CLINICAL TRIAL PROTOCOL

	Document Number:	**c03559983-04**
EudraCT No.:	2016-000285-28	
BI Trial No.:	1346.9	
BI Investigational Product(s):	BI 425809	
Title:	A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia	
Brief Title:	Clinical trial of BI 425809 effect on cognition and functional capacity in schizophrenia.	
Clinical Phase:	II	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	Phone: Fax:	
Status:	Final Protocol **(Revised Protocol (based on global amendment No. 3))**	
Version and Date:	**Version:**	**Date:**
	4.0	**28 Mar 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 425809	
Protocol date: 24 Feb 2016	**Trial number:** 1346.9		**Revision date:** 28 Mar 2019

Title of trial:	A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia
Coordinating Investigator:	Phone: Fax:
Trial site(s):	Multi-centre trial
Clinical phase:	II
Objective(s):	The primary objectives of this trial are to provide proof of clinical concept (PoCC) and dose finding data in patients with schizophrenia on stable antipsychotic treatment who are treated with oral once daily administration of BI 425809 or placebo. Other objectives of this trial are to assess the safety of BI 425809.
Methodology:	Multi-centre, randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial
No. of patients:	720 patients
total entered:	504 patients
each treatment:	84 patients per active treatment arm; 168 patients in placebo arm
Diagnosis :	Patients with established Schizophrenia (as per DSM-5) who are clinically stable

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Main criteria for inclusion:	1. Patients must be capable of providing signed and dated written informed consent by date of Visit 1 in accordance with GCP and the local legislation 2. Men or women who are 18-50 years (inclusively) of age at time of consent 3. Established schizophrenia (as per DSM-5) with the following clinical features: • Outpatient, with no hospitalisation for worsening of schizophrenia within 3 months (hospitalisation for social management and/or day hospital programs within this time are acceptable) prior to randomization • Medically stable over the prior 4 weeks and psychiatrically stable without symptom exacerbation within 3 months prior to randomization • Patients who have no more than a “moderate severe” rating on the Positive and Negative Syndrome Scale (PANSS) positive items P1, P3-P7 (item score ≤ 5) and no more than a “moderate” rating on the PANSS positive item P2 (item score ≤ 4) 4. Current antipsychotic and concomitant psychotropic medications as assessed at Visit 1 must meet the criteria below: • Patients may have up to 2 antipsychotics (typical or atypical) • Patients must be maintained on current typical and/or atypical antipsychotics other than Clozapine and on current dose for at least 4 weeks prior to randomization and/or maintained on current long acting injectable antipsychotic and current dose for at least 3 months prior to randomization • Patients must be maintained on current concomitant psychotropic medications, anticholinergics, antiepileptics and/or lithium for at least 3 months prior to randomization and on current dose for at least 4 weeks prior to randomization
Test product(s):	BI 425809
dose:	2 mg q.d.

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	5 mg q.d. 10 mg q.d 25 mg q.d.
mode of administration:	Tablet, p.o.
Comparator products:	Matching placebo
dose:	Not applicable
mode of administration:	Tablet, p.o.
Duration of treatment:	12 weeks
Endpoints	**Primary endpoint:** • Change from baseline in cognitive function as measured by the composite MATRICS consensus cognitive battery (MCCB) score after 12 weeks of treatment **Secondary endpoints:** • Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score after 12 weeks of treatment • Percentage of patients with (serious) adverse events ((S)AEs) (including clinically relevant abnormalities of physical examination, vital signs, ECG and laboratory tests
Safety criteria:	• Occurrence of Protocol-specified AESI (adverse events of special interest) • Worsening of disease state as assessed by PANSS • Suicidality as assessed by C-SSRS
Statistical methods:	A multiple comparison procedure with modelling (MCPMod) approach is used in

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	this proof of clinical concept (PoCC) and dose finding trial to define one or more suitable doses with respect to the efficacy and safety of BI 425809 for further testing in pivotal phase III trials in patients with schizophrenia on stable antipsychotic treatment. A set of six plausible dose response patterns is considered with pre-specified parameters. If the overall MCPMod test is statistically significant, rejecting the null hypothesis of a flat dose response relation across doses for BI 425809 under study and placebo over 12 weeks for the primary endpoint with a contrast test controlled for the family-wise type I error rate at one-sided alpha=0.05, PoCC is established. After establishing the PoCC, a fitted model will be obtained via weighted model averaging across the significant models based on the Akaike Information Criterion and the target dose(s) can be determined from that model by incorporating information on the minimum clinically relevant effect as well as safety information.		

FLOW CHART

Trial Periods	**Screening Period***	**Randomized Treatment Period**					**End of Trial**	
Visit	**1**	**2**[7]	**3**	**4**[7]	**5**	**6 (e)EOT**[4,7]	**Follow-up 1**[4,5]	**Follow up 2**[4,5]
Weeks	**-4 to -1**		**3**	**6**	**9**	**12**		
"Days" from date of first randomized treatment	**-28 to -7**	**1 (***)**	**22**	**43**	**64**	**85**	**EOT +7**	**EOT +28**
Time window for visits	-28 to -7days	None	±3 days	±3 days	±3 days	+3 days	±3 days	±7 days
Informed consent(**)	X							
Demographics	X							
Medical history	X							
Physical examination	X	X		X		X		X
Vital signs	X	X		X		X		X
Height	X							
Weight	X	X		X		X		X
Safety Laboratory tests(urine/blood)	X	X		X		X		X
Pregnancy test [1]	X	X	X	X	X	X		
Drug screen test (urine)	X	X		X		X		
12 lead-ECG[13]	X	X		X		X		X
in-/exclusion criteria	X	X						
Contact IRT	X	X		X		X		
Randomization		X						
Dispense trial drug		X		X				
Administer trial drug		X	X	X	X			
Termination of trial drug						X		
MCCB	X	X		X		X		
eC-SSRS	X[8]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
PANSS[6]	X	X		X		X		
ScoRS[6]		X				X		
M.I.N.I.	X							
Adverse events	X	X	X	X	X	X	X	X
Compliance check			X	X	X	X		
Concomitant therapy	X	X	X	X	X	X	X	X
Completion of patient participation (****)								X

(*) The Screening Visit has to be performed from - 28 days to -7 days prior first drug administration

(**) Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

Patients who failed screening may repeat the screening phase once after discussion between investigator and sponsor. The patient who will be rescreened needs to be re-consented

***) Day of Randomization / Day of first intake of randomized medication

(****) Completion of patient participation also needs to be completed if the patient withdraws prematurely following randomization (see Section 3.3.3)

[1] women of childbearing potential must perform urine (dipstick) pregnancy test at Visit 1 (Screening Visit), Visit 2, Visit 3, Visit 4, Visit 5, (e)EOT Visit. Urine pregnancy test can be performed more frequently if required by local regulation.

[4] An early End of Treatment (eEOT) Visit, as well as a Follow-up Visit 1 and 2, should be performed for any patient who discontinues study medication prematurely; the eEOT Visit should be completed as soon as possible after study medication is stopped.

[5] Follow-up visits are designed to capture withdrawal effects: immediate effects at 1 week after last intake of trial medication and based on half-life, again at 4 weeks after last intake of trial medication). Follow-up visit 1 may be conducted as a phone visit.

[6] Informant ratings are needed for SCoRS and PANSS ratings. In person ratings are preferred whenever possible. However, if the informant is not available for in person ratings, telephone interview is acceptable. The informant must be available for a telephone interview at the visits indicated in the flowchart.

[7] Study procedures of Screening Visit (Visit 1), Visit 2, Visit 4 and (e)EOT Visit can be split into 2 sequential days. If the study procedures are split into 2 sequential days, the MCCB, should be performed at the first day of the two sequential days (i.e., the day prior to Day 1), and the psychopathologic assessments (e.g. SCoRS, PANSS) should be performed on the second day.

