C19, and that in PMs CYP1A2 is the major CYP450 isoform involved in the metabolism of BI 409306 (Study 1289_0035).

BI 409306 enters the CSF as shown in trial 1289.3 (U12-2165) after single dosing from 25 to 200 mg. The maximum concentration (C_{max}) of BI 409306 in plasma was achieved between 0.75 h and 1.25 h after drug administration and between 1.50 h and 2.00 h after drug administration in CSF. As such, the maximum CSF concentrations were reached approximately 0.75 h to 1.25 h after the maximum plasma concentrations and increased with increasing dose. The dose-adjusted gMean (90% CI) CSF to plasma ratio of the BI 409306 C_{max} was 28.31% (25.42% to 31.53%). After attainment of C_{max}, BI 409306 concentrations declined in a monophasic manner in CSF with a similar terminal half-life compared to plasma (1.28 h to 2.35 h in plasma and 1.24 h to 1.62 h in CSF).

For further details please see the current version of the BI 409306 Investigator's Brochure (C02101303).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is designed to evaluate the ocular safety, tolerability and pharmacokinetics of BI 409306 film coated tablets administered in 25mg q.d. or 100 mg q.d. given orally for 14 days in patients with schizophrenia or Alzheimer's disease, and compared to age-comparable healthy volunteers.

There are currently no approved medications indicated for the treatment of cognitive impairment in schizophrenia, and currently approved AD treatment is purely symptomatic. Registered symptomatic treatment consists of acetylcholinesterase inhibitors (AChE-Is) and memantine. AChE-Is in general and donepezil in particular can be currently regarded as gold standard for treatment of mild to moderate AD. As the AD research interest are moving toward more effective symptomatic treatment options and new compounds with a disease-modifying potential, the current focus on a symptomatic treatment that proves to be more efficacious than the currently available compounds (AChEIs, memantine) in improving both existing cognition deficits and the ability to better perform activities of daily living would provide a substantial benefit to patients.

Safety data from five phase I studies are available (U12-1034; U13-1182; U12-2165; U13-1303; c02098989) in healthy young and healthy elderly volunteers, and one study in patients with schizophrenia (Study 1289.18, c02318916). In all six studies, the most frequent drug related adverse events were visual side effects (such as sensation of flashing lights, altered colour perception, photophobia/ increased sensitivity to light or blurred vision) that occurred shortly after dosing of BI 409306 and mostly resolved within 1 hour. Therefore they are in close connection to maximum BI 409306 plasma concentrations as the concentration-time profile sharply and steeply peak within the first 1-2 hours and then rapidly decline afterwards. Further preclinical investigations were performed that link PDE9 expression and function in rat and human retina to these clinical findings. This study will further characterize the effect of BI 409306 on ophthalmologic physiology in patients with AD, patients with CIAS, and healthy volunteers.

Mismatch negativity (MMN), P1, N1 and P3a, and evoked gamma power are auditory ERP components that have emerged as translational biomarkers with promising applications for use in clinical studies to assess drug sensitivity.

Patients with schizophrenia and Alzheimer's disease have been shown to have abnormal electroencephalographic (EEG) gamma-band responses (GBRs) associated with sensory (R14-4685; R14-4695; R14-4678; R14-4679; R14-4680), perceptual (R14-4681) attentional (R14-4682), and cognitive control (R14-4677) processes. Glutamatergic neurotransmission at NMDA receptors provides excitatory regulation of parvalbumin fast-spiking interneurons, contributing to the generation of gamma oscillations in pyramidal cell networks (R14-4684). Gamma oscillatory activity non-invasively measured by EEG in patients with schizophrenia is of interest because disrupted GABAergic and glutamatergic cortical activity have been implicated in the pathophysiology of the illness.

MMN, P1, N1 and P3a components are sequentially evoked as an ERP complex in response to unattended changes in background stimulation (R14-4688; R14-4689). Since these measures require no overt behavioral response and can be elicited even in the absence of directed attention (R14-4688; R14-4690), they are presumed to reflect a predominantly automatic or pre-conscious process of detecting a "mismatch" between the deviant stimulus and a sensory–memory trace (R14-4683).

Previous studies have demonstrated that MMN, P1, N1 and P3a are each significantly correlated with distinct domains of cognitive (R14-4687) and psychosocial functioning (R14-4686).

Because of the established link between these ERP components, the glutamatergic system, and cognitive deficits in AD and schizophrenia, they will be measured in healthy volunteers, AD patients and schizophrenia patients to further understand the effect of BI 409306 (R14-3419, R14-3418, R14-3420).

Single dose of 100 mg BI 409306 in Chinese CYP2C19 poor metabolizers subjects showed a rapid and short lasting increase in supine pulse rate of 12.9 ± 4.4 bpm. Further observations on this population revealed a BI 409306 plasma concentration dependent increase in supine pulse reaching a maximum of 7-13 bpm (median) at high exposure (median C_{max} was achieved at 0.417 h) approximately 25 min minutes post dose in Trial 1289.4 and ranged from 0.167 to 0.750 h post dose) and disappeared rapidly with declining concentrations (c02098989). This study will include 24-hour heart rate monitoring to further explore the cardiac safety of BI 409306.

The ophthalmologic physiology and neurophysiological biomarkers observations, along with the additional safety and pharmacokinetic profiles will support further studies to define safety and efficacy of BI 409306 in patients with AD and CIAS.

2.2 TRIAL OBJECTIVES

Primary objective:

To investigate the ocular safety of BI 409306 in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers following oral administration of 25 mg and 100 mg over 14 days.

Secondary objectives:

To evaluate the systemic safety and pharmacokinetics of BI 409306 in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers following oral administration of 25 mg and 100 mg over 14 days.

It is not planned to test any statistical hypotheses. See Section 5 for details on safety endpoints.

2.3 BENEFIT - RISK ASSESSMENT

The target structure (PDE9) for the compound BI 409306 is widely distributed in various tissues and organs but predominantly localized throughout the specific brain areas (hippocampus, cortex, olfactory bulb, striatum, thalamus, hypothalamus, amygdala, midbrain, cerebellum (R12-4412, R10-5402).

The enzymatic action of cyclic nucleotide PDEs is the primary mechanism for inactivation of cAMP/cGMP by hydrolyzing. Inhibition of PDE9 increases the intracellular availability of the second messenger cGMP and consequently could have a positive effect on several aspects of cognition, including information processing, attention, memory and executive functioning. Based on its mechanism of action and its preclinical profile, including the in vitro, in vivo pharmacology data, the data from toxicology studies in two species as well as the data obtained in the clinical studies (U12-1034, U12-2165, U13-1182), there is no indication that BI 409306 should be regarded as a high risk compound.

Overall, BI 409306 shows a favorable nonclinical safety profile. There was no genotoxic potential of BI 409306. The toxicological profile of BI 409306 is characterized by cardiac effects which seem to be consistent with those described for phosphodiesterase inhibitors in general. Previous clinical trials found that BI 409306 was well tolerated in young and elderly healthy subjects in single doses of 0.5 to 350 mg and multiple doses up to 100 mg once daily. The most frequent drug related adverse events were visual side effects that occurred shortly after dosing and mostly resolved within 1 hour. All adverse effects generally were restricted to high dose levels and were reversible (U12-1034; U13-1182; U12-2165; U13-1303). Cardiac function will be monitored during the study, along with a 24-hour ambulatory heart rate monitoring (cf. Flow Chart).

As with all drugs, the potential for hypersensitivity and allergic reactions have to be taken into consideration when BI 409306 is administered. Other risks are inherent to any early clinical trial such as unexpected adverse clinical or laboratory event. Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure subjects´ safety.

No studies have been done with BI 409306 in pregnant women or women who are nursing their infants. It is unknown if BI 409306 is safe for pregnant women, unborn babies and infants who are nursing. It is unknown either if BI 409306 has an effect on sperm or eggs. Hence, female subjects who are nursing or pregnant are not allowed to join the study. Female subjects who are of child-bearing potential must accept to use a reliable form of birth control throughout the trial and follow-up period.

A potential effect of BI 409306, a centrally acting compound, on suicidality cannot be ruled out. Therefore, suicidality monitoring will be performed pre-dose and throughout the study to ensure that potential suicidality will be recognized in order to apply appropriate action.

This is an experimental drug at an early stage of testing and therefore an individual benefit cannot be guaranteed. The study procedures (e.g. ocular assessments, 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 AD and CIAS patients. Even if there is no direct benefit for the subjects during participation in this trial, it can be assumed that the trial results may contribute to better drug development in future.

This study will explore the ophthalmologic changes with respect to the visual acuity effects and other neurophysiological changes in order to further investigate the safety, tolerability and pharmacokinetics of the doses of BI 409306 (25 mg and 100 mg) that were already established to be within the safety margin of therapeutic dose.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-center, double-blinded, parallel groups study in patients with mild Alzheimer's Dementia (AD) and cognitive impairment associated with schizophrenia (CIAS), and healthy volunteers (HV).

Approximately 60 subjects (20 with AD, 20 with CIAS, and 20 age-comparable HV) who met the eligibility criteria will be randomized into either the BI 409306 25mg or 100 mg treatment group according to the study design provided (see Figure 3.1: 1). Refer to Section 3.3.2 for description of age-comparable healthy volunteers (e.g. definition of low age group and high age group).