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

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

[13] It is recommended that the 12-lead ECG is performed 3-5 hours after intake of trial drug on visits 4 and (e)EOT.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDNF	Brain-Derived Neurotrophic Factor
BI	Boehringer Ingelheim
BP	Blood pressure
CIAS	Cognitive Impairment Associated with Schizophrenia
CML	Local Clinical Monitor
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
C-SSRS	Columbia Suicide Severity Rating Scale
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic Acid
DSM - 5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicinal Agency
(e) EOT	(early) End of Treatment
EPS	Extrapyramidal symptoms
ERG	Electroretinogram
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set

FC	Flow Chart
FDA	Food and Drug Administration
GCP	Good Clinical Practice
eGFR	Estimated glomerular filtration rate
GLYT 1	Glycine Transporter 1
HA	Health Authorities
Hb	Hemoglobin
Hct	Hematocrit
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS consensus cognitive battery
MCH	Mean cell hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCPMod	Multiple Comparison Procedure with Modelling techniques
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Drug Regulatory Activities
M.I.N.I	Mini International Neuropsychiatric Interview
MMRM	Mixed effects Model Repeated Measures
MRD	Multiple-rising dose
MST	Medical Sub team
NMDA	N-methyl-D-aspartate
NMDA-R	N-methyl-D-aspartate receptor
NOAEL	No-observed-adverse-effect level
PANSS	Positive and Negative Syndrome Scale
PCP	Phencyclidine
PI	Principal Investigator
p.o.	per os (oral)
PoCC	Proof of Clinical Concept
PoM	Proof of Mechanism
PR	Pulse rate

q.d.	quaque die (once a day)
RBC	Red blood cell
RDC	Remote Data Capture
RDW	Red blood cell distribution width
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
SCoRS	Schizophrenia Cognition Rating Scale
SOP	Standard Operating Procedure
SRD	Single-rising dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCM	Trial Clinical Monitor
TIBC	Total Iron Binding Capacity
TMS	Transcranial Magnetic Stimulation
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid-stimulating hormone
VAS	Visual Analogue Scale
WBC	White blood cell
WoCBP	Women of child-bearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Schizophrenia is a serious mental illness that is chronic and disabling in its clinical course. It has been long hypothesized that deficits in glutamatergic signaling may underlie schizophrenia, including negative and cognitive symptoms (R13-4521). Existing treatment options for schizophrenia (i.e. first- and second-generation antipsychotics) are primarily efficacious in treating positive symptoms and have limited efficacy for treating the cognitive and negative symptoms. Inhibition of GLYT 1 aims at improving NMDA receptor hypoactivation in patients with schizophrenia by increasing the concentration of the NMDA receptor co-activator glycine in the synaptic cleft, thereby leading to improvement of negative and cognitive symptoms in patients with schizophrenia (as add-on therapy to antipsychotics).

Schizophrenia has a life-time prevalence of approximately 1%, with almost equal distribution worldwide and comparable incidence between men and women.

Schizophrenia is a heterogenous syndrome defined by hallucinations, delusions, social withdrawal, restricted emotional experiences and expressions, and disorganized behavior. Although the current diagnostic systems emphasize positive and negative symptoms of the illness, early descriptions of schizophrenia viewed cognitive impairment as a core feature. Kraepelin described a wide range of cognitive deficits in characterizing the illness, including attention, memory, retention, association, mental efficiency, judgment, syntax, as well as processes and fluidity in thoughts (Ref: Kraepelin 1919 Dementia Praecox and paraphrenia). Bleuer described deficits in associative thinking as a core feature of schizophrenia and viewed hallucinations as rather accessory (Ref: Bleuler 1950 Dementia Praecox or the group of schizophrenias).

Cognitive impairments are a core feature of schizophrenia and have been shown to be a major determinant of poor functional outcome. As a group, patients with schizophrenia perform significantly worse than controls on almost all neuropsychological tests. While many neuropsychiatric disorders are associated with some degree of cognitive dysfunction, the impairments seen in schizophrenia tend to be more severe and more independent of symptomatic state (R10-5111).

A meta-analysis of more than 200 studies in Schizophrenia which included neurocognitive assessments between 1980 and 1997 reported an overall mean of about one standard deviation in cognitive performance compared to community controls (R15-3853). Another meta-analysis of studies in the following decade produced similar magnitude of deviation from population norms (R15-3854). The magnitude of difference in composite cognition measures from healthy volunteers is comparable or greater than the effect sizes reported for moderate to severe traumatic brain injury (R15-3852).
Around 20-60% of the variance in functional outcome in schizophrenia is explained by cognitive performance (R10-5094; R10-5096; R10-5100; R10-5104).

As of yet, no drug has been approved for the treatment of cognitive impairment in schizophrenia. Antipsychotics have demonstrated mild beneficial effects on cognition in schizophrenia (R15-5596; R15-5580). However, antipsychotics also adversely affect some aspects of cognitive function, such as processing speed (R15-5595).
Various glutamatergic agents have been tested for the treatment of schizophrenia. Targets include NMDA receptor co-factor glycine site, including agonists D-gycine, D-serine, and partial agonist D-cycloserine, as well as glycine transporters, such as sarcosine and bitopertin. D-cylcoserine has shown modest reductions in negative symptom scores (R15-5877), but in another study, it did not differentiate from placebo (R15-5838). In the latter study, D-cycloserine separated from placebo in improvement in cognitive function, driven by outlier responders. When d-cycloserine was dosed once a week, there was significant improvement in negative symptoms, most pronounced in affective flattening and anhedonia (R15-5584). D-serine has also produced inconsistent results on positive, negative and cognitive symptoms of schizophrenia (R15-5615; R15-5578; R15-5639). Inconsistent results were seen from sarcosine trials as well (R13-4524; R13-4448; R15-5616).

Conventional antipsychotics (including both first- and second generation antipsychotics) have only modest effects on cognitive performance (and also negative symptoms) and no drugs have yet been approved for the treatment of CIAS or negative symptoms.
Data from several cross-sectional and longitudinal studies suggest that ameliorating cognitive deficits can benefit a range of functional measures, which may have significant economic impact (R10-5108). The potential to increase functional recovery is therefore a major motivation for developing novel treatments for CIAS.

1.2 DRUG PROFILE

In addition, the GLYT1 inhibitor prototype sarcosine has shown to improve positive, negative, and cognitive symptoms in patients with schizophrenia (R13-4447; R13-4524). It is therefore thought that treatment with BI 425809 has the potential to improve cognitive functioning in patients with schizophrenia.

In a proof of clinical concept trial of another GLYT1 inhibitor, bitopertin, efficacy signals were observed in negative symptoms of schizophrenia (R13-4509), but not replicated in phase III trials (R14-4313; R15-1273).

The safety observations from clinical trials have replicated findings from other compounds with the same mode of action (R13-4450; R13-4451; R13-4508). Potential risks associated with BI 425809 are transient visual disturbances, and somnolence. Based on class-effect, BI 425809 may have the potential to be associated with hemoglobin decrease (R15-1266; R15-1273; R15-1270).

Clinical experience in humans

At the time of preparation of this clinical trial protocol, BI 425809 has been used in seven phase I trials:

- 1346.1 Single rising dose (SRD) trial: completed, report archived
- 1346.2 Multiple rising dose (MRD) trial: completed, preliminary data available
- 1346.3 Proof of mechanism trial: completed, report archived
- 1346.4 Single rising dose (SRD) in Japanese and Chinese trial: completed, preliminary data available
- 1346.10 Itraconazole-interaction trial: completed, report archived
- 1346.22 interaction with cytochrome P450 and P-glycoprotein substrates trial: completed, report archived
- 1346.18 DDI strong CYP3A4 inducer, completed

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

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is designed to investigate whether BI 425809 as an add-on therapy to antipsychotics can improve cognitive symptoms in patients with schizophrenia.

Ophthalmological sub-study:
This trial will further characterize the ocular safety of BI 425809 and effects on ophthalmologic physiology in patients with CIAS. Therefore, a sub-set of patients will undergo special ocular safety assessments.

The sub-studies are described in detail in Appendix 10.8 of this protocol and implemented in the country(ies) planned to participate in this sub-study.

2.2 TRIAL OBJECTIVES

The primary objectives of this trial are to provide proof of clinical concept (PoCC) and dose finding data in patients with schizophrenia on stable antipsychotic treatment who are treated with oral once daily administration of BI 425809 or placebo. Other objectives of this trial are to assess the safety
The PoCC and dose finding are achieved through the primary endpoint comparison (mean change from baseline in composite MCCB score at Week 12) of the four BI 425809 doses (2 mg q.d., 5 mg q.d., 10 mg q.d. and 25 mg q.d.) and placebo. A non-flat dose response relationship between the BI 425809 doses and placebo is tested using the multiple comparison procedures and modelling (MCPMod) approach (R10-1424; R15-1961).

2.3 BENEFIT - RISK ASSESSMENT

The overall safety profile of BI 425809 is outlined in the current IB c02156531
Drug-related risks and safety measures

Considering the chronic and severe disease burden of CIAS, the potential therapeutic benefits are assessed to outweigh the currently understood potential risks of the treatment.

Based on non-clinical toxicology data, clinical data from other compounds in the same class, and subjects exposed in phase I trials, BI 425809 is assessed to be generally safe and well-tolerated. Most common AEs were CNS related, headache being the most frequent. There is potential for BI 425809 to be associated with transient visual disturbances, and somnolence. These effects are understood to be mostly mild to moderate and transient.

Decreased hemoglobin is also considered to be a potential risk based on preclinical data and class effect; however, no clear decrease in hemoglobin was seen in BI 425809-treated subjects compared to placebo in phase I trials so far (of up to 14 days duration). Patients with hemoglobin less than 120 g/L (12g/dL) in men or 115g/L (11.5g/dL) in women will be excluded from participation.

Administration with strong CYP3A inhibitor/ inducers did significantly impact the total exposure of BI 425809. As BI 425809 is a sensitive substrate of CYP3A4, co-administration of moderate to strong CYP3A4 inhibitors and inducers are excluded during the participation in this trial. Furthermore, as data of the DDI cocktail study 1346.22 suggest that BI 425809 is a mild CYP3A4 inducer, clinical monitoring is considered necessary when co-administering sensitive substrates of CYP3A4 at least to the highest tested dose of 25 mg BI 425809. Sensitive CYP3A4 substrates with a narrow therapeutic index are excluded during this trial.

Regarding the potential risk while operating machinery, please refer to Section 4.2.2.2.

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

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

Placebo Risks and Risks of stopping study drug

There is currently no approved medication indicated for treatment of cognitive impairment in schizophrenia. Since an approved, effective comparator is not available for this study, a placebo control group is being used in this study design. It should be noted that all patients, including those randomized to the placebo group, are permitted to remain on other antipsychotic and psychotropic medications.

According to the medication assignment planned in this trial, 67% of the patients will receive BI 425809 and 33% of patients will be assigned to placebo. Patients treated in this clinical trial should be in stable clinical status and on stable doses of antipsychotic and concomitant psychotropic medications. Participation will not alter current disease treatment. Assignment to the placebo arm or stopping the study drug during the treatment period is not associated with a higher risk since patients should remain on their stable treatment regimen. Additionally, BI 425809 targets the cognitive symptoms in schizophrenia and there is no preclinical evidence suggesting an effect on positive or negative symptoms of schizophrenia. Psychiatric events, positive and negative symptoms, and suicidality will be monitored throughout the study to ensure that worsening of pre-existing conditions or any newly occurring events are detected and actions taken according to stopping criteria.

This is an experimental drug at an early stage of testing and therefore an individual benefit cannot be guaranteed. Potential efficacy has been demonstrated by pre-clinical behavioral cognition models. Given the acceptable safety profile in nonclinical and toxicology studies and the good tolerability in clinical studies performed until this date, and careful monitoring planned during the study visits, the sponsor feels the risks to the participating patients are minimized and balanced by a potential benefit due to the intensive medical care received. Additional justification is the possibility to further develop treatment options to improve cognition as a treatment for an unmet medical need.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

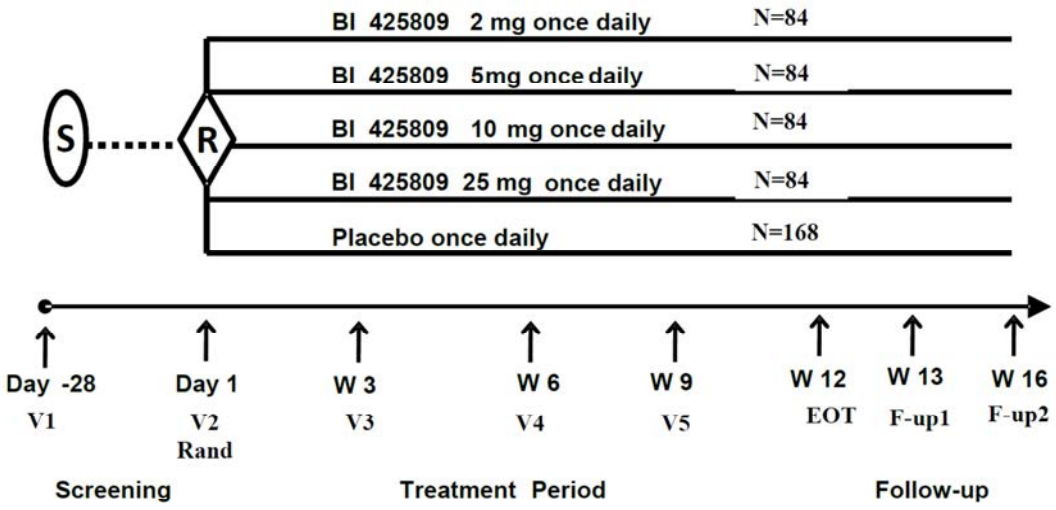

Figure 3.1:1 Trial design

This is a 12-week, multi-center, multi-national, randomized, double-blind, double dummy, placebo controlled parallel group trial in patients with schizophrenia. In total, 504 patients with schizophrenia on stable antipsychotic treatment and meet the entrance criteria are planned to be randomized into this trial.

Patients are enrolled in the trial once informed consent has been signed. Patients suitable after screening will be randomized to the 12 week treatment period assigned at a ratio of 1:1:1:1:2 to one of five arms:

- 2 mg BI 425809
- 5 mg BI 425809
- 10 mg BI 425809
- 25 mg BI 425809
- placebo

The randomized treatment will be double blind.

After completion of the 12-week double-blind treatment period, or following early discontinuation of trial medication at any time point, patients will complete the 4 week follow-up period, with two follow up visits to capture immediate effects at 1 week after last

intake of trial medication and again at 4 weeks after last intake of trial medication. Safety will be formally evaluated at each visit until end of the observational period which is 28 days after end of treatment or for an appropriately longer time in case of unresolved adverse events. Individual patient participation is concluded when the patient has completed their last planned visit.

3.1.1 Administrative structure of the trial

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

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

has been selected as service provider to support the following tasks related to the neuropsychological assessments: necessary rater prequalification, rater training, provision of rater materials and central review of assessments (details will be provided in the ISF).

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

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

A Coordinating Investigator is nominated and will be responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in ISF.

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

A parallel group design was chosen for this trial to detect the effects of BI 425809 compared to placebo on cognition in patients with schizophrenia on stable antipsychotic treatment. The primary analysis of efficacy is planned for 12 weeks of treatment. The 1 and 4 weeks post-treatment follow-up visits is considered to be sufficient to evaluate the pharmacodynamic effect of BI 425809 after discontinuation, to capture withdrawal effects and allow for assessment of reversibility of any unexpected side-effects.

Proof of clinical concept and dose finding are combined within this single phase II trial. In order to achieve both aims in an efficient way, i.e., with a comparably large success probability, the generalized MCPMod approach (R10-1424) has been implemented as the statistical design. This approach is able to incorporate potential relationships between the different doses into the evaluations via optimal test contrasts which increases the probability of success compared with clinical multiple comparison procedures. MCPMod has been evaluated by the EMA recently and is considered to be an efficient statistical methodology for model-based design and analysis of phase II dose finding studies under model uncertainty (EMA qualification opinion). As a second step for designing the trial efficiently the allocation ratio has been chosen to be 1:1:1:1:2 for the treatment groups compared with the placebo. Thereby the success probability of the trial is increased further compared to a balanced allocation ratio whilst keeping the risk of a false positive outcome at the same level. A sufficiently broad set of candidate shapes for the dose-response relationship has been chosen including monotonic and non-monotonic options. Details of the statistical approach including the set of candidate models as well as a sample size justification are given in Section 7.

3.3 SELECTION OF TRIAL POPULATION

It is planned that around 80 trial centres in 11 countries will be participating in this trial and a sufficient number of patients will be screened for the trial to ensure that 504 patients are randomized to trial treatment.

It is expected that approximately 5-10 patients will be randomized at each trial center. If enrolment is delayed, additional sites may be recruited.
To avoid differential center influence on study results, permission to randomize more than 20 patients per site must be obtained from the TCM. This will only be allowed after a careful review of the enrolment status and of the site.

Screening of patients for this trial is competitive, i.e., screening for the trial will stop at all centers when such a number of patients has been screened that it is anticipated that a sufficient number of patients will be randomized to trial treatment. Investigators will be notified when the appropriate number of patients has been screened and screening is complete, and will not be allowed to recruit additional patients for this trial. Patients who have completed Visit 1 procedures prior to notification of the termination of recruitment will be allowed to continue in the trial, if they meet all entry criteria and they are able to follow the visit schedule specified in the protocol.

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

3.3.1 Main diagnosis for trial entry

Only patients with established Schizophrenia (as per DSM-5) who are clinically stable will be screened for suitability for the study. Inclusion will be based upon a complete medical history, including physical examination, vital signs, 12-lead ECG and clinical laboratory tests Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1) Patients must be capable of providing signed and dated written informed consent by date of Visit 1 in accordance with GCP and the local legislation.

2) Men or women who are 18-50 years (inclusive) of age at time of consent

3) Established schizophrenia (as per DSM-5) with the following clinical features:
   - Outpatient, with no hospitalization for worsening of schizophrenia within 3 months (hospitalization for social management and/or day hospital programs within this time are acceptable) prior to randomization
   - Medically stable over the prior 4 weeks and psychiatrically stable without symptom exacerbation within 3 months prior to randomization
   - patients who have no more than a “moderate severe” rating on the PANSS positive items P1, P3-P7 (item score ≤ 5) and no more than a “moderate” rating on the PANSS positive item P2 (item score ≤ 4)

4) Current antipsychotic and concomitant psychotropic medications as assessed at Visit 1 must meet the criteria below:
   - patients may have up to 2 antipsychotics (typical and/or atypical)
   - patients must be maintained on current typical and/or atypical antipsychotics other than Clozapine and on current dose for at least 4 weeks prior to randomization and/or maintained on current long acting injectable antipsychotics and current dose for at least 3 months prior to randomization
   - patients must be maintained on current concomitant psychotropic medications, anticholinergics, antiepileptics and/or lithium for at least 3 months prior to randomization and on current dose for at least 4 weeks prior to randomization.