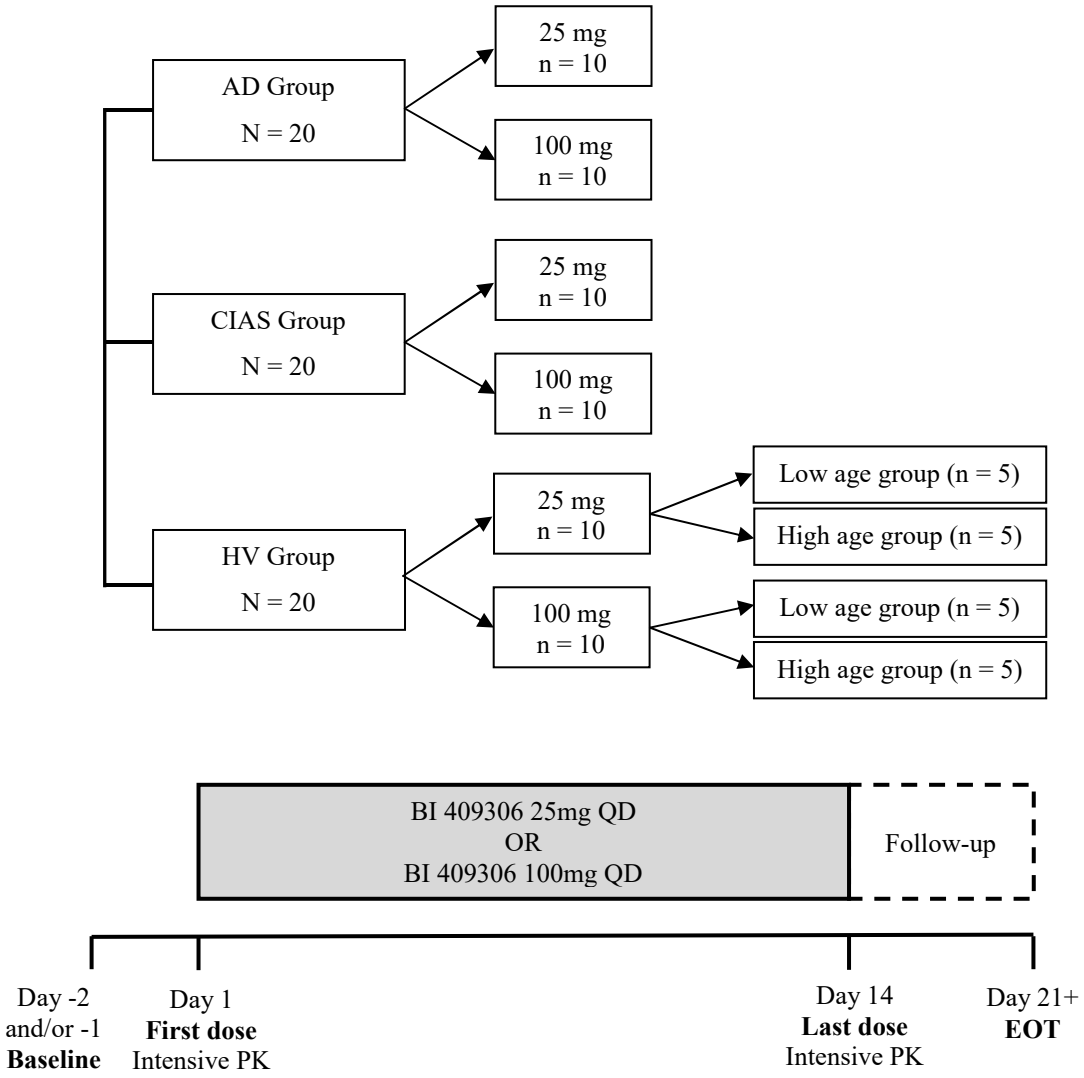


Figure 3.1: 1 Overview of study design

Subject's participation starts once they have signed the informed consent form. Eligible patient/volunteers enter the trial (Figure 3.1: 1) at Visit 2, are treated for 14 days with either the BI 409306 25mg or 100 mg and are then followed up for an additional 1-2 weeks. Patient/volunteer participation is concluded when they have completed the End-of-Trial (EOT) visit at Day 21+ (unless the patient is lost to follow up, informed consent is withdrawn or early discontinued). For more details about the visit schedule please cf. Flow Chart.

Adverse events that begin during treatment with all trial medications (BI 409306 25mg or 100 mg), or in the 7-day interval thereafter of the residual effect period (REP), will be considered "on treatment events". For more details about the safety assessment in this trial cf. Sections 5.2 and 7.3.3.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim.

Boehringer Ingelheim (BI) will appoint a Trial Clinical Monitor (TCM), who is responsible for coordinating the activities required to manage the trial in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the clinical trial team in the preparation, conduct and reporting of the trial, order materials as needed for the trial, ensuring appropriate training of the clinical monitor local (CML), clinical research associates (CRAs) and investigators.

Data management and statistical evaluation will be performed by BI according to BI SOPs. For these activities, a Trial Data Manager (TDM) and Trial Statistician (TSTAT) will be appointed.

Documents on participating investigators, including their curricula vitae, will be filed in the TMF.

The Investigator Site File (ISF) will be maintained at the sites as required by local regulation and BI SOPs. A copy of the ISF documents will be kept as an electronic document in BIRDS according to BI SOPs.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

This randomised, double-blinded, parallel group design was chosen for this study to observe the effects of BI 409306 within the patient groups (AD, CIAS) and healthy volunteers for two treatments. Each eligible patient or healthy volunteer will be blindly randomized to either the BI 409306 25 mg or 100 mg dose treatment. The patient or healthy volunteer will be dispensed three tablets from the study medication carton assigned. If randomized to the 25 mg dose group, they will be taking one BI 409306 25 mg and two BI 409306 50 mg matching placebo tablets; or to the 100 mg dose group, one BI 409306 25 mg matching placebo and two BI 409306 50 mg tablets.

The population/patient group sizes (20 subjects with 10 per dose group) are in general considered sufficient for the exploratory nature of this study.

The healthy volunteer group acts as the control, with double blinding to provide additional control. Refer to Section 3.3.2 for description of age-comparable healthy volunteers.

3.3 SELECTION OF TRIAL POPULATION

This study is planned as a -multi-center with approximately 60 male and female subjects will be entered into this study: 20 patients with AD, 20 patients with CIAS, and 20 HV (see Figure 3.1: 1).

A log of all subjects included in the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether or not they have been treated with investigational product. Re-screening of not yet randomised patients can be allowed in exceptional cases but should be discussed on a case-by-case basis between the study site, monitor staff and with the TCM.

3.3.1 Main diagnosis for study entry

Patients with established diagnoses of schizophrenia age 18-55 years (per Diagnostic and Statistical Manual of Mental Disorders version V (DSM-V)), or Alzheimer's Disease patients 55-85 years old currently treatment-naïve or on stable treatment(s) of at least 3 months before screening, or healthy volunteers (age-comparable to the two patient groups).

3.3.2 Inclusion criteria

1. Schizophrenia group:
   a. Patients with established diagnoses of schizophrenia (per Diagnostic and Statistical Manual of Mental Disorders version V (DSM-V, R14-2136)) with the all of the following clinical features:
      i. Clinically stable and are in the residual (non-acute) phase of their illness for at least 8 weeks prior to randomisation
      ii. Current antipsychotic and concomitant psychotropic medications must meet the criteria below:
      ii)-1. Maintained on current atypical (second generation) antipsychotic medications (in any approved dosage form) other than Clozapine and on current dose for at least 8 weeks prior to randomisation, and/or
      ii)-2. Maintained on current typical (first generation) antipsychotic medications and on current dose for at least 6 months, optionally combined with anticholinergics if treated with a stable dose for at least 6 months prior to randomisation, and/or
      ii)-3. Maintained on current concomitant psychotropic medications other than anticholinergics, antiepileptics and lithium, and on current dose for at least 8 weeks prior to randomisation. Antiepileptics and lithium are allowed if initiated at least 6 months prior to randomisation.
      iii. Have no more than a ''moderate'' severity rating on hallucinations and delusions (Positive and Negative Syndrome Scale (PANSS)–positive syndrome Hallucinatory Behavior item score ≤ 4 and Delusions item score ≤ 4)

iv. Have no more than a ‘‘moderate’’ severity rating on positive formal thought disorder (PANSS–positive syndrome Conceptual Disorganization item score ≤ 4)

v. Have a minimal level of extrapyramidal symptoms (Simpson-Angus Scale total score < 6) and depressive symptoms (PANSS–general psychopathology syndrome Depression item score ≤ 4)

b. Male or female patients age 18 to 55 years.

OR

Alzheimer’s Disease group:

a. Patients with diagnosis of mild Alzheimer’s Dementia based on DSM-V and in accordance with the recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease (R13-4115).
b. Mini-Mental State Examination (MMSE, R02-0395) score of 18-26.
c. Male or female patients age 55 to 85 years, who have not been taking acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and/or memantine for at least 3 months or on stable dose of acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and/or memantine at least 3 months before randomization. Patients older than 85 years may be included based on an acceptable general health status, (e.g. concomitant diseases, physical capability to follow the required study procedures [visits etc.]) per investigators judgement.
d. Availability of a pre-existing cranial computer tomography (CCT) or magnetic resonance imaging (MRI) scan of the brain (initiation of radiological imaging is not required) not older than one year prior to screening; if not available, a CCT must be performed at screening. Results of radiological brain imaging must be compatible with Diagnosis of Alzheimer Disease and exclusion of relevant signs indicative of potential vascular dementia (see also exclusion criteria).
e. If needed, a caregiver may be present during site activities.

OR

Age-comparable male or female healthy volunteers age 18 to 85 years. Healthy volunteers older than 85 years may be included based on an acceptable general health status, (e.g. concomitant diseases, physical capability to follow the required study procedures [visits etc.]) per investigators judgement:

a. After 10 patients with schizophrenia (as described above) are entered into the study, the median age of the group will be computed. Five healthy volunteers at or below the median age but greater than 18 years old (low age group) and five healthy volunteers above the median but less than 55 (high age group) will be entered into the study.
b. Similarly, after 10 patients with AD are entered , the median age will be computed. Five healthy volunteers at or below the median age but greater than 55 years old (low

age group) and five healthy volunteers above the median (high age group) will be entered into the study.

2. Subjects must exhibit reliability and physiologic capability, per investigator judgment, to comply with all protocol procedures.

3. Signed and dated written informed consent by date of Visit 1 in accordance with GCP and the local legislation. If the patient needs a legal representative, then this legal representative must give written informed consent as well.

3.3.3 Exclusion criteria

1. Presence of active ocular conditions with or without visual impairment due to any causes (e.g. cataract, chorioretinal macular lesion, amblyopia, active diabetic retinopathy, uncontrolled glaucoma, active inflammation or infection, etc.) in one eye or both eyes at the screening phase that may interfere with the ocular assessments or analyses and interpretation of the results from this study, in the clinical judgment of the investigator.

2. Planned ocular treatment (e.g. intravitreal antivascular growth factor, corticosteroids) or surgery during the study period.

3. Current or planned use of ocular or systemic corticosteroids.

4. Current or planned use of medications known to be toxic to the retina, lens, optic nerve (e.g. choroquine/hydrochoroquine, chlorpromazine, tamoxifen, desferoximine, etc.).

5. Subjects treated with more than two antipsychotic medications (including more than two dosage forms).

6. Subjects needing to take long-acting hypnotics or anxiolytic (i.e. Diazapam).

7. Subjects taking medications that are known to be strong or moderate CYP1A2 inhibitors (For a list of strong and moderate CYP1A2 inhibitors please consult the ISF Section 11 “Safety Information”).

8. Dementia in AD patients, secondary to other disorders (based on clinical data and/or current laboratory findings and/or on a pre-existing cranial MRI or CCT which is not older than 12 months prior to screening visit)*, for example: small vessel disease, neurosyphilis, craniocerebral trauma.

   *If it is not already available then a CCT scan must be performed at screening.

9. Neurological disease (other than Dementia of Alzheimer Type such as: Lewy body dementia - primary diagnosis, Huntington’s disease, Parkinson’s Disease encephalitis, epilepsy, vascular or multi-infarct dementia, stroke, congenital mental deficiency, or multiple sclerosis), or mental retardation.

10. For AD patients, the following drugs are prohibited for 3 months prior to randomization and for the duration of the trial:
    a. tricyclic antidepressants,
    b. antidepressants that are monoamine oxidase inhibitors,
    c. neuroleptics with moderate or greater anticholinergic potency (e.g., chlorpromazine, fluphenazine, loxapine, perphenazine, thioridazine),
    d. anticholinergic medications.
    e. Intake of St. Johns wort, Carbamazepine and extracts from Ginko as they are relevant CYP2C19 inducers.

    The following drugs may be given as needed if the total daily dose was stable 8 weeks prior to randomization and is expected to be stable for the duration of the trial:
    a. neuroleptics listed in Section 4.2.2,
    b. benzodiazepines and sedatives listed Section 4.2.2.

11. Substantial concomitant cerebrovascular disease (defined by a history of a stroke/intracranial haemorrhagia temporally related to the onset of worsening of cognitive impairment), per investigator judgment.

12. Any suicidal ideation of type 4 or 5 in the Columbia Suicidal Severity Rating Scale (C-SSRS) in the past 3 months (i.e. active suicidal thought(s) with intent but without specific plan, or active suicidal thought(s) with plan and intent).

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

14. History or diagnosis of symptomatic and unstable/uncontrolled gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, haematological or hormonal disorders.

15. For female subjects:

Pre-menopausal women (last menstruation ≤1 year prior to informed consent) who:

- are nursing or pregnant or
- are of child-bearing potential and are not practicing an acceptable method of birth control, or do not plan to continue using this method throughout the trial until 28 days after the last treatment administration, and do not agree to submit to periodic pregnancy testing during participation in the trial. Acceptable methods of birth control include tubal ligation, vasectomized partner, transdermal patch, intra uterine devices/systems (IUDs/IUSs), combined estrogen-progestin oral contraceptives as well as implantable or injectable hormonal contraceptives unless they are a moderate to strong CYP1A2 inhibitor – see Section 4.2.2.1. Complete sexual abstinence (if acceptable by local health authorities) is allowed when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Double barrier methods are permissible (if acceptable by local health authorities).

For male subjects:
Men who are able to father a child, unwilling to be abstinent or use adequate contraception for the duration of study participation and for at least 28 days after treatment has ended.

16. Known history, or new diagnosis per screening labs, of HIV infection.

17. Significant renal disease (primary or secondary) (for example severe renal impairment (CLCR < 30 mL/min).

18. Bodyweight < 50 kg.

19. Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3x upper limit of normal (ULN) as determined during screening.

20. History of neurologic (e.g. stroke, seizure without a clear and resolved etiology, concussion accompanying loss of consciousness) or psychiatric condition that the investigator deems may interfere with interpretability of data.

21. History of malignancy within the last 5 years, except for basal cell carcinoma.

22. Planned elective surgery requiring general anaesthesia, or hospitalisation during the study period.

23. Significant history of drug dependence (with the exception of nicotine dependence) or abuse (including alcohol, as defined in DSM-V or in the opinion of the investigator) within the last two years prior to informed consent, or a positive urine drug screen for cocaine, opioid, phencyclidine (PCP), amphetamine or marijuana at screening.

24. Clinically significant uncompensated hearing loss in the judgment of the investigator. Use of hearing aids is not allowed.

25. Known hypersensitivity to drug product excipients (gelantin, povidone K25, lactose monohydrate, microcrystalline cellulose, pregelatinized starch, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate, hypromellose, propylene glycol, titanium dioxide, talc and iron oxide yellow).

26. Participation in another trial with an investigational drug or procedure within 30 days prior to screening or previous participation in any BI 409306 study.

27. Any evidence of a clinically relevant concomitant disease, or clinical condition that in the opinion of the investigator would jeopardize patient’s safety while participating in this trial.

28. Subjects not willing or able to comply with the protocol requirements or considered unreliable by the Investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual patient must be withdrawn from the treatment if:

- The patient withdraws consent, without the need to justify the decision.
- The patient needs any invasive procedure such as cataract surgery, laser photocoagulation or retinal surgery during the study period.
- The patient needs any invasive procedure as cardiac catheterism or stent.
- The patient becomes pregnant during the trial. Patient will be followed up until birth or otherwise termination of the pregnancy.
- The patient needs to take concomitant drugs that interfere with the investigational product(s), in the clinical judgment of the investigator.
- The patient is no longer able to participate for other medical reasons (e.g. surgery, AEs, or other diseases).
- The patient needs to stop all current antipsychotic or concomitant psychotropic medications.
- The patient's disease state dramatically worsens, in clinical judgment of investigator.
- The patient experiences clinically significant loss of visual acuity and/or any ocular symptoms/signs attributable or not to the study medication, by the investigator's judgment (e.g. acute loss of vision ≥ 5 letters, new macular changes such as intra- or sub-retinal fluids or haemorrhage, etc.).
- The patient exhibits suicidality, in the clinical judgment of the investigator or according to criteria below:
  - Any suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)
  - Any suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought(s) with intent but without specific plan, or active suicidal thought(s) with plan and intent).

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

Subjects who discontinue participation after signing the informed consent form but prior to randomization (Visit 2) will be considered screening failures. For screening failure subjects, the demographic, AE, concomitant medication and randomization eCRFs in RDC must be completed. The subjects will be identified as screen failures in the randomization eCRF and no further follow-up is required. SAEs occurring in subjects after having discontinued in the study due to screening failures, and who did not receive any study medication, do not need to be reported, unless the investigator considers the SAE related to the screening procedures.

Subjects who discontinue or withdraw from the study after randomization (Visit 2) will be considered as "early discontinuations" and the reason for premature discontinuation must be recorded in the eCRFs (cf. Section 6.2.3 for early discontinuation procedures). The data will

be included in the trial database and will be reported. Subjects who withdraw or discontinue from the trial after randomization will not be replaced.

3.3.4.2 Discontinuation of the trial by the sponsor

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

Failure to meet expected enrolment goals overall or at a particular trial site,
Emergence of any efficacy/safety information that could significantly affect continuation of the trial,
Violation of GCP, the approved CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

BI 409306, as a film-coated tablet, will be produced by Boehringer Ingelheim Pharma GmbH & Co. KG. Each film-coated tablet contains 25 mg or 50 mg BI 409306, or matching placebo blistered in 7-count Alu blister strips.

Eligible subjects will be assigned to each treatment group (25 mg or 100 mg) alternatively in the order that they randomized (cf. Section 3.1 and Section 3.3.2).

4.1.1 Identity of BI investigational product and comparator product

The following table summarizes the information about the investigational products as used in this trial:

Table 4.1.1: 1 BI 409306, 25 mg and 50 mg

Substance:	BI 409306
Pharmaceutical form:	Film-coated tablet
Manufacturer:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit Strength:	25 mg, 50 mg
Daily dose:	25 mg q.d. or 100 mg q.d.
Route of administration:	Per os (oral)
Posology:	Once daily
Duration of use:	14 days

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

Substance:	BI 409306
Pharmaceutical form:	Film-coated tablet
Manufacturer:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit Strength:	N/A
Daily dose:	N/A
Route of administration:	Per os (oral)
Posology:	Once daily
Duration of use:	14 days

4.1.2 Method of assigning subjects to treatment groups

Subjects eligible for the trial will be assigned at random in a 1:1 ratio of 25 and 100 mg dose per group at Visit 2 (cf. Section 3.1). Details on randomization are provided in Section 7.5. Assignment to the treatment groups will be determined at the site by having the next lowest sequentially numbered medication kit within each subject population group assigned (AD group, CIAS group, HV/AD low age group, HV/AD high age group, HV/CIAS low age group, HV/CIAS high age group). The assigned medication number will be entered in the eCRF and the corresponding medication kit should be given to the patient/healthy volunteer.

Using this procedure, the Investigator and study staff will be blinded to the assignment to which the patient was randomized. Note that the medication numbers assigned to the patient are different from the patient number.

4.1.3 Selection of doses in the trial

According to the result of previous trials, BI 409306 was well tolerated in young and elderly healthy subjects in single doses of 0.5 to 350 mg and multiple doses up to 100 mg once daily. The doses selected for this trial cover the estimated therapeutic range and include a safety margin (cf. Section 1.2).

4.1.4 Drug assignment and administration of doses for each patient

Patient/healthy volunteer will be assigned study medication and the first dose administered on site at Visit 3, Day 1. Other doses may be administered at home, according to the home visits optional schedule as specified in the Flow Chart. Each patient/healthy volunteer will be administered three tablets, one from each blister dispensed. Table 4.1.4: 1 outlines the treatment and administration of dose for each patient/volunteer.

Table 4.1.4: 1 BI 409306 and matching placebo treatment, oral administration

Treatment Group	Total Drug Administered	Packaging
BI 409306 25 mg	BI 409306 25 mg active	Orange-Label 25 mg Blister
	BI 409306 50 mg matching PBO BI 409306 50 mg matching PBO	Blue-Label 50 mg Blister
BI 409306 100 mg	BI 409306 25 mg matching PBO	Orange-Label 25 mg Blister
	BI 409306 50 mg active BI 409306 50 mg active	Blue-Label 50 mg Blister

The study medication will be administered with about 240 mL of water in the sitting/standing position under supervision of the investigating physician or designee.

Subjects are not allowed to lie down during the 2 hours following drug administration except for medical examination. They are not allowed to sleep. Water is allowed ad libitum except for one hour before and after drug administration. During in-patient, standardized meals will be served at 1, 5 and 10 hours (± 1 hour) following drug administration post dose on days 1 and 14. Additionally, snacks will be served at 7 hour and 13 hour (± 1 hour) post dose on all days. The time of last meal before drug administration will be recorded on PK blood draw Days 1 and 14.

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

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Subjects, investigators and everyone involved in analysing or with an interest in this double blind study will remain blinded with regard to the randomized treatment assignments until after database lock.

The randomization code will be kept secret by Clinical Trial Support up to database lock. They will only release it in accordance with BI standard operating procedures.

The study will only be unblinded after all Adverse Event (AE) related eCRF / electronic data have been entered into the trial data base and after AE related queries have been resolved.

4.1.5.2 Procedures for emergency unblinding

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

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany. The clinical trial supply consists of patient specific kits with trial identification that hold the trial medication. The blister within the clinical trial supply kits are labelled with:

- Trial number
- Name of product and strengths
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term “for clinical trial use”
- Sponsor name and address

- Storage conditions
- Use by date
- Medication number
- Batch number

Label examples are given in the Investigator Site File (ISF).

All drug supplies will be shipped to sites in the initial shipment with re-supply as needed.

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging under the labeled storage conditions. The trial medication must be stored securely, e.g. in a locked cupboard or at a pharmacy. It may only be dispensed to trial subjects according to the protocol by authorized personnel as documented in the Trial Staff List in the ISF.

All unused medication must be returned to the sponsor. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

4.1.8 Drug accountability

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

The investigator / pharmacist / investigational product storage manager will receive the investigational products delivered by the sponsor when the following requirements are fulfilled:

- approval of the study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol
- availability of the proof of a medical licence for the principal investigator,
- availability of the FDA Form 1572.

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

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial subjects. The investigator / pharmacist / investigational product storage manager will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational product(s) received from the sponsor. At the time of return to the sponsor, the investigator / pharmacist / investigational product storage manager must verify that all unused or partially used/expired 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

There are no special emergency procedures to be followed. No rescue medication, emergency procedure or additional treatment is foreseen for this study.

Throughout the duration of the trial subjects should continue to take their current antipsychotic and concomitant psychotropic medications, the dose of which should remain unchanged unless necessary for the welfare of the patient. These medications will not be provided as part of the clinical trial supplies, unless required by local laws and regulations. Any change in dose of antipsychotic and concomitant psychotropic medications should be recorded in the source documentation and on the appropriate pages of the eCRF.

Any additional treatment that is considered necessary for the patient's/healthy volunteer's welfare may be given at the discretion of the Investigator.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Any medication that may interfere with the action of BI 409306 or whose action may be altered by concomitant administration of BI 409306 during the treatment period and the 14-day follow-up period, in the clinical judgment of the investigator, is not permitted.

Chronic use (≥ 14 days) of topical or systemic corticosteroids is restricted during the study period.

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

No entering or modification of smoking-cessation programs may occur during the conduct of the trial.

Patient will not begin or increase frequency/duration of psychotherapy during the study period, receive electroconvulsive therapy, nor begin any type of non-Western therapies.

For CIAS patients, use of hypnotics and anxiolytics is not prohibited; however, these medications should be administered to patients according the instruction below:

- Long-acting hypnotics and anxiolytics (i.e. Diazepam) are not permitted during the study period.
- Short-acting or intermediate-acting hypnotics and anxiolytics (e.g. lorazepam and zaleplon) are permitted if treated with a stable dose for at least 8 weeks.
- Short-acting hypnotics and anxiolytics are allowed if taken PRN.
- Short-acting or intermediate hypnotics and anxiolytics should not be taken within 8 hours of study procedures.

Also for CIAS patients:

- Use of Clozapine (atypical antipsychotic medication) is not permitted during the study period.
- Anticholinergics are allowed to be used if subjects are on first generation antipsychotics and have been treated at a stable dose for at least 6 months prior to randomisation.
- Antiepileptics and lithium are allowed if initiated at least 6 months prior to randomisation.