5) Women of child-bearing potential* must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. Such methods should be used throughout the study and the patient must agree to periodic pregnancy testing during participation in the trial. A list of contraceptive methods meeting these criteria will be provided in the patient information

   *Women of childbearing potential are defined as:
   Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as describe below.
   Women not of childbearing potential are defined as: Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy.

6) Patients must exhibit reliability, physiologic capability, and an educational level sufficient to comply with all protocol procedures, in the investigator's opinion

7) Patients must have an identified informant who will be consistent throughout the study. It is recommended that the informant should interact with the subject at least 2 times a week.

3.3.3 Exclusion criteria

1) Patients who on the Mini-international neuropsychiatric Interview (M.I.N.I) have a categorical diagnosis of another current major psychiatric disorder

2) Diseases of the central nervous system that may impact the assessment of the cognitive tests as per investigator's opinion

3) A movement disorder due to antipsychotic treatment not currently controlled with anti-EPS treatment or another movement disorder (e.g. Parkinson´s disease)

4) Patients receiving another investigational drug or procedure within 30 days or 6 half-lives (whichever is longer) or participation in another trial with any cognitive enhancing therapy or procedure within the last 6 months prior to randomization

5) Patients participating in any formal cognitive remediation programme for at least 4 sessions within the last 4 weeks prior to randomization

6) Patients who have received electroconvulsive therapy within 6 months prior to randomization

7) Patients who have been on BI 409306, encenicline or other investigational drug testing effects on cognition in schizophrenia within the last 6 months prior to randomization or who have previously been on bitopertin

8) Patients who have participated in a clinical trial with repeated MATRICS Consensus Cognitive Battery (MCCB) assessments within the last 6 months prior to randomization

9) Patients who required change in ongoing stable benzodiazepine or sleep medication regimen within the last 4 weeks prior to randomization

10) Patients who have been treated with Clozapine within 6 months prior to randomization

11) Patients who received treatment with medical devices (e.g. TMS, neurofeedback) for any psychiatric condition within the last 3 months prior to randomization

12) Patients taking strong or moderate CYP3A4 inhibitors or inducers within the last 30 days prior to randomization (A list of strong or moderate CYP3A4 inhibitors and inducers will be provided in the ISF.)

13) Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or herbal remedies (see Section 4.2.2.2)

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

15) 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 with intent but without specific plan, or active suicidal thought with plan and intent) prior to randomization

16) In the judgment of the investigator any clinically significant finding of the physical examination (including BP, PR and ECG) or laboratory value (as measured by the central laboratory at visit 1) that would jeopardize the patient´s safety while participating in the trial and their capability to participate

17) Any symptomatic/unstable/ uncontrolled or clinically relevant concomitant disease or
any other clinical condition that would jeopardize the patient´s safety while participating in the trial and capability to participate in the trial as per investigator´s opinion.

18) Severe renal impairment defined as an eGFR < 30mL/min/1.73m² in the screening central lab report

19) Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 times upper limit of normal (ULN) as determined in the screening central lab report

20) Known history of HIV infectionand/or a positive result for ongoing Hepatitis B or C infection on the Visit 1 central lab report

21) Medical history of primary or recurrent malignant disease with the exception of resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ or in situ prostate cancer with a normal prostate specific antigen (PSA) post treatment

22) Significant or unstable physical condition that in the investigator´s judgement may require change in medication or hospitalisation that would impact cognitive function, or planned elective surgery requiring general anesthesia during the study period

23) Hemoglobin less than 120 g/L (12g/dL) in men or 115 g/L (11.5g/dL) in women

24) History of hemoglobinopathy such as thalassemia major or sickle-cell anemia

25) Women who are pregnant, nursing, or who plan to become pregnant while in the trial or
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

26) Significant history of drug abuse disorder (including alcohol, as defined in DSM-5-substance use disorder or in the opinion of the investigator) within the last 6 months prior to informed consent, or a positive urine drug screen at screening **(**except for Benzodiazepines taken according to prescription and as an ongoing, stable regimen **)(**for a list of drugs assessed in the urine drug screen, please refer to Table 5.3.3:1).

27) Patients who are not fluent in the language of the batteries/questionnaires which will be used in the country

28) Patients for which cognitive impairment or symptom severity compromises the validity of the cognitive outcome measures, in the clinical judgement of the investigator

29) Patient who did not make an effortful attempt to complete the cognition battery at screening in the clinical judgement of the investigator

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

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

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision
- The patient needs to take concomitant drugs that interfere with the investigational product(s) in the clinical judgement of the investigator´s (please refer to Section 4.2.2).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- The patient exhibits suicidality, in the clinical judgement 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 with intent but without specific plan, or active suicidal thought with plan and intent)
- The patient needs to stop all current antipsychotic or concomitant psychotropic medications.
- The patient's disease state dramatically worsens, in clinical judgement of investigator

If a patient becomes pregnant during the trial the study medication will be stopped, the patient will be discontinued from the trial and the patient will be followed up until birth or otherwise termination of the pregnancy. For further information, including the process for follow-up on the outcome of the pregnancy please see Section 5.3.7.

A patient can be discontinued after discussion between Sponsor and Investigator if eligibility criteria are being violated, or if the patient fails to comply with the protocol (e.g. nonattendance at study assessments).
Patients who 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 and in the source documents. The data will be included in the trial database and will be reported.
Patients who withdraw or discontinue from the trial after randomization will not be replaced.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3.
For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the (e)CRF. These data will be included in the trial database and reported.

Patients who drop out prior to randomization will be considered screening failures. They will be recorded as screening failures in the Electronic Case Report Form (eCRF) and no further follow-up is required. The data will be included in the trial database and will be reported.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

BI 425809 tablets have been manufactured by BI Pharma GmbH & Co. KG

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

The characteristics of the test products are as shown below.

Table 4.1.1: 1 Test product 1:

Substance:	BI 425809
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	1mg
Posology	2-0-0 for the dose group of 2mg
Route of administration:	oral

Table 4.1.1: 2 Test product 2:

Substance:	BI 425809
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	5 mg
Posology	1-0-0 for the dose group of 5mg 2-0-0 for the dose group of 10mg
Route of administration:	oral

Table 4.1.1: 3 Test product 3:

Substance:	BI 425809
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	25 mg
Posology	1-0-0 for the dose group of 25mg
Route of administration:	oral

The characteristics of the reference products are as shown below.

Table 4.1.1: 4 Reference product 1:

Substance:	Placebo matching BI 425809 1mg and 5mg
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	-
Posology	1-0-0 for the dose group of 5mg 2-0-0 for the dose group of 25mg and the placebo dose group
Route of administration:	oral

Table 4.1.1: 5 Reference product 2

Substance:	Placebo matching BI 425809 25 mg
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	-
Substance:	Placebo matching BI 425809 25 mg
Posology	1-0-0 for the dose group of 2mg, 5mg, 10mg and the placebo dose group
Route of administration:	oral

4.1.2 Method of assigning patients to treatment groups

During Visit 2 and after the patient's eligibility has been confirmed, the treatment will be assigned via Interactive Response Technology (IRT). To facilitate the use of the IRT, the Investigator will receive all necessary instructions. A copy of the IRT manual will be available in the ISF.

Patients will be randomly assigned, in a 1:1:1:1:2 ratio to either

i. 2mg BI 425809
ii. 5mg BI 425809
iii. 10mg BI 425809
iv. 25mg BI 425809
v. Placebo

Details on randomization are provided in Section 7.6.

Patient assignment to the treatment groups will be determined by a computer generated random sequence. Access to the randomization code will be controlled and documented. For further details please refer to Sections 4.1.5.1 and 4.1.5.2.

The kit(s) corresponding to the assigned medication number(s) should be given to the patient and the number of the kit(s) that was/were dispensed will be entered in the eCRF.

Using this procedure, relevant parties will be blinded to the treatment group assignment.

4.1.3 Selection of doses in the trial

According to the result of previous trials, BI 425809 was well tolerated in healthy subjects in single doses of up to 150 mg and multiple doses of up to 75 mg bid (150mg per day).
The doses selected for this trial cover the estimated therapeutic range and include a safety margin (Please refer to Section 1.2 for more details).

4.1.4 Drug assignment and administration of doses for each patient

Dispensing of kits for the double-blind treatment period will begin at Visit 2. Trial medication kits will be provided at Visit 2 and Visit 4. At each of these visits, medication assignment will be provided through IRT. The assigned medication number(s) must be entered in the eCRF, and the corresponding medication kit(s) must be given to the patient. The duration of treatment is 12 weeks. At both Visit 2 and Visit 4 patients will receive one treatment kit containing supplies for 42 treatment days (plus 7 day reserve).

Following the screening period, patients who qualify according to entry criteria will be randomized to one of the five treatment groups of the treatment period to be evaluated as outlined in Table 4.1.4: 1.

Since the tablet size of 1mg and 5 mg is smaller than the tablets size of 25mg, the number of tablets per day will be 3 for all treatments (once daily) to maintain blinding.