For AD patients, intake of the following medications with the mentioned exceptions is prohibited during the entire duration of the trial including follow-up:

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

  Note: Zolpidem (10 mg/day), chloral hydrate (1 g/day), triazolam, quetiapine, temazepam and oxazepam if needed for sleep are allowed as needed. Olanzapine or risperidone are allowed as needed for occasional intake in case of psychotic symptoms.
- Agents having central dopamine antagonist activity, i.e. reserpine, methyldopa, antiemetic's etc. However, the serotonin and combined serotonin/norepihnephrine Re-Uptake Inhibitors (SSRIs/SNRIs) like fluoxetin, es-citalopram, citalopram, sertalin, venlafaxin, duloxetin are allowed, but paroxetine is excluded. Other antidepressant drugs without anticholinergic effects may be given as needed if the total daily dose was stable 8 weeks prior to randomization and is expected to be maintained for the duration of the trial.
- Intake of other phospodiesterase inhibitors (for example theophylline, roflumilast, sildenafil, tadalafil, vardenafil, avanafil).

- Intake of St. Johns wort, Carbamazepine, extracts from Gingko, artemisinin, enzalutamide, efavirenz, lopinavir, ritonavir, tipranavir, rifampicin as they are relevant CYP2C19 inducers.
- Initiation of non-prescription drugs or vitamins including medical nutrition formulations. However if such medications were initiated before Visit 1, then they can be continued concomitantly during the study.

4.2.2.2 Restrictions on diet and life style

Because psychoactive drugs may impair thinking, judgment, and/or motor skills, subjects will be cautioned about operating machinery, including automobiles, until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities.

Subjects should not abuse of alcohol or drugs during study as defined in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), or in the opinion of the investigator, or as indicated by a positive urine drug screen for cocaine, opioid, PCP, amphetamine, heroin, or marijuana during the trial.

There are no other restrictions on diet, exercise, or smoking except that the patient's usual habits, including nicotine and caffeine intake, should not be drastically changed. Also refer to Section 4.1.4 for further intake guidelines.

4.3 TREATMENT COMPLIANCE

Subjects who are non-compliant, e.g., they do not appear for treatment or violate the restrictions, may be withdrawn from the trial at the discretion of the investigator and the eCRF will be completed accordingly (for further procedures cf. Section 6.2.3). If a patient withdraws during the treatment period, after first administration of the study drug, a complete post examination, done at EOT, will be performed.

Compliance will be assured by administration of all study medication under supervision of the investigating physician or a designee.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACODYNAMICS

5.1.1 Endpoints of efficacy

Efficacy measurements will not be performed.

5.1.2 Assessment of efficacy

Not applicable

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoint:

- The number (%) of subjects with AEs, coded to the MedDRA-SOC 'Eye disorders', as determined by the investigator at End of Trial

Secondary endpoint:

- The number (%) of subjects with drug-related AEs as determined by the investigator at End of Trial

Further safety and tolerability will be assessed in a descriptive way based on:

- Adverse events (ocular and systemic)
-

- Occurrence of Protocol-specified AESI (adverse events of special interest)

5.2.2 Assessment of adverse events

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) and includes clinically significant ophthalmological findings, EEGs, periodic physical examinations, measurement of vital signs, assessment of cardiac function with periodic ECGs and 24-hour heart rate monitoring, monitoring of laboratory tests (i.e. haematology, chemistry, coagulation, urine analysis), pregnancy test etc., as outlined in the Flow Chart. Ocular and systemic safety will be captured and analysed separately.

5.2.2.1 Definitions of adverse events

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

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

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

- 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.

Every occurrence of cancer or exacerbation of an existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

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 system.

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 5.2.2.2.

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood 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 subjects showing these lab abnormalities need to be followed up according to the drug-induced liver injury (DILI) checklist provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure 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.
- Clinically significant loss of vision (assessed by BCVA) based on investigator's judgment
- Clinically significant change of color vision (assessed by F-M 100) based on investigator's judgment
- Marcus Gunn pupil sign
- Acute corneal edema
- Increase of IOP ≥ 30 mmHg
- Retinal vascular occlusion and/or retinal hemorrhage or edema
- Blurred papillary margin (papillary-edema)

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

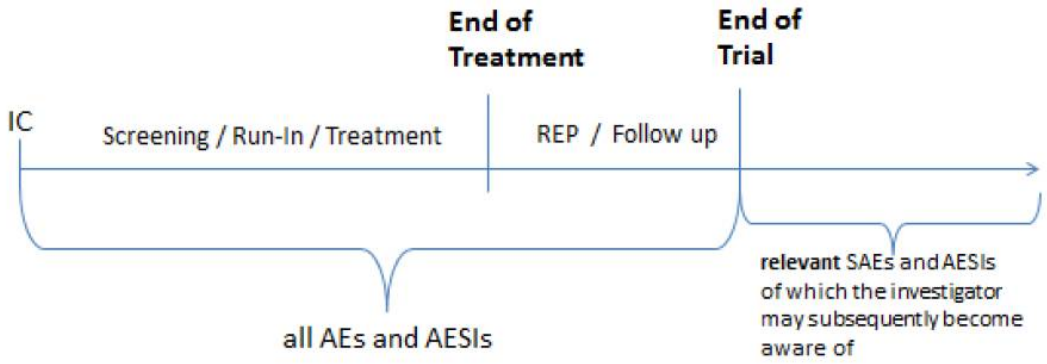
Causal relationship of AEs
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

5.2.2.2 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 AESIs.



The REP is defined as 7 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 (cf. Section 7.3.3). Events which occurred after the REP will be considered as post treatment events.

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 through the SAE reporting process, not on eCRF.

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 (SAE form and 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.

Information required
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug(s) and a Non-Investigational Medicinal Product (NIMP).

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 trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's (form and 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).

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

5.2.3 Assessment of safety laboratory parameters

The laboratory tests listed in Table 5.2.3: 1 will be performed at the central laboratory service provider. Fasting is not required. Instructions on collection, handling/ processing, and shipping of the samples will be provided in the investigator site file by the central laboratory. For time points of laboratory sampling refer to the Flow Chart.

Laboratory results of the subjects will be available to the respective investigator and to the BI Clinical Monitor (central laboratory website), and selected abnormal laboratory alerts will be sent automatically to the sites and to the sponsor within 24 hours.

Clinically relevant laboratory values should be commented on lab report print-outs if there is no validated and certified e-medical record for the comments of laboratory data. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit lab kit and should be repeated until normalisation or stabilisation or until an alternative explanation has been found.

Table 5.2.3: 1 Routine Laboratory test

Haematology • Hematocrit (Hct) • Hemoglobin (Hb) • Red Blood Cell Count/ Erythrocytes (RBC) • Reticulocyte Count • White Blood Cells / Leukocytes (WBC) • Platelet Count/ Thrombocytes	• Differential. Automatic (manual if differential automatic is abnormal) - Neutrophils - Eosinophils - Basophils - Monocytes - Lymphocytes
Coagulation • Partial Thromboplastin Time (=aPTT)	• Prothrombin time (Quick and INR)
Chemistry • AST(SGOT) • ALT(SGPT) • Alkaline Phosphatase (AP) • Albumin • Creatine Kinase (CK) • CK-MB, only if CK is elevated • Gamma-Glutamyl Transferase (GGT/γ-GT) • Lactic Dehydrogenase (LDH) • Calcium Sodium • Potassium Chloride • Bicarbonate	• Glucose • Creatinine • BUN • Bilirubin Total • Bilirubin Direct • Bilirubin Indirect • Protein Total • Uric Acid • Cholesterol Total • Triglycerides
Pregnancy test (females only)	Human urine chorionic gonadotropin
Urinalysis[1] (Stix) • Urine Nitrite • Urine Protein • Urine Glucose • Urine Ketone • Urobilinogen	• Urine Bilirubin • Urine RBC/ Erythrocytes • Urine WBC/ Leukocytes • Urine pH • Urine creatinine
Urine-Sediment (microscopic examination), (only if urine analysis abnormal) • Urine Sediment Bacteria • Urine Cast in Sediment	• Urine Squamous Epith Cells • Urine Sediment RBC/ Erythrocytes • Urine Sediment WBC/ Leucocytes

[1] At screening, baseline andend of trial.

The following tests will be performed only at screening examination; the results will not be part of the Clinical Trial Report. Exclusionary testing may be repeated during the screening period if necessary. Subjects must have a negative drug screening prior to inclusion in the study.

Table 5.2.3: 2 Exclusionary Laboratory test (screening visit only)

Drug Screening (Urine)	
• Cannabis	• Cocaine
• Barbiturates	• Amphetamines
• Opiates	• Methadone
	• Phencyclidine

5.2.4 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow Chart. ECG will be recorded after the subjects have rested for at least 5 minutes in a supine position. The investigator or a designate will 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.

ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected by the investigator for safety reasons. The recordings will be checked for pathological results (to be reported as baseline conditions or AEs) by the investigator. Any ECG abnormalities will be carefully monitored and if necessary the patient will be removed from the trial and medically treated. Baseline will be the measurements taken prior to the first administration. Notable findings are defined as occurrence of any QTc interval from any individual >450 ms, >480 ms or >500 ms or the occurrence of any individual increase from baseline by >30 ms or >60 ms.

5.2.5 Physical examination

The physical examination will be carried out within -28 to -3 days before the study (Screening), on Day -2 or -1 (Baseline), Day 7 and End of Trial examination (7-14 days after the last drug administration for each patient). At the screening visit, a complete medical examination will include documentation of patient information, informed consent, demographics including height and weight, smoking and alcohol history, relevant medical history and concomitant medication, review of inclusion/exclusion criteria, review of vital signs (BP, PR), 12-lead ECG and laboratory, and a physical examination. At the End of Trial examination, it will include review of vital signs, 12-lead ECG and laboratory, and a physical examination. Adverse events and concomitant therapies will be assessed throughout the study.

Physical examination will include weight and an examination of general appearance, skin, lungs, heart, abdomen, lymph nodes, extremities and basic nervous system evaluation.

Information about the physical examination must be present in the source documentation at the study site. Physical examination and ECG data are not collected on eCRF, however, any significant findings made after the start of study drug which meet the definition of an AE must be recorded as the Adverse Event in eCRF.

5.2.6 Vital signs

Vital signs (orthostatic measurements of systolic/diastolic blood pressure and pulse rate as outlined below) will be recorded at the time points and study visits as described in the Flow Chart, including the End of Trial visit.

Orthostatic measurements:

1) Have the patient lie down for at least 5 minutes
2) Measure blood pressure and pulse rate in supine position
3) Have the patient stand and measure blood pressure and pulse rate immediately after the patient stand up
4) Repeat blood pressure and pulse rate measurements after standing 3 minutes

Only on Day 1, the following additional vital sign assessments need to be performed which include (cf. Flow Chart):

- Pulse rate is to be measured in a supine position after at least 5 minutes of rest pre-dose and at the time points of post-dose PK sampling until 110 mins post-dose (20 ±5 min, 30 ±5 min, 45 ±10 min and 90 ±20 min). Pulse rate should be taken before the respective blood for PK sampling is drawn.
- Orthostatic measurements of systolic/diastolic blood pressure and pulse rate are to be done at pre-dose (baseline) and at 70~110 minutes post dose.

All above mentioned procedures are to be performed in a quiet environment and unexpected disturbances have to be avoided. In case of an unexpected disturbance (for example slamming door) this measurements may be repeated.

If there is a finding which meets any withdrawal criterion (see Section 3.3.4.1), the subject should be removed from study participation. The investigator may repeat the post-dose pulse rate assessment at any other visit under the conditions described for Day 1 if deemed clinically necessary for any reason.

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

5.2.7 24-hour holter monitoring

Holter monitoring will be performed over a 24 hour period at Screening and repeated again on Day 3. Holter data will be recorded using equipment provided and also analysed by a central ECG vendor. Holter monitoring procedure is to be initiated after all other laboratory related tests are completed.