Table 4.1.4: 1 Treatment administration per dose group and day (first treatment period)

Treatment group	Dose	Total units per daily dose
BI 425809 2mg	BI 1mg/BI 1mg /placebo 2**	3
BI 425809 5mg	BI 5mg/placebo 1*/placebo 2**	3
BI 425809 10mg	BI 5mg/BI 5mg/placebo 2**	3
BI 425809 25mg	Placebo 1*/placebo 1*/BI 25mg	3
Placebo	Placebo 1*/placebo 1*/placebo 2**	3

*placebo 1 matching BI 425809 1mg and 5mg tablets
**placebo 2 matching BI 425809 25mg tablets

Patients should be instructed to take three tablets orally with water and with or without food in the morning, except for visit days where patients will be given their daily dose at the trial site. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. On days prior to a visit, the dose should be taken approximately 24 hours before the planned dose at the visit.
The first dose of study medication will be taken at the end of Visit 2 under supervision of the investigator or site staff. The last dose of study medication should be taken on the day before the End of Treatment visit.

Patients should be instructed not to take their trial medication in the morning before visit days, as they will be dosed at the site. Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day.
A dose reduction of BI 425809 is not possible.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after database lock. However, due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's drug safety group to access the randomization code for individual patients during study conduct. In such cases, access to the code will only be permitted by authorized drug safety representatives. Access to the code will be via the IRT system.
The randomization code will be kept blinded by Clinical Trial Support up to database lock.
Please refer to Section 4.1.5.2 for the rules regarding breaking the code for an individual or for all patients in emergency situations.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / Pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants.
However, due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's drug safety group to access the randomization code for individual patients during study conduct.

Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the Sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page and in the source documents. In case third party needs to break the code, however, when the Investigator cannot be reached, the code can be opened by calling emergency code manager.

4.1.6 Packaging, labelling, and re-supply

Trial medication will be labelled with the trial identification and medication code number. It will be dispensed as indicated in the Flow Chart. At each dispensing, supplies for 42 treatment days (plus 7 day reserve) will be given to the patient.

Supply and re-supply will be managed by the IRT according to the IRT Manual.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The Investigator < and/or > Pharmacist < and/or > investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator
- **For US**: Availability of Form 1572

The Investigator < and/or > Pharmacist < and/or > investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposal of unused products.

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

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

No rescue medication, emergency procedure or additional treatments are foreseen for this trial.
Throughout the duration of the trial patients should continue to take their current antipsychotic and concomitant psychotropic medications, the dose of which should remain unchanged if at all possible. 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 welfare may be given at the discretion of the Investigator.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following drugs are prohibited for 6 months prior to randomization and during the trial period:

- Clozapine (atypical antipsychotic medication),
- Sarcosine, cycloserine, serine and glycine,
- stimulants (e.g. methylphenidate, dextroamphetamine) and modafinil
- tricyclic antidepressants

In addition, the following drugs are restricted for the timeframes specified below:

- Patients should not be on maintenance therapy with opioids (e.g. methadone, suboxone) during the trial period.
- Systemic steroids should be discontinued more than 30 days prior to randomization.
- Use of Olanzapine is permitted but should be limited to a maximum daily dose of 25mg during the trial period.
- patients must be maintained on current concomitant psychotropic medications, anticholinergics, antiepileptics and/or lithium for at least 3 months prior to randomization and on current dose for at least 4 weeks prior to randomization and during the trial period.
- Patients should not receive more than 4mg benztropine or no more than 50mg diphenhydramine (or equivalent doses of other anticholinergic or antihistaminic medication) and should receive the last dose at least 8hrs before cognitive testing during the trial period.
- New or changes in dose and frequency of psychosocial treatments, including but not limited to social skills treatment or vocational treatment is not permitted during the trial period. If patients are on these treatments, this should have not been started or changed in the past three months prior to randomization.
- Patients participating in any formal cognitive remediation program for at least 4 sessions within the last month prior to randomization are excluded.
- Use of moderate or strong CYP3A4 inhibitors or inducers is not permitted within the last 30 days prior to randomization and during the trial participation. (For a list of moderate or strong CYP3A4 inhibitors and inducers, see Investigator Site File).
- CYP3A4 sensitive drugs with narrow therapeutic index (such as cyclosporine or fentanyl, refer to list in ISF) are not permitted during the trial period.
- Please note: CYP3A4 and CYP2B6 sensitive drugs may have decreased levels of exposure when given concomitantly with BI 425809. Investigators should assess if dose adjustments and/or monitoring of the underlying disease is clinically required for patients who are taking such drugs. For a list of CYP3A4 and CYP2B6 sensitive drugs please refer to the ISF.
- Any medication that may interfere with the action of BI 425809 or whose action may be altered by concomitant administration of BI 425809 during the treatment period and

the 4-week follow-up period, in the clinical judgment of the investigator, is not permitted.
- 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 trial period, receive electroconvulsive therapy, nor begin any type of traditional/complementary therapies. Use of hypnotics and anxiolytics is not prohibited; however, there should be no change in benzodiazepine or sleep medication regimen within the last 4 weeks prior to randomization. Last intake before cognitive testing should be at least 8 hours.

4.2.2.2 Restrictions on diet and life style

Dietary supplements and products including St. John's wort (Hypericum perforatum) and herbal remedies that may impact the assessment of cognitive tests in the investigator´s judgement are not permitted starting 7 days before the first administration of trial medication until the end of treatment.

As a general precaution for CNS- active drugs, it is recommended that subjects should exercise caution when driving or operating machinery after drug administration.

Patients should not abuse of alcohol or drugs during study as defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or in the opinion of the investigator, or as indicated by a positive urine drug screen. For a list of drugs assessed by the urine drug screen please refer to Table 5.3.3:1.

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 significantly changed.

Patients do not have to come fasted to any trial visit.

4.3 TREATMENT COMPLIANCE

Study medication will be dispensed to the patient at the study site by responsible site personnel. Details regarding dispensing of the study medication to each participating patient, including patient identification, the amount of study drug dispensed, the date the drug was dispensed, and the numbers of tablets returned to the site will be recorded in the drug accountability log. All dispensed study drug should be recorded in the drug accountability log of the investigator site file.

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

Based on tablet counts, treatment compliance will be calculated as the number of tablets taken, divided by the number of tablets which should have been taken according to the

scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorized by the Sponsor.

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

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

Change from baseline in cognitive function as measured by the composite MCCB score after 12 weeks of treatment is the primary efficacy endpoint.

The 10 tests of the MCCB with corresponding cognitive domains are listed in Table 5.1.1: 1 below:

Table 5.1.1: 1 MCCB tests and cognitive domains (R13-2373)

Test	Domain
Trail Making Test, Part A (TMT)	Speed of Processing
Brief Assessment of Cognition in Schizophrenia, symbol coding subtest (BACS SC)	Speed of Processing
Hopkins Verbal Learning Test – Revised (HVLT-R), immediate recall	Verbal Learning
Wechsler Memory Scale, 3rd ed. Spatial span subtest (WMS-III SS)	Working Memory (nonverbal)
Letter-Number Span test (LNS)	Working Memory (verbal)
Neuropsychological Assessment Battery, mazes subtest (NAB mazes)	Reasoning and Problem Solving
Brief Visuospatial Memory Test- Revised (BVMT-R)	Visual Learning
Category Fluency test, animal naming	Speed of Processing
Mayer-Salovey-Caruso Emotional Intelligence Test, managing emotions branch (MSCEIT™ ME)	Social Cognition
Continous Performance Test, Identical Pairs version (CPT-IP)	Attention/ Vigilance

5.1.2 Secondary Endpoint(s)

- Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score after 12 weeks of treatment is the secondary efficacy endpoint.

  The 20 items of the SCoRS specifically assess cognitive functioning in each of the **seven** MCCB cognitive domains:
  - Memory: 4 items
  - Learning: 2 items
  - Attention: 3 items
  - Working Memory: 2 items
  - Problem Solving 3 items
  - Processing/Motor speed: 2 items
  - Social Cognition: 3 items
  - Language: 1 item

- Percentage of patients with (S)AEs (including clinically relevant abnormalities of physical examination, vital signs, ECG test and laboratory tests)

Further safety endpoints:

Further exploratory endpoints to assess safety are as shown below:

- Occurrence of Protocol-specified AESI (adverse events of special interest)
- Worsening of disease state as assessed by PANSS
- Suicidality as assessed by C-SSRS

5.2 ASSESSMENT OF EFFICACY

5.2.1 Assessment of primary and secondary efficacy endpoints

Change in cognitive function, everyday living skills and disease state will be measured by the batteries, scales and questionnaires listed below.

MATRICS Consensus Cognitive Battery (MCCB) will be used to evaluate the effects of BI 425809 on cognitive functions at Screening Visit (Visit 1), Randomization Visit (Visit 2, baseline), Visit 4 and (early) End of Treatment visit (e)EOT Visit.
MCCB comprises 10 tests, which assess 7 cognitive domains, including speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. (R13-2347; R13-2373)

Schizophrenia Cognition Rating Scale (SCoRS) will be used to evaluate the everyday functional capacity at Randomization Visit (Visit 2) and (early) End of Treatment visit ((e)EOT Visit).
SCoRS is a 20-item interview-based assessment of cognitive deficits and the degree to which they affect day-to-day functions. Each item is rated on a 4-point scale. Higher ratings reflect a greater degree of impairment. The composite score will be the average of non-missing response. If five or more of the 20 items is missing, the composite score will be missing (R13-2345; R16-4322).

M.I.N.I
The Mini-international neuropsychiatric interview is a short structured clinical interview which enables researchers to make diagnoses of psychiatric disorders (R07-1303). It should be performed at Screening Visit for eligibility confirmation.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

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

A complete physical examination including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system will be performed. The physical examination will include examination of known and suspected sites of disease. A complete PE is also required at EOT Visit (week 12) or at early discontinuation (eEOT Visit).

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

Body weight and height will be measured as indicated in the Flow Chart.

5.3.2 Vital Signs

Vital signs will be recorded at the study visits as described in the Flow Chart, including the (early) End of Treatment visit and the Follow-up Visit 2 (4 weeks after the end of treatment). Temperature, systolic/diastolic blood pressure, pulse rate will be measured after patients have been sitting comfortably for at least five minutes. The height is measured only at screening visit (Visit 1).
Blood pressure measurement can be done manually or electronically (preferably with the same device at every visit).

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

5.3.3 Safety laboratory parameters

The laboratory tests listed in Table 5.3.3: 1 will be performed at the central laboratory service provider. Patients do not have to be fasted for the blood sampling for the safety laboratory. Instructions on collection, handling/ processing, and shipping of the samples will be provided in the investigator site file by the central laboratory. For time points of laboratory sampling refer to the Flow Chart.

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

Laboratory values that are out of range should be commented on lab report print-outs and evaluated by the investigator for clinical significance. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit lab kit and should be repeated until normalization or stabilization or until an alternative explanation has been found.

Clinically significant abnormal laboratory results should be reported by the investigators in eCRF either on baseline condition (from V1 test) or on adverse event page (from subsequent visits test).
The following lab parameters will not be determined at each study visit:

- TSH at screening only
- Vitamin B12 and folate at screening only

Table 5.3.3: 1 Safety laboratory tests

Category	Test name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) (for patients with >2g/dL decrease in hemoglobin since baseline, the following tests will be added: serum ferritin, serum iron, TIBC, reticulocyte index) Red Blood Cell Count/ Erythrocytes Reticulocyte Count White Blood Cells / Leukocytes Platelet Count/ Thrombocytes MCV, MCH, RDW, MCHC
	Diff. Automatic (manual if diff. automatic is abnormal) - Neutrophils - Eosinophils - Basophils - Monocytes - Lymphocytes
Chemistry	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Lipase
Chemistry	Amylase Calcium Sodium Urea (BUN) Potassium Glucose Creatinine Vitamine B12 Bilirubin Total, fractionated if increased Protein, Total C-Reactive Protein Cholesterol, total Triglycerides TSH Folate eGFR

Table 5.3.3: 1 Safety laboratory tests (cont.)

Category	Test name
Pregnancy test (females only)	Human urine chorionic gonadotropin
Urinalysis (Stix)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH Urine creatinine
Drug screening (urine)	Cannabis Benzodiazepine Barbiturates Opiates Cocaine Amphetamines Methadone PCP
Infections screening (only at the screening visit)	Hepatitis B Surface antigen (qualitative) Hepatitis C antibodies (qualitative)

5.3.4 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow Chart. Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 – V6) will be recorded using equipment provided by a central ECG vendor. The ECGs will be recorded for at least 10 second duration after the subjects have rested for at least 5 minutes in a supine position. Electrode placement will be performed according to the method of Einthoven/Goldberger (ankles and wrists). At all time points indicated in the Flow Chart, single ECGs will be recorded. ECG recordings at planned time points may be repeated for quality reasons like alternating current artefacts, muscle movements and electrode dislocation. In this case the repeated ECG recordings will be used if quality was better.

The investigator or a designee 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.

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

All ECGs will be transmitted electronically to the central ECG vendor in order to enable a centralized and independent re-evaluation of all 12-lead ECGs. A centralized and independent re-evaluation will be done. Abnormalities detected during this centralized ECG evaluation will not necessarily qualify as AE.
Central evaluation on individual ECG level will be performed by the vendor and a report will be provided to the site. Decisions on eligibility for the trial and treatment or further follow-up of any findings are in the responsibility of the investigator.

5.3.5 Other safety parameters

5.3.5.1 Assessment of disease state

Positive and Negative Syndrome Scale (PANSS) will be used to evaluate the disease state. It contains 30-items including seven positive symptom items, seven negative symptom items and 16 general psychopathology symptom items. Each item is scored on the same seven-point severity scale. Fourteen of the PANSS items require input from an informant. A trained rater interviews the patient and the informant, estimated to take 30-40 minutes for evaluating the subjects' disease state at Screening Visit (Visit 1), Visit 2, Visit 4 and (e)EOT Visit. If the patient's disease state dramatically worsens, the patient should be withdrawn from the trial (Please refer to Section 3.3.4.1). Any person who has been capable of observing the patient over the past week may act as the informant. It is recommended that the informant should interact with the subject at least 2 times a week. If the informant is not available for in person interview at the scheduled visit, telephone interview is acceptable.

5.3.5.2 Assessment of suicidality

Suicidal risk is assessed by the eC-SSRS (electronic version).

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behavior and ideation. The computer-automated eC-SSRS is a self-rated version of the C-SSRS using phone. Subjects who do not have suicidal behavior or ideation will answer a limited number of questions and will usually complete the assessment in about 3 minutes. Subjects with significant suicidal ideation or behavior may require up to 10 minutes answering all relevant questions. This assessment should be conducted early in the visit to provide sufficient time for the report to be received at the trial site prior to subject departure. At the conclusion of each assessment, the site will receive an eC-SSRS Findings Report via email or fax. The report presents the findings for suicidal ideation, intensity of ideation, suicidal behavior, and lethality / medical damage (for actual suicide attempts only).

The C-SSRS / eC-SSRS has been widely used in large multinational clinical trials. The eCSSRS will be administered at the screening visit (using the 'screening / baseline' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening visit. The life time history of suicidal ideation and behavior will also be recorded. After the screening visit the assessment 'since last visit' will be performed at each clinic or phone visit ('since last visit' version). The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. In cases when assessments need to be validated, the investigator-rated paper CSSRS questionnaire is to be used by a psychiatrist trained and certified for this questionnaire in order to collect data in a systematic way. The investigator rating on investigator-rated CSSRS will supersede the findings from the telephone interview.
If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/ or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

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

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

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

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:
- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,

- is a congenital anomaly/birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

All reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior from prospective monitoring in CSSRS (see Section 5.3.5.2 for details) that occur after the baseline visit are also considered to be life-threatening and must be reported as SAEs by the investigator.

For each negative report (suicidal ideation type 1, 2 or 3) after start of the trial, the investigator is to decide based on clinical judgment whether it represents an adverse event (AE) as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

For 'Self-injurious behavior, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between the discontinuation of the drug and must be reported as described in Section 5.3.7 Adverse event collection and reporting, subsections "AE collection" and "AE reporting to sponsor and timelines".

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

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

The latest list of "Always Serious AEs" can be found in the RDC. A copy of the latest list of "Always Serious AEs" will be provided to you upon request. These events should always be reported as SAEs as described in Section 5.3.7.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI

need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

The following are considered as AESIs:

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

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

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

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.

5.3.7 Adverse event collection and reporting

AE Collection
The following must be collected and documented on the appropriate CRF(s) / eCRF by the Investigator:

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

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

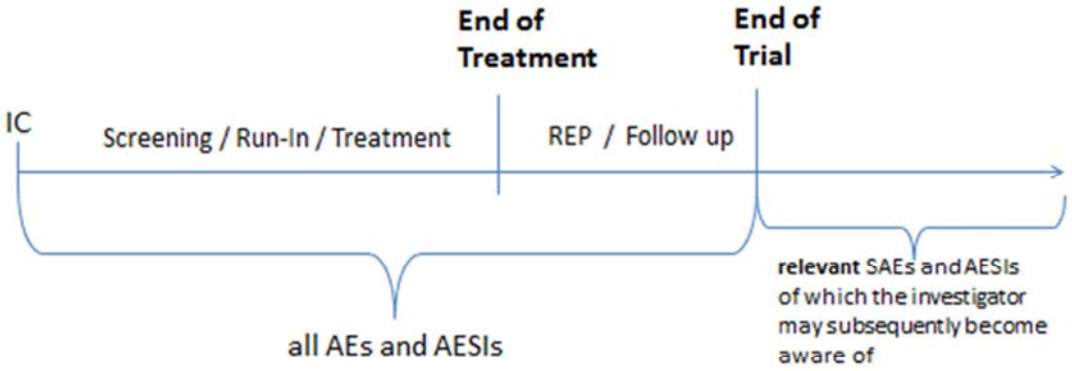

Figure 5.3.7: 1 Collection and reporting of AEs/SAEs during the study

The REP is defined as 11 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment (please also see Section 7.3.4). Events which occurred after the REP will be considered as post treatment events.