5.4 APPROPRIATENESS OF MEASUREMENTS

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

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values and ECG. These primary and secondary endpoints are standard and accepted for evaluation of safety and tolerability of an oral drug, and they are widely used in this kind of study.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and exact clock time of study medication administration as well as of pharmacokinetic sampling times will be documented in the eCRFs. These actual sampling times will be used for determination of pharmacokinetic parameters.

5.5.1 Pharmacokinetic endpoints

Pharmacokinetic parameters of BI 409306 will be determined as secondary endpoints:

- $C_{max,ss}$ - maximum measured concentration of the analyte in plasma at steady-state
- $t_{max,ss}$ - time from dosing to maximum measured concentration of the analyte in plasma at steady-state.

At Day 14, BI 409306 pharmacokinetics will be presumed to be at steady state for these endpoints.

5.5.2 Methods of sample collection

Plasma sampling for pharmacokinetic analysis

For quantification of BI 409306 and metabolites (CD 13896 and CD 14084) plasma concentrations, approximately 6 mL of blood will be taken from a forearm vein in a K_2-EDTA (dipotassium ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube at the time points listed in the Flow Chart.

The EDTA-anticoagulated blood samples will be centrifuged as soon as possible after collection. Centrifugation will last for about 10 minutes (at about 2000 x g to 4000 x g) at 4-8°C. Three plasma aliquots will be prepared and stored in polypropylene tubes. The first two

aliquots should contain at least 1 mL plasma whereas the third aliquot should contain the remaining plasma. Until shipment on dry ice to the analytical laboratory, plasma samples will be stored frozen in an upright position at about –20°C or below until transfer on dry ice to the analytical laboratory. The third aliquot will be shipped after the bioanalyst has acknowledged safe arrival of the first and second aliquots. At the analytical laboratory the plasma samples will be stored at about –20°C or below until analysis.

The sample tube labels should list at least the following information: study number, subject number, visit, planned time and aliquot. Further information such as matrix and analyte may also be given.

After completion of the study the plasma samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 3 years after the final study report has been signed.

5.5.3 Analytical determinations

The concentrations of BI 409306 and its two major metabolites in plasma will be determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay.

Analysis of BI 409306 and its two major metabolites in PK plasma study samples will be performed using validated LC-MS/MS assays.

Analysis of BI 409306 and the two major metabolites (CD 13896 and CD 14084) will be performed at:

Boehringer Ingelheim Pharma GmbH & Co. KG
Drug Metabolism and Pharmacokinetics Germany
G144
Birkendorfer Straße 65
88397 Biberach/ Riß, Germany

5.6 BIOMARKER

Not applicable.

5.7 PHARMACODYNAMICS

Not applicable.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All subjects are to adhere to visit schedule as specified in the Flow Chart. With the exception of the Screening visit and End of Trial visit where there is an allowable time window for visit scheduling, all other visits starting at Day -2 or -1 (Baseline) to Day 14 must occur on the scheduled day.

The following study visits: Visits 4-6 (Day 2-4), Visit 8 (Day 6), Visits 10-14 (Day 9-12), may be conducted as home visits in lieu of study center visits.

In-patient stay is optional. If feasible for in-patient stay, the following procedures would apply: eligible study participants will be admitted to the study center in-patient facility for overnight stays. All CIAS patients will remain in-patient for the duration of the treatment period, starting on Day -2 and will be allowed to leave after the last study procedure and after their fitness has been confirmed by the investigator on Day 14. AD patients and healthy volunteers will check into clinic on Day -2 and remain in-patient till Day 1, return for daily visits till Day 12, and check into clinic again on Day 13 to Day 14. If there is a need that required AD subjects to remain in-patient, then the CIAS schedule plan may be ultilized, per investigator discretion.

Exact times of measurements outside the permitted time windows will be documented. Time windows are permitted as follows:

- General medical/physical examination: at screening (-3 to -28 days prior to the first study day), on Day -2 or -1 (Baseline), Day 7 and at the End of Trial (within 14 days following the last trial procedure).
-

- For planned individual plasma concentration sampling refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter. In the event that a sample time point is not adhered to or missed, subsequent samples should be taken based on the time of drug administration.
- The designation “before” on study Day 1 refers to the time period of within 2 hours before drug administration (see Flow Chart), (i.e. study measurements and assessments scheduled to occur “before” have to be performed and completed within 2 hours prior to drug administration).
- In-patient meal and snacks times may be ± 1 hour of planned times, if applicable.

Relevant time violations will be identified and their handling discussed no later than at the Blinded Report Planning Meeting (BRPM).

If a study visit is missed, subjects should continue to the next planned visit and study procedures per Flow Chart.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and baseline period

No trial procedures should be performed until the patient has provided written informed consent in accordance with GCP and local legislation. Once the patient/healthy volunteer has signed consent, a patient number will be assigned and enrolment will be recorded on the eCRF and Subject Enrolment Log in the ISF.

For the medical examination, vital signs, 12-lead ECG, and laboratory examinations during the screening visit, cf. Section 5.2. The screening investigations will be performed within -3 to -28 days preceding the first study drug administration.

6.2.2 Treatment periods

If the patient/healthy volunteer has completed screening and has been determined potentially eligible by the investigator, the following baseline investigations will be performed on Day -2 and/or -1:

- Physical examination including vital signs
-
- Review Adverse Events (AEs) and Concomitant Therapies (CTs)
- Clinical laboratory/urinalysis
- Review Inclusion/Exclusion criteria
-

Subjects, who meet all the inclusion criteria, and none of the exclusion criteria, will be eligible for the study. Eligible subjects will be randomized (cf. Section 4.1.2).

Each randomized participant will receive study medication daily from Day 1 through 14 according to the Flow Chart. Study drug will be taken orally in the morning of each treatment day under direct supervision of the investigator or designee.

The measurements performed during the treatment period are specified under Section 5.2 of this protocol and Flow Chart.

For details on time points for collection of plasma samples for PK analysis, cf. Flow Chart and Sections 5.5.1 and 5.5.2.

In general, if several measurements including venipuncture are scheduled for the same point of time, venipuncture should be the last of the measurements due to its inconvenience to the patient and possible influence on physiologic parameters.

6.2.3 End of trial and follow-up period

The End of Trial visit will be performed 7 to 14 days after last drug administration. EOT evaluation will include a physical exam, vital signs, 12-lead ECG, standard laboratory tests, and review of AEs and CTs.

All clinically significant abnormal values (including laboratory parameters) will be followed up using the appropriate tests until a return to a medically acceptable level is achieved.

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

In case of premature discontinuation from the 14 day treatment, (e.g. removal of patient from treatment due to AE or abnormal laboratory test result), the EOT visit should be performed within 7 days of last intake of study drug.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a Phase Ic, randomised, parallel-group, double-blind study.

The primary objective is to investigate the ocular safety of BI 409306 in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers following oral administration of 25 mg and 100 mg over 14 days.

The primary endpoint is number (%) of subjects with AEs, coded to the MedDRA-SOC 'Eye disorders', as determined by the investigator at End of Trial.

The secondary objectives are the evaluation of systemic safety and exploration of the pharmacokinetics of BI 409306.

Secondary endpoints include the number (%) of subjects with drug-related AEs as determined by the investigator at End of Trial. Secondary endpoints also include the following pharmacokinetic parameters of BI 409306:

- $C_{max,ss}$ - maximum measured concentration of the analyte in plasma at steady-state (Day 14).
- $t_{max,ss}$ - time from dosing to maximum measured concentration of the analyte in plasma at steady-state (Day 14).

The derivation of the PK parameters is given in Appendix Section 10.1.

No statistical testing will be performed on the primary and secondary endpoints.

General tolerability will be evaluated on the basis of the following investigations: physical examination, vital signs (BP, PR), 12-lead ECG (electrocardiogram), clinical laboratory tests (haematology, clinical chemistry and urinalysis) and adverse events.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses. Descriptive statistics will be presented.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

All subjects who received at least one dose of study drug will be included in the assessment of ocular adverse events. Safety analyses will be performed in accordance with BI standards, essentially, tabulations of frequencies/proportions will be displayed.

Ocular adverse events will be those events coded to the SOC 'Eye disorders'.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA). The analysis of adverse events will be based on the concept of treatment emergent adverse events. All adverse events occurring before drug intake will be assigned to "screening". All adverse events occurring between drug intake until 7 days (inclusive) after last treatment administration will be assigned to "treatment". Adverse events occurring after this period and prior to End of Trial will be assigned to "post-treatment". Adverse events occurring after End of Trial will be considered "post-study". Independent of this rule, the relationship of an adverse event to the study drugs treatments will be assessed by the investigator. Adverse event information as reported in the CRFs will be aggregated in a two-step process. First, multiple recordings (AE occurrences) of the same adverse event will be combined into one AE episode (collapsing). The second step will combine all of the AE episodes of an adverse event into one AE record as needed for by-subject summaries (condensing). The evaluation of adverse events will comprise various frequency tabulations.

7.3.2 Secondary analyses

Secondary endpoints include the number (%) of subjects with drug-related adverse events (AEs) as determined by the investigator. Details regarding AE analyses are provided in Section 7.3.1.

Pharmacokinetic analyses are described in Section 7.3.5.

7.3.3 Safety analyses

All treated subjects will be included in the safety analysis. However, if a treated subject has no post-randomization data, this subject will not be included in the safety analyses. 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 7 days (inclusive) after last treatment administration. 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).

Laboratory and other safety

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 subjects with abnormal values or clinically relevant abnormal values.

Vital signs (BP, PR) will be measured in supine and standing positions. Descriptive statistics will be provided for both positions separately. Orthostatic testing is done by comparing the individual results of both measurements (supine and standing).

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

7.3.4 Interim analyses

No interim analysis is planned, but in the event that AD recruitment goals are not met as planned, the CIAS and age-comparable healthy volunteers may be unblinded for analysis after the last CIAS and the corresponding 10 age-comparable healthy volunteers have completed the study.

7.3.5 Pharmacokinetic analyses

For pharmacokinetic analysis and displays, concentrations will be used in the same format as reported in the bioanalytical report. Only concentrations within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. For derivation of pharmacokinetic parameters see Appendix Section 10.1.2.

Non-compartmental pharmacokinetic analyses of the plasma concentration-time data will be performed using a validated software program and for this purpose the actual sampling time for pre-dose samples will be set to zero. Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic and geometric mean and the planned blood sampling times will be used. If the actual sampling time deviates significantly from the planned time, the corresponding plasma concentration will be excluded from the calculation of descriptive statistics.

7.3.6 Pharmacogenomic analyses

7.4 HANDLING OF MISSING DATA

With respect to safety evaluations, it is not planned to impute missing values other than AE start dates and times.

For handling of missing data in PK evaluation, refer to Appendix Section 10.1.2.

7.5 RANDOMISATION

Subjects will be randomized in blocks to double-blind treatment. Equal numbers of subjects will be randomized to each treatment group. BI will arrange for the randomization and the packaging and labelling of study 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 Clinical Trial Report.

A blinded randomization list will be provided to the site. It will list sequential medication numbers. Study medication kits will be labelled using these medication numbers. The site will be instructed to use designated blocks of medication numbers for Alzheimer's patients, for schizophrenia patients, for healthy volunteers in the lower age category and for healthy volunteers in the higher age category. The site will be instructed to assign one medication numbers to each subject sequentially at the time of randomization. Medication number will be captured on the eCRF.

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 60 subjects in this study: 20 healthy volunteers; 20 patients with Alzheimer's disease and 20 patients diagnosed with schizophrenia. The planned sample size is not based on a power calculation nor on statistical consideration. The size of 10 subjects per population and per dose group is in general considered as sufficient for the exploratory evaluation of multiple dose ophthalmologic assessment, safety and pharmacokinetics.