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

Before administration of study medication at Visit 2, site staff will remind patients to report "any unusual visual perception they may experience". If patients report a change in perception or any vision-related AE, site staff must record the patient's verbatim description in the source documents and report it in the same way in the CRF (and SAE form, if applicable). A local ophthalmology assessment will be required if any visual AE is rated as moderate or severe by the subject or at the discretion of the PI. The ophthalmologist will act as a consultant to the Investigator and may offer advice on the proper management and treatment for the reaction.

In case of anemia with unknown reason as measured by the central laboratory the investigator should consult with an internist. Any clinically relevant finding from the internist´s consultation should be reported as an AE.

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

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

Information required
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form, 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 the trial procedures outlined under Section 6.2.

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

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

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

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

Pregnancy
In 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 unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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).

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are acceptable measurements and commonly used in monitoring safety aspects or assessing treatment response in patients with CIAS.

The scheduled measurements are appropriate to see drug induced changes in physical examination, vital signs, ECG and standard laboratory values. These primary and secondary efficacy endpoints and safety endpoints are standard and accepted for evaluation of safety and tolerability of an oral drug, and they are widely used in this kind of studies. The period of 12 weeks of treatment with BI 425809 is deemed appropriate to see a change in cognitive function in schizophrenic patients.
Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart with time window for rescheduling. Preferably the visits should be conducted in the morning.

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

The end of the trial is defined as “last patient out”, i.e. last visit completed by the last patient. If the reason for removal of a patient from the treatment is an adverse event or an abnormal laboratory test result, the patient must be followed until they are resolved, or deemed reasonably followed up by the investigator on consultation with BI. When the total sample size for the main study is reached, randomization in the imaging sub-study will stop and this may result in the number of patients randomized in the sub-study being less than 150 which is the planned sample size for the sub-study.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

- Each assessment of the Neuropsychological Rating Scales should preferentially be done by the same members of the site staff for a given patient throughout the study period.

- In addition, it is recommended that MCCB and SCoRS should not be administered to a patient by the same rater at the same visit to prevent bias on the SCoRS ratings.

- The MCCB should always be performed at the same time of the day, within a window of +/- 60 minutes at Visit 1, 2, 4 and/or (e) EOT. Preferably, the assessment of the MCCB is done in the morning. If the cognitive testing can’t be started at the same time within the allowed time frame (±60 minutes) at a scheduled visit, the visit should be rescheduled within the allowed visit window.

- Study procedures of Screening Visit (Visit 1), Visit 2, Visit 4 and (e)EOT Visit can be split into 2 sequential days. If the study procedures are split into 2 sequential days, the MCCB,
  should be performed at the first day of the two sequential days (i.e., the day prior to Day 1), and the psychopathologic assessments should be performed on the second day.

- During the testing, patients are allowed to take short breaks as needed, in the judgement of the rater/investigator.

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

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

Patients do not have to come fasted for any trial visit.

6.2.1 Screening and run-in period(s)

Screening Period
After patients have been informed about the trial, written informed consent in accordance with GCP and the local legislation must be obtained prior to any study related procedures taking place. Once consented, the patient is considered to be enrolled in the trial and to have started screening. The patient should be recorded on the enrolment log and be registered in the IRT system as a screened patient.

One additional written informed consent for unspecified pharmacogenomics study must be obtained if the patient is willing to provide the blood sample for DNA banking.

Screening (Visit 1) should take place from -28 days to -7 days before Visit 2.

Demographics consist of gender, age, ethnicity, smoking and alcohol history and will be obtained after the main informed consent form is signed.

Baseline Conditions
BP should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see Section 5.3.2.

A 12-lead ECG will be taken. The investigator will review the ECG recording and record any ECG abnormality of clinical significance under baseline conditions.

Any abnormal condition of clinical significance identified during physical examination, vital signs, 12 lead ECG and/or laboratory assessment should be recorded as a baseline condition All concomitant medications will be documented after the informed consent of main study is signed.

Once Visit 1 procedures are complete and laboratory results are received, inclusion/exclusion criteria must be reviewed again. If the patient is still eligible according to inclusion/exclusion criteria, the patient should be contacted to schedule next visit.

If a patient does not meet inclusion/exclusion criteria the patient must be recorded in eCRFs as a screen failure. Patient must be registered as screen failure in IRT.

Patients who failed screening may repeat the screening phase once after discussion between investigator and sponsor. Rescreening will only be allowed if the reasons for screening failure were reversible and have been resolved, based on investigator judgement. Permission to rescreen patients must be obtained from the TCM. The patient who will be rescreened needs to be re-consented. All the study procedures of Screening Visit (Visit 1) must be repeated.

Medical History:
Psychiatric and relevant non-psychiatric history will be obtained after the main informed consent form is signed.

Baseline disease state will be assessed by PANSS. Positive scale item P1-P7 will be used for confirming the eligibility of study inclusion criterion # 3 at Visit1 and Visit 2.

The MCCB, M.I.N.I and the Baseline/screening scale of the eC-SSRS will be administered for eligibility confirmation.
Cognitive assessments of Screening Visit should be done at least 7 days prior to cognitive baseline assessments performed at Visit 2.

6.2.2 Treatment period(s)

The randomized treatment period is from Visit 2 to Visit (e) EOT.

Patients should not take trial medication before coming to the clinic.

Throughout the treatment period, BP should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see Section 5.3.2

Randomization visit 2
As soon as eligibility of a screened patient is confirmed, the patient may enter the study and Visit 2 can be conducted. This visit includes the assessment of the endpoints and randomization via IRT. IRT should not be called before the patient has completed the assessment of the neuropsychological endpoints.

At the start of Visit 2 it should be ensured that all Visit 1 procedures have been successfully completed and eligibility has been confirmed (including results of the neuropsychological rating scales performed at Visit 1).

Study procedures have to be completed according to the Flow Chart.

Sufficient trial drug for 42 treatment days (plus 7 day reserve) will be dispensed. The study medication will be assigned by the IRT at Visit 2.
Patients should be instructed not to take their trial medication before the visits as they will be dosed while in the clinic.

Visit 3, Visit 5
Study procedures have to be completed according to the Flow Chart.

The visits be performed at week 3 (Visit 3) and week 9 (Visit 5) after randomization to

- determine trial medication compliance: Remaining trial medication will be counted. If non-compliance is detected, refer to Section 4.3.
- check for Adverse Events and changes in concomitant medication

- Women of childbearing potential must perform urine dip stick pregnancy test.
- eC-SSRS will be completed by the patient

Patients should be instructed to bring all trial medication (used and unused blisters) with them.

Visit 4
Study procedures have to be completed according to the Flow Chart.

The MCCB should be performed at the same time of day as at V2 (+/- 60 minutes time window).

Sufficient trial drug for 42 treatment days (plus 7 day reserve) will be dispensed. The study medication will be assigned by the IRT at Visit 4.
The 1st dose of study medication from the newly assigned medication kit will be taken at the clinic Patients should be instructed not to take their trial medication before the visit as they will be dosed while in the clinic after safety lab are taken.

End of Treatment (Visit 6):
Study procedures have to be completed according to the Flow Chart.

Cognitive assessments of EOT Visit cannot be performed before Day 85. The final evaluation of cognitive function must be performed after patients complete 12-week treatment period. For the patients who discontinue the study medication early, the cognitive assessments of (e)EOT Visit must be performed within 7 days after last dose intake.

6.2.3 Follow Up Period and Trial Completion

Follow up visits will be conducted as described in the Flow Chart at 1 week after end of treatment to capture early withdrawal effects and at 4 weeks after treatment based on the half-life of the trial medication.
If patient discontinues trial medication early, termination of trial medication page must be completed and Follow-up Visits should be completed at 1 and 4 weeks after eEOT Visit.

Follow-up visit 1 (1 week after end of treatment) can be conducted as a phone contact.
AEs which have not recovered at Follow-up Visit 2 should be followed until they are resolved, or deemed reasonably followed up by the investigator on consultation with BI.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Refer to Section 3.1 for details on the design of this trial.

The primary objectives of this trial are the establishment of proof-of-concept with respect to a non-flat dose-response curve together with the definition of one or more suitable doses with respect to the efficacy and safety of orally administered once daily dosing of BI 425809 for further testing in pivotal phase III trials in patients with schizophrenia on stable antipsychotic treatment. For this purpose the MCPMod approach is employed (R10-1424; R15-1961).

The primary endpoint is change from baseline in cognitive function as measured by the composite MCCB score after 12 weeks of treatment. Change from baseline in everyday functional capacity as measured by SCoRS global ratings after 12 weeks of treatment is the secondary endpoint.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis is that there is a flat dose response pattern across placebo and any dose of BI 425809 within the tested dose range of 0 to 25mg on the mean change in the composite MCCB score from baseline to Week 12. The alternative hypothesis is that there is a non-flat dose response pattern indicating a benefit of BI 425809 compared to placebo.

The MCPMod procedure allows simultaneous evaluation of different plausible dose response patterns whilst protecting the overall probability of type I error (one-sided alpha of 0.05). The pre-specified dose response patterns and the corresponding parameters are outlined in Section 7.3.1 and Section 7.7.

7.3 PLANNED ANALYSES

The following patient analysis sets are defined for this trial:

- Treated Set (TS): includes all patients who signed informed consent and were treated with at least one dose of the trial medication. Patients in TS are analyzed under the actual trial medication received at randomization. The TS is used for safety analyses as well as demographics and baseline characteristics.

- Full Analysis Set (FAS): includes all patients in treated set who had non-missing baseline and at least one non-missing post-baseline and on-treatment measurement on any efficacy endpoint. Patients in FAS are analyzed according to the intent-to-treat

principle, i.e., patients in FAS are analyzed under the randomized trial medication. The FAS is used for efficacy analyses.

Data from patients who were screened but not randomized will be listed but not included in any summary or inferential statistics. Specifications or important protocol violations will be provided in the TSAP.

7.3.1 Primary endpoint analyses

7.3.1.1 Primary analysis of the primary endpoint

The analyses of PoCC and dose finding are carried out using the MCPMod approach (R10-1424) in combination with Mixed effects Model Repeated Measures (MMRM) approach (R15-4293) whereby several plausible dose response patterns/models are evaluated, while keeping full control of the overall type I error rate of 5% 1-sided, to identify the best-fitting model or subset of models. The MMRM model as specified in Section 7.3.1.2 will be fitted for the MCPMod.

For the PoCC testing and for the sample size calculation, the basic shape of each of the models to be tested must be pre-defined. Six different models are considered in the analysis: linear, linear in log, Emax, Sigmoid Emax, logistic and beta model. Except in the beta model, the maximum effect is assumed to be achieved at the maximum dose being tested. For the sample size calculation, the maximum standardized effect size is assumed to be 0.35. Further details are given in Section 7.7.

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

- Linear: no assumptions needed
- Linear in log: no assumptions needed
- Emax: 20% of the maximum effect is achieved at 2 mg
- Sigmoid Emax: 25% of the maximum effect is achieved at 5 mg
  75% of the maximum effect is achieved at 10 mg
- Logistic: 10% of the maximum effect is achieved at 5 mg
  50% of the maximum effect is achieved at 10 mg
- Beta model: 75% of the maximum effect is achieved at 2 mg
  87.5% of the maximum effect is achieved at 5 mg
  25% of the maximum effect is achieved at 25 mg
  Maximum effect achieved at 10 mg
  Scalar parameter = 26

PoCC is established if at least one model is statistically significant, rejecting the null hypothesis of a flat dose response relation over 12 weeks for the primary endpoint (mean change from baseline in composite MCCB score) jointly for each of the candidate dose response models with a contrast test controlled for the family-wise type I error rate at one-sided $\alpha = 0.05$.

If PoCC is established, the best-fitting model(s) from the above set of six models can be refitted to the data without any parameter assumptions to generate new estimates of the model parameters from the data. The final model will be obtained via weighted model averaging across the significant models based on the Akaike Information Criterion (AIC) (the smaller the AIC value the better the model fit). The target dose(s) can then be determined from that model by incorporating information on the minimum clinically relevant effect as well as safety information. The target dose should be chosen within the dose range investigated (0mg-25mg) though the actual modelling will be performed on a broader range of doses including extrapolation.

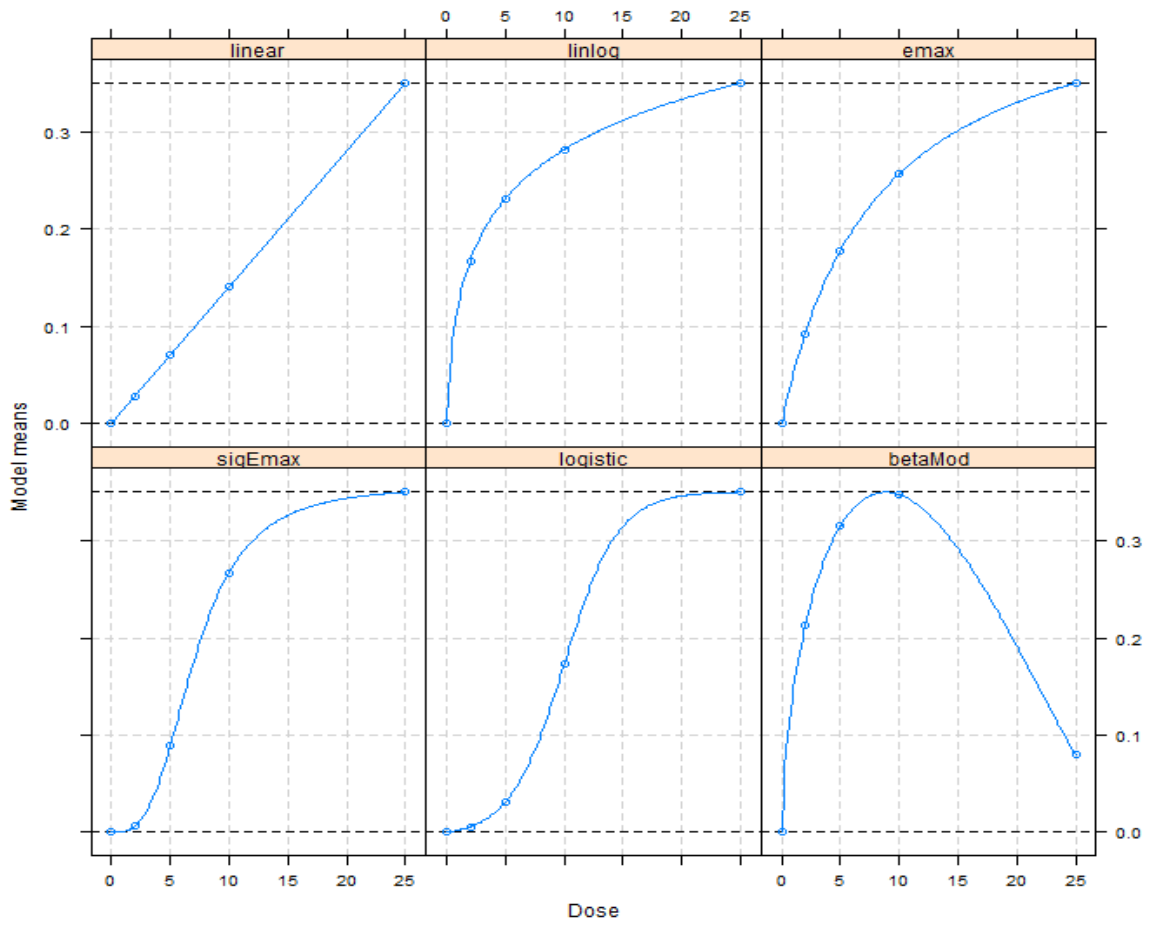

Figure 7.3.1.1: 1 Shape of the dose response patterns considered plausible in the MCPMod

7.3.2 Secondary endpoint analyses

If considered relevant, the MCPMod approach will also be applied to the secondary efficacy endpoint. In addition, exploratory treatment comparisons will be conducted using an MMRM approach similar to the one specified for the primary efficacy endpoint. More details on the analysis of secondary efficacy endpoint will be specified in the TSAP.

7.3.4 Safety analyses

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

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

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

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

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

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at the specific time points. In general, for completely missing visits missing data will not be imputed and will be handled through the MMRM using a restricted maximum likelihood method under the “missing at random” assumption. Details on the handling of missing data will be specified in the TSAP prior to unblinding.

7.6 RANDOMIZATION

Eligible patients will be randomized with ratio of 1:1:1:1:2 to BI 425809 2 mg, 5 mg, 10 mg 25 mg and placebo. The randomization will be implemented in blocks to achieve balanced allocation to each treatment arm. In addition, randomization will be stratified for the main study alone and for the main study and the imaging substudy, i.e., patients who give consent to participate in the imaging substudy besides the main study will be randomized with the same ratio of 1:1:1:1:2 to the five treatment arms as for those who consent to the main study but do not consent to participate in the imaging substudy. When the total sample size for the main study is achieved, the randomization to the stratum of the imaging sub-study will stop.

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

7.7 DETERMINATION OF SAMPLE SIZE

For the purposes of calculating the sample size for this phase II trial, we consider a range of standardized effect sizes showing better efficacy of BI 425809 as compared to placebo in the composite MCCB score change from baseline after 12 weeks of treatment, i.e., 0.3, 0.35, 0.4 and 0.45, and assume the six candidate dose response patterns as described in Section 7.3.1.1. Since the randomization allocation ratio for the four BI 425809 dose arms and placebo is 1:1:1:1:2, the sample size required for the placebo arm and the active treatment arms are displayed separately. Table 7.7: 1 below gives the sample size calculations under different effect sizes