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) and relevant BI Standard Operating Procedures (SOPs).

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

The Investigator 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.

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.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

Prior to patient participation in the trial, written informed consent must be obtained from each patient (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 patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

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

8.2 DATA QUALITY ASSURANCE

This trial will be conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, local regulations and the company standard operating procedures (SOPs).

A central laboratory will be used to collect, analyze and report the results of all blood samples and cultures. Centralized Holter Monitoring will be utilized for this trial. Data will be collected using a Remote Data Capture (RDC) system.

Training will be provided to all investigators, coordinators and field monitors to ensure consistency and accuracy of the data. The data will be source verified by the field monitors.

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

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

Electronic Case Report Forms (eCRFs) for individual subjects will be provided by the sponsor via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
Data reported on the eCRF 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.

For the eCRF, the following data need to be derived from source documents:

- Patient identification (gender, date of birth)
- 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"

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

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfill the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the BI 409306 this is the current version of the Investigator's Brochure (C02101303). The current version of the IB is to be provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements.

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 END OF TRIAL

The end of the trial is defined as the last clinical study visit for the last participating subject (e.g. End of Trial visit, 7-14 days after last drug administration). Cf. Section 6.2.3 for further information and details regarding follow-up of AEs or ongoing abnormal findings.

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10. APPENDICES

10.1 PHARMACOKINETIC METHODS

10.1.1 Evaluation of Pharmacokinetic Parameter

Individual $C_{max(ss)}$, $t_{max(ss)}$, $C_{t,N}$ and $C_{pre,N}$ values will be directly determined from the plasma concentration time profiles of each subject. If the same $C_{max(ss)}$ concentration occurs at different time points, $t_{max(ss)}$ is assigned to the first occurrence of $C_{max,ss}$.

AUC: The area under the curve will be calculated using the linear up/log down algorithm. If an analyte concentration is equal to or higher than the preceding concentration, the linear trapezoidal method will be used. If the analyte concentration is smaller than the preceding concentration, the logarithmic method will be used.

Linear trapezoidal rule ($t_2 > t_1$ and $C_{t2} \geq C_{t1}$):

The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1\text{-}t2} = 0.5 \times (t_2 - t_1) \times (C_{t1} + C_{t2})$$

Logarithmic trapezoid rule ($t_2 > t_1$ and $C_{t2} < C_{t1}$):

The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1-t2} = \frac{(t_2 - t_1) \times (C_{t2} - C_{t1})}{\ln(C_{t2}/C_{t1})}$$

$R_{A,Cmax}$: Accumulation ratios are derived as follows for the respective doses (e.g. after 14th dose $R_{A,Cmax,14}$):

$$R_{A,C\max} = \frac{C_{\max,ss}}{C_{\max}}$$

Metabolic ratio: With respect to $C_{max,ss}$

$$RC_{\max,ss,Met} = \frac{C_{\max,ss,metabolite}}{C_{\max,ss,parent}}$$

gMean, gCV: The geometric mean (gMean) and coefficient of variation, gCV (given in %), will be calculated by the formulae:

$$\text{gMean} = \exp\left[\frac{1}{n}\sum_{i=1}^{n}\ln(x_i)\right] = \exp\left[\overline{\ln(x_i)}\right]$$

$$gCV(\%) = 100 \cdot \sqrt{\exp\left[Var(\ln(x_i))\right] - 1}$$

where

$$Var(\ln(x_i)) = \frac{1}{n-1}\sum_{i=1}^{n}\left[\ln(x_i) - \overline{\ln(x_i)}\right]^2$$

10.1.2 Handling of missing data

10.1.2.1 Plasma concentration - time profiles

Concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the limit of quantification), and NOP (no peak detectable) will be ignored and not replaced by zero at any time point (applies also to the lag phase including the pre-dose value). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA, NOP are included).

10.1.2.2 Pharmacokinetic parameters

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

If the predose concentration before the first dose is less than or equal to 5% of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e. the predose value will not be changed to zero). If the predose value is greater than 5% of C_{max}, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately.

Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.
- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		26-June-2015
EudraCT number		NA
BI Trial number		1289.27
BI Investigational Product		BI 409306
Title of protocol		Randomised, parallel-group, double-blind study of systemic and ocular safety and pharmacokinetics of BI 409306 in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Protocol Synopsis
Description of change		Revise criteria for Alzheimer's disease: Diagnosis: Patients with schizophrenia in stable clinical status and on stable antipsychotic treatment **OR** patients with diagnosis of mild Alzheimer's disease **currently treatment-naïve or** on stable **treatment(s)** ~~donepezil~~ **OR** age-comparable healthy volunteers. Main criteria for inclusion: Patients with diagnosis of mild Alzheimer's Dementia according to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines

Number of global amendment		1
		for Alzheimer's disease, who are **currently treatment-naïve or** on stable treatment of **acetyl cholinesterase inhibitors and/or memantine** ~~donepezil~~ for at least 3 months before ~~screening~~ randomization. A MMSE (Mini-Mental-State-Examination) score between 18-26, and age 55 - 85 years with availability of pre-existing brain CCT or MRI compatible with diagnosis of Alzheimer's disease.
Rationale for change		Widen the restriction criteria for Alzheimer's subjects.
Section to be changed		Protocol Synopsis, Flow Chart and through out protocol
Description of change		Change of terminology from End of Study to End of Trial for the last study visit: End of ~~Study~~ **Trial**
Rationale for change		To align with RDC system set-up and reporting
Section to be changed		Flow Chart footnotes and Section 6.1
Description of change		Add texts: **If there is a need that required AD subjects to remain in-patient, then the CIAS schedule plan may be ultilized, per investigator discretion.**
Rationale for change		To allow for AD subjects to remain in-patient if required.
Section to be changed		Flow Chart footnotes, Figure 3.1.1, Sections 5.2.5, 6.1, 6.2.2
Description of change		Add or remove text to allow Visit 2 procedures to be completed either on Day -2 or Day -1: Footnote 5: In addition, urine (dipstick) pregnancy tests will be performed at Visit 2 ~~(Day -1)~~. Figure 3.1.1, Sections 5.2.5, 6.1: Day **-2 or** -1 (Baseline) Section 6.2.2: If the patient/healthy volunteer has completed screening and has been determined potentially eligible by the investigator, the patient/healthy volunteer will be admitted to the

Number of global amendment		1
		in-patient facility on Day -2 and the following **baseline** investigations will be performed on Day **-2 and/or** -1.
Rationale for change		To allow some baseline procedures to be completed either on Day -2 and/or Day -1 of Visit 2.
Section to be changed		Flow Chart footnotes, Sections 5.2.7, 6.2.1
Description of change		Change text: Footnote: The 24-hour heart rate monitor will be set up after completion of **all laboratory** ~~other study~~ procedures and removed at about the same time the following day. Section 5.2.7: Holter monitoring procedure is to be initiated after all other **laboratory** ~~study~~ related tests are completed. Section 6.2.1: The holter monitor will be set up after completion of all other **laboratory** ~~study~~ procedures.
Rationale for change		Allow for other procedures to be completed while subject is on holter monitor to better replicate normal daily activities
Section to be changed		Section 3.3.2
Description of change		Revise criteria for Alzheimer's disease: Alzheimer's Disease group: a. Patients with diagnosis of mild Alzheimer's Dementia ~~according to~~ **based on DSM-V and in accordance with** the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease (R13-4115). c. Male or female patients age 55 to 85 years, who ~~are~~ **have not been taking acetyl cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and/or memantine for at least 3 months or** on stable dose of ~~donepezil~~ acetyl cholinesterase **inhibitors (donepezil, galantamine, rivastigmine) and/or memantine** at least 3 months before ~~screening~~

Number of global amendment		1
		randomization.
Rationale for change		Widen the restriction criteria for Alzheimer's subjects.
Section to be changed		Section 3.3.3
Description of change		Remove exclusion text: 10. Subjects ~~already having received anti-dementia drugs other than donepezil (such as acetyl cholinesterase inhibitors (galantamine, rivastigmine, tacrine, phenserine) or memantine) or~~ having participated in studies on innovative causal interventions on AD (patients who stopped treatment of these drugs due to lack of efficacy or tolerability will not be enrolled).
Rationale for change		Widen the restriction criteria for Alzheimer's Disease subjects.
Section to be changed		Section 3.3.3
Description of change		Add text: 25. Clinically significant uncompensated hearing loss in the judgment of the investigator. Use of hearing aids is **not** allowed.
Rationale for change		Use of hearing aids is contra-indicated for administering of auditory stimuli for EEG procedures.
Section to be changed		Section 4.2.2.1
Description of change		Revise text: ~~Only~~ Short-acting hypnotics and anxiolytics are ~~permitted the~~ **allowed if taken** PRN ~~medications~~.
Rationale for change		To clarify use as PRN during study
Section to be changed		Section 5.2.2.2
Description of change		Moving statement regarding reporting of AEs after End of Trial to paragraph after REP, away from eCRF reference.
Rationale for change		To clarify that after End of Trial, (S)AE should be reported via SAE reporting process, not eCRF.
Section to be changed		Section 5.2.5
Description of change		Revise text:

Number of global amendment		1
		Physical examination will include **weight and** an examination of general appearance, skin, lungs, heart, abdomen, lymph nodes, extremities and basic nervous system evaluation. Information about the physical examination must be present in the source documentation at the study site. **Physical examination and ECG data are not collected on eCRF, however, any** significant findings made after the start of study drug which meet the definition of an AE must be recorded as the Adverse Event in eCRF.
Rationale for change		To clarify collection of weight during physical exams and data from physical exams and ECG will not be collected on eCRF.
Section to be changed		Section 5.2.8
Description of change		Revise text: All assessments should be ~~completed~~ **evaluated** by an ophthalmologist or certified ~~opticians~~ **ophthalmic technicians**, with the exception of F-M 100 which may be completed by trained technician at the principal investigator's site.
Rationale for change		To clarify that all ocular assessments should be evaluated by ophthalmologist or certified ophthalmic technicians.
Section to be changed		Section 5.2.8
Description of change		Revise text: <u>Best Corrected Visual Acuity (BCVA)</u> The refractive error using Refraction Chart R will be determined at the baseline visit and ~~used~~ **collected** throughout the remainder of the study period **when BCVA is performed**. Both eyes will be evaluated separately and the results captured in the eCRF, as well as the occurrence of any deviations from ETDRS chart reading.
Rationale for change		To clarify collection of refractive error when BCVA are performed.
Section to be changed		Section 5.2.8
Description of change		Add text: <u>Spectral domain optical coherence tomography</u>

Number of global amendment		1
		(SD-OCT) High definition optical coherence tomography (spectral domain OCT) (Cirrus HD-OCT, Model #4000) will be performed to evaluate the retinal and sub-retinal structures of both eyes. The central retinal thickness, along with other anatomical findings such as presence or not of intra-retinal fluid, sub-retinal fluid, **and choroid** and retinal pigmented epithelial layer changes will be documented and recorded in the eCRF.
Rationale for change		To clarify collection of choroid durin OCT assessments.
Section to be changed		Section 5.2.8
Description of change		Revise text: Pupil Diameter Measurement Both left and right pupil measurements will be taken separately using a pupil gauge under standardized lighting conditions, by the same ophthalmologist or ~~certified optician~~ **technician** at Day -1 (Baseline), Day 2, Day 4, Day 5 (peak exposure), Day 7, Day 14 and at End of Trial. Measurements for each eye will be recorded in the eCRF.
Rationale for change		To clarify procedure performed by appropriate technician.
Section to be changed		Section 5.3.3.1
Description of change		Add text: Blood samples collected in PAXgene Blood DNA tubes have to be stored and shipped at a temperature of **approximately** -20°C or below. Once frozen, thawing of the samples should be avoided.
Rationale for change		For allowance of storage flexibility.
Section to be changed		Section 5.2.3
Description of change		Add text: **Coagulation** • **Partial Thromboplastin Time (=aPTT)** • **Prothrombin time (Quick and INR)**
Rationale for change		Added missing lab assessments.

Number of global amendment		1
Section to be changed		Section 7.3.4
Description of change		Revise and add text: No interim analysis ~~will be conducted~~ **is planned, but in the event that AD recruitment goals are not met as planned, the CIAS and age-comparable healthy volunteers may be unblinded for safety analysis after the last CIAS and the corresponding 10 age-comparable have completed the study.**
Rationale for change		To allow for the analysis of the CIAS and healthy volunteer groups in the event that the AD group is not fully recruited.

Number of global amendment		2
Date of CTP revision		29-Feb-2016
EudraCT number		NA
BI Trial number		1289.27
BI Investigational Product		BI 409306
Title of protocol		Randomised, parallel-group, double-blind study of systemic and ocular safety and pharmacokinetics of BI 409306 in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title Page
Description of change		Revised text: ~~Principal~~ **Coordinating** Investigator
Rationale for change		Adding role of Coordinating Investigator as study design changed from single to multi-sites study.
Section to be changed		Protocol Synopsis
Description of change		Revised text to include Coordinating Investigator contact information: **Coordinating** Investigator Changed Trial Site to **multi-center** Revised text in Methodology: ~~Single~~ **Multi-center**

Number of global amendment		2
Rationale for change		Changing study from single to multi-center study design.
Section to be changed		Flow Chart
Description of change		Removed laboratory assessments 'X' at Visits 5 and 12.
Rationale for change		To reduce procedural burden for patients, and there is no safety need to have <7 days interval for laboratory assessments.
Section to be changed		Flow Chart
Description of change		Added C-SSRS assessements 'X' for Visits 3 and 16.
Rationale for change		To accommodate assessment completed at every clinic visit per FDA guidance, if there is no overnight/in-patient stay.
Section to be changed		Flow Chart
Description of change		Removed all visual assessments 'X[11]' planned for Visits 4, 6 and 9. Footnote for 11 for these assessments were also deleted and shifted previous footnotes 12 to 11, 13 to 12 and 14 to 13.
Rationale for change		To reduce procedural burden for patients as previous test schedule was considered to be more frequent than necessary.
Section to be changed		Flow Chart, Footnotes
Description of change		Revised text as noted: #2, added statement: I**n-patient stay is optional. If feasible for in-patient stay.** #11 footnote was deleted, and thus shift original numbers 11-14 to only 11-13. #12 (now #11), edited text: Visual procedures to be completed at estimated peak exposure time point (20-~~45~~ **90** minutes after dosing). Visual procedures at peak exposure time point can be completed within the time window on any treatment days between Day 5 and Day 10 ~~(except Day 7)~~. Dosing on these days may be

Number of global amendment		2
		done at the ophthalmologist office at the discretion of the investigator. #13 (now #12), edited text: The Event Related Potentials (ERP) component of the EEG will be performed at peak exposure time point (20-~~45~~ **90** minutes after dosing) on Day 13 following resting EEG.
Rationale for change		To allow for in-patient stay as optional, and extend the peak exposure timeframe.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Edited text: This is a ~~single~~ **multi-**center, double-blinded, parallel groups study
Rationale for change		Changed study plan to add more sites to study
Section to be changed		Section 3.3 Selection of Trial Population
Description of change		Edited text: This is a ~~single site~~ **multi-center**, double-blinded, parallel groups study
Rationale for change		Changed study plan to add more sites to study
Section to be changed		Section 3.3.1 Main diagnosis for study entry
Description of change		Revised text: Patients with established diagnoses of schizophrenia age 18-55 years (per Diagnostic and Statistical Manual of Mental Disorders version V (DSM-V)), or Alzheimer's Disease patients 55-85 years old currently ~~on stable~~ **treatment-naïve or on stable treatment(s)** ~~donepezil~~ of at least 3 months before screening, or healthy volunteers (age-comparable to the two patient groups).
Rationale for change		From Amendment 1 that was inadvertently left unchanged.
Section to be changed		Section 5.2.8 Ophthalmological examination
Description of change		Removed text: Best Corrected Visual Acuity (BCVA)

Number of global amendment		2
		BCVA will be determined and recorded at Day -1 (Baseline), ~~Day 2, Day 4,~~ Day 5 (peak exposure), ~~Day 7,~~ Day 14 and at End of Trial. Pupil Diameter Measurement Both left and right pupil measurements will be taken separately using a pupil gauge under standardized lighting conditions, by the same ophthalmologist or technician at Day -1 (Baseline), ~~Day 2, Day 4,~~ Day 5 (peak exposure), ~~Day 7,~~ Day 14 and at End of Trial. Measurements for each eye will be recorded in the eCRF. Anterior and posterior biomicroscopy The anterior and posterior chamber slit lamp examination will be performed in both eyes, at Day -1 (Baseline), ~~Day 2, Day 4,~~ Day 5 (peak exposure), ~~Day 7,~~ Day 14 and at End of Trial. Intra-Ocular Pressure Measurement (IOP) Intra-ocular pressure of both eyes will be measured separately using the Goldmann applanation tonometry (Haag Streit AT900). IOP of both eyes will be measured separately at Day -1 (Baseline), Day 5 (peak exposure), ~~Day 7,~~ Day 14 and at End of Trial. The results will be entered in the eCRF.
Rationale for change		To correspond to the procedures removed from Flow Chart.
Section to be changed		5.3.1.2 Assessment of suicidality
Description of change		Removed text: The C-SSRS will be administered by the medical qualified clinician or expert clinician and will be assessed at the screening visit with the aim to exclude patients with active moderate or severe symptomatology prior to the Screen Visit, or recent (or current) suicidal or suicide attempt according to the C-SSRS (baseline/screening version). Subsequently, the C-SSRS "since last visit" assessment will be performed at each clinic visit ~~after Visit 3 and~~ as shown in the Flow Chart.

Number of global amendment		2
Rationale for change		To note assessments to be completed at every clinic visit.
Section to be changed		Section 5.3.2.1 Electroencephalography (EEG)
Description of change		Revised text: Event Related Potentials: These ERPs will be measured in healthy volunteers, AD patients and schizophrenia patients at baseline and Day 13 at peak exposure time point (20-~~45~~ **90** minutes after dosing). Method: *MMN/P1/N1/P3a Paradigm*: Auditory stimuli will be presented to participants at 85 dB sound pressure level **or adjusted hearing threshold** via Etymotic ER3-A insert earphones.
Rationale for change		To expand the peak exposure timeframe, and allow for patients with low hearing threshold to still be able to pick up auditory stimuli.
Section to be changed		Section 6.1 Visit Schedule
Description of change		Revised text: **In-patient stay is optional. If feasible for in-patient stay,** eligible study participants will be admitted to the study center in-patient facility for overnight stays.
Rationale for change		To allow for in-patient stay as optional, providing flexibility for patients and sites.
Section to be changed		Section 6.1 Visit Schedule
Description of change		Revised text: 7. Peak exposure time point is approximately 20-~~45~~ **90** minutes after dosing. Visual tests should be performed within this time range. Visual procedures at this time point can be completed within the time window on any treatment days between Day 5 and Day 10 ~~(except Day 7)~~. Dosing on these days may be done at the ophthalmologist office at the discretion of the investigator.

Number of global amendment		2
		• In-patient meal and snacks times may be ± 1 hour of planned times, **if applicable**.
Rationale for change		To align with previous revisions, and to allow flexibility if patients opt to stay in-patient.
Section to be changed		Section 6.2.2 Treatment periods
Description of change		Revised text: If the patient/healthy volunteer has completed screening and has been determined potentially eligible by the investigator, ~~the patient/healthy volunteer will be admitted to the in-patient facility on Day -2 and~~ the following baseline investigations will be performed on Day -2 and/or -1.
Rationale for change		To align with previous revisions that in-patient stay is optional.
Section to be changed		Section 6.2.2 Treatment periods
Description of change		Revised text: Each randomized ~~patient~~ **participant** will receive study medication daily from Day 1 through 14 according to the Flow Chart. Study drug will be taken orally in the morning of each treatment day under direct supervision of the investigator or designee.
Rationale for change		To align the language for patients and healthy volunteers.
Section to be changed		Section 7.1 Statistical Design - Model
Description of change		Revised text: All collected timepoints for all endpoints will be assessed. However, for the first 5 endpoints listed above emphasis will be on change from baseline at the estimated peak exposure timepoint, 20-~~45~~ **90** minutes after dosing between Days 5 and 10.
Rationale for change		To align with previous revisions to expand peak exposure timeframe.

Number of global amendment		2
Section to be changed		Section 7.3.4 Interim analyses
Description of change		Revised text: No interim analysis is planned, but in the event that AD recruitment goals are not met as planned, the CIAS and age-comparable healthy volunteers may be unblinded for ~~safety~~ analysis after the last CIAS and the corresponding 10 age-comparable **healthy volunteers** have completed the study.
Rationale for change		To allow flexibility to analyze other parameters, other than safety.

Number of global amendment		3
Date of CTP revision		22-Feb-2017
EudraCT number		NA
BI Trial number		1289.27
BI Investigational Product		BI 409306
Title of protocol		Randomised, parallel-group, double-blind study of systemic and ocular safety and pharmacokinetics of BI 409306 in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Protocol Synopsis: Main criteria for inclusion, Section 3.3.2 Inclusion Criteria
Description of change		Revised and added texts: Patients with diagnosis of mild Alzheimer's Dementia …, and age at least 55 - 85 years with availability of pre-existing brain CCT or MRI compatible with diagnosis of Alzheimer's disease. **Patients older than 85 years may be included based on an acceptable general health status, (e.g. concomitant diseases, physical capability to follow the required study procedures [visits etc.]) per investigators judgement.** OR Age-comparable healthy volunteers age 18 to 85 years. **Healthy volunteers older than 85 years may be included based on an acceptable**

Number of global amendment		3
		general health status, (e.g. concomitant diseases, physical capability to follow the required study procedures [visits etc.]) per investigators judgement. b. Similarly, after 10 patients with AD are entered , the median age will be computed. Five healthy volunteers at or below the median age but greater than 55 years old (low age group) and five healthy volunteers above the median ~~but less than 85~~ (high age group) will be entered into the study.
Rationale for change		For consistency with other studies in the same project (studies 1289.5 and 1289.7) and to provide flexibility for subjects who may be interested in participating in the study.
Section to be changed		Flow Chart, Section 6.1 Visit Schedule
Description of change		Asterisks added in Flow Charts to Visits 4, 5, 6, 8, 10, 11, 12, 13, and 14, with corresponding footnote: ****Home visits may be conducted for these visits in lieu of study center visits.** Added texts to visit schedule: **The following study visits: Visits 4-6 (Day 2-4), Visit 8 (Day 6), Visits 10-14 (Day 9-12), may be conducted as home visits in lieu of study center visits.**
Rationale for change		To potentially reduce subject burden and provide increased flexibility and convenience if subjects opt to participate in home visits in lieu of study center visits.
Section to be changed		Flow Chart – Footnote #2, Section 6.1 Visit Schedule
Description of change		Added text: In-patient stay is optional. If feasible for in-patient stay, **the following procedures would apply:** eligible study participants will be admitted to the study center in-patient facility for overnight stays.
Rationale for change		Clarified that procedures in the in-patient stay section only applies to those subjects who stay in-patient at the clinic during the study.

Number of global amendment		3
Section to be changed		Section 1.2.4 Pharmacokinetic profile in humans
Description of change		Added text: **A drug-drug interaction with fluvoxamine, a strong inhibitor of CYP2C19 and CYP1A2 induced a 30-fold increase of the total plasma exposure (AUC_{0-24}) and a 6-fold increase in Cmax of BI 409306. Mainly non-PMs (10 out of 13 subjects) and only 1 PM were included in the study. These results suggest that in non-PM, CYP1A2 is involved in BI 409306 metabolism, in addition but to a lesser extent to CYP2C19, and that in PMs CYP1A2 is the major CYP450 isoform involved in the metabolism of BI 409306 (Study 1289_0035).**
Rationale for change		Include results from clinical DDI study 1289_0035.
Section to be changed		Section 3.3 Selection of trial population
Description of change		Added text: A log of all subjects included in the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether or not they have been treated with investigational product. **Re-screening of not yet randomised patients can be allowed in exceptional cases but should be discussed on a case-by-case basis between the study site, monitor staff and with the TCM.**
Rationale for change		For consistency with other studies in the project (Studies 1289.5 and 1289.7) and to provide subjects a second chance to participate.
Section to be changed		Section 3.3.3 Exclusion Criterion #3
Description of change		Per Administrative change letter, v1 dated 31-Oct-2016, the bold text below were added to Exclusion #3. 3. Current or planned use of ocular or systemic corticosteroids, **which in the clinical judgment of the investigator and ophthalmologist will interfere with the ocular assessments in the study.** Further consideration reverted this criterion back to the original text:

Number of global amendment		3
		3. Current or planned use of ocular or systemic corticosteroids. ~~**which in the clinical judgment of the investigator and ophthalmologist will interfere with the ocular assessments in the study**~~ The current wording in this amendment supercedes all previous Administrative change letters.
Rationale for change		No change to text from previous amendment. This is noted here to provide the sequence of changes per Administrative change and to document the final wording for this amendment.
Section to be changed		Section 3.3.3 Exclusion Criterion #7, Section 4.2.2.1 Restrictions
Description of change		Revised text: 7. Subjects taking medications that are known to be strong or moderate ~~CYP3A4~~ **CYP1A2** inhibitors (For a list of strong and moderate ~~CYP3A4~~ **CYP1A2** inhibitors please consult the ISF Section 11 “Safety Information”). Use of medications that are known to be strong or moderate ~~CYP3A4~~ **CYP1A2** inhibitors is not permitted. (For a list of strong and moderate ~~CYP3A4~~ **CYP1A2** inhibitors please consult the ISF Section 11 “Safety Information”).

Number of global amendment		3
Rationale for change		Clinical data (Study 1289_0023) did not show evidence for clinically significant changes in exposure to BI 409306 after CYP3A4 inhibition. Recent data (Study 1289_0035) showed that CYP1A2 inhibitors do have an effect on BI 409306.
Section to be changed		Section 3.3.3 Exclusion Criterion #10
Description of change		Deleted text: ~~10. Subjects having participated in studies on innovative causal interventions on AD (patients who stopped treatment of these drugs due to lack of efficacy or tolerability will not be enrolled).~~ All exclusion criteria following are re-numbered.
Rationale for change		This criterion is not relevant to this safety, non-efficacy study.
Section to be changed		Section 3.3.3 Exclusion Criterion #15
Description of change		Added text: For female subjects: • Pre-menopausal women (last menstruation ≤1 year prior to informed consent) who: • are nursing or pregnant or are of child-bearing potential and are not practicing an acceptable method of birth control, or do not plan to continue using this method throughout the trial until 28 days after the last treatment administration, and do not agree to submit to periodic pregnancy testing during participation in the trial. Acceptable methods of birth control include tubal ligation, vasectomized partner, transdermal patch, intra uterine devices/systems (IUDs/IUSs), combined estrogen-progestin oral contraceptives as well as implantable or injectable hormonal contraceptives **unless they are a moderate to strong CYP1A2 inhibitor – see section 4.2.2.1.**
Rationale for change		Recent data (Study 1289_0035) showed that CYP1A2 inhibitors do have an effect on BI 409306.

Number of global amendment		3
Section to be changed		Section 4.1.4 Drug Assignment, Section 6.2.2 Treatment periods
Description of change		Added text: Patient/healthy volunteer will be assigned study medication and **the first dose** administered on site at Visit 3, Day 1. **Other doses may be administered at home, according to the home visits optional schedule as specified in the Flow Chart.** Each patient/healthy volunteer will be administered three tablets, one from each blister dispensed. Table 4.1.4: 1 outlines the treatment and administration of dose for each patient/volunteer.
Rationale for change		To allow for dosing during home visits.
Section to be changed		Section 4.1.6 Packaging, labelling, and re-supply
Description of change		Revised text: All drug supplies will be shipped **to sites** in the initial shipment~~, no~~ **with** re-supply **as needed** ~~is planned~~.
Rationale for change		To allow for re-supply of expired study drugs.
Section to be changed		Section 4.2.1 Rescue medication
Description of change		Deleted text: ~~Use of donepezil is allowed in this study, as a drug-drug interaction (DDI) is not expected with this drug, commonly used in AD patient population. Specifically, BI 409306 is predominantly metabolized by CYP2C19 with minor contribution from CYP3A4, which are not inhibited by donepezil. Also, BI 409306 is not a substrate of the DDI relevant renal and hepatic drug transporters. As such, donepezil is not expected to increase exposure to BI 409306.~~ ~~While potential of donepezil to induce CYP2C19 or CYP3A4 is not known, but any potential time dependent decrease in BI 409306 exposure will be evident based on Day 1 and Day 14 pharmacokinetics.~~ ~~Donepezil is metabolized by CYP3A4 and CYP2D6. BI 409306 is not expected to inhibit CYP3A4, CYP2D6 or any renal or hepatic transporters relevant for drug-drug interaction.~~

Number of global amendment		3
		~~Also, BI 409306 is not an inducer of CYP450 enzymes. As such, BI 409306 is not expected to either increase or decrease donepezil exposure.~~
Rationale for change		No longer relevant per Study 1289_0023.
Section to be changed		
Section to be changed		Section 5.3.2.1 Electroencephalography (EEG)
Description of change		Revised texts: Event Related Potentials: ERPs are a noninvasive method of measuring the distinct electrocortical processing stages enabling cognition and have become a popular tool in neuroscience, and increasingly in clinical and pharmacological investigations. In particular, the **MMN and** P3a~~, P1, N1 and MMN~~ components have been widely applied in the scientific study of cognitive dysfunction, because they reflect attentional and memory processes and **their amplitude is** ~~they are~~ reduced in both disorders and may be used as biomarkers of Alzheimer´s disease and Schizophrenia (R14-3416; R14-3417). These ERPs will be measured in healthy volunteers, AD patients and schizophrenia patients at baseline and Day 13 at peak exposure time point (20-90 minutes after dosing). **In addition to MMN and P3a, further ERP parameters of interest might also be assessed and evaluated.**

Number of global amendment		3

~~**Function**~~	~~**ERP Component**~~
~~Sensory registration~~	~~P1, N1 amplitude~~
~~Sensory Discrimination and Echoic Memory~~	~~MMN amplitude~~
~~Orienting of Attention~~	~~P3a amplitude~~
~~Multi-regional brain communication~~	~~Evoked gamma power~~

Method:
EEG data will be continuously recorded and referenced offline. ~~Vertical and horizontal electro-oculograms, recorded from electrodes above and below the left eye and at the outer canthi of both eyes, respectively, will be used to correct EEG for eye movement and blink artifacts. An electrode will be placed at the tip of the nose for additional offline re-referencing positions.~~ All EEG setup and data acquisition will take approximately 60 minutes with breaks. Subjects will be assessed on EEG biomarkers in the same **sequential** order: ~~resting state EEG (5 minutes),~~ ~~MMN/P1/N1/P3a~~ **ERPs via Passive Auditory Oddball paradigm** (20 minutes), ~~GBR~~ **Auditory Steady State Response paradigm** (5 minutes), **and then resting state EEG (5 minutes)**. ~~The study team has extensive experience in the testing of thousands of subjects using the above paradigms and are thus well-positioned to monitor the comfort and tolerability of the subjects.~~

~~*MMN/P1/N1/P3a*~~ ***Passive Auditory Oddball*** *Paradigm* ***for Assessing ERPs***:
Auditory stimuli will be presented to participants at 85 dB sound pressure level. ~~or adjusted hearing threshold via Etymotic ER3-A insert earphones (Etymotic Research, Inc., Elk Grove Village, Illinois). The MMN/P3a paradigm will be comprised of a~~ **A** pseudorandom sequence of tones **will be presented to participants where** ~~,~~ ~~of which 82%~~ **85%** are standards (50 msec, 1000 Hz) and **15% differ in their duration or duration plus pitch (125 msec, 1000 Hz or 1500 Hz)**. ~~18 are deviants (6% per deviant type): for duration MMN, deviants are 100 milliseconds, 1000 Hz; for frequency MMN, deviants are 50~~

Number of global amendment		3
		~~milliseconds, 1500 Hz; for double-deviant MMN, deviants are 100 milliseconds, 1500 Hz.~~ All tones have 5 millisecond rise/fall times and are presented with a 500-millisecond stimulus onset synchrony. Participants will be instructed to ignore auditory stimuli while they view a silent cartoon movie. **Independent component analyses will be used to correct for ocular and other artifacts in the continuous EEG recordings. After artifact correction, ERP averaging of standards and each deviant type will be generated.** ~~Conventional ERP averaging of standards and each deviant type will be generated. ERP data will then be low-pass filtered at 20 Hz and baseline corrected prior to generating deviant-standard difference waves. MMN amplitude will be defined as the peak area between 140 and 200 milliseconds in each deviant type difference wave; P1 will be defined as the peak area between 50-150 msec; N1 will be defined as the negative peak area between 100-200 msec; P3a will be defined as the peak area between 250-350 msec in each deviant type difference wave. Scalp topography plots activity will be inspected to ensure that each subject is showing the expected pattern of activity (i.e., negativity at frontocentral regions and polarity inversion at the mastoids for MMN, positivity at frontocentral regions for P3a).~~ ***Auditory Steady State Response*** ~~*Gamma Band Entrainment*~~ *Paradigm:* **Gamma** evoked ~~EEG~~ power **and phase locking** will be assessed in response to 40-Hz stimulation at Fz, as this is the electrode with maximal responses and relationships to cognition as per established methods which demonstrated impairments in large cohorts of CIAS patients (R14-4685). The stimuli will be 1-millisecond duration, ~~93~~ **85** dB clicks presented in 500 msec trains. Blocks contain 200 trains of clicks with 500-millisecond intertrain intervals. **For evoked power analyses, the averaged epochs across the click trains will be transformed into power spectra by means of fast Fourier transform**

Number of global amendment		3
		(FFT). ~~For evoked power analyses, averages will be computed on 120 artifact-free epochs in each block and digitally filtered using a zero-phase shift, 10-60 Hz bandpass filter (24 dB/octave). The averaged epochs across the click trains (0-512 msec) will then be transformed into power spectra by means of fast Fourier transform (FFT) using a bin width of 1.95 Hz for the assessment of evoked power analyses.~~ **Gamma phase locking will be calculated following wavelet transformation of the segmented data. Mean values across the 40 Hz frequency layer will be obtained for the each of the six 100-ms windows from -100 to 500 ms relative to stimulus onset.**
Rationale for change		Texts revised to describe actual EEG assessment performed.
Section to be changed		Section 6.1 Visit Schedule
Description of change		Added text: **The following study visits: Visits 4-6 (Day 2-4), Visit 8 (Day 6), Visits 10-14 (Day 9-12) may be conducted as home visits in lieu of study center visits.** If a ~~clinic~~ **study** visit is missed, subjects should continue to the next planned visit and study procedures per Flow Chart.
Rationale for change		To allow for home visits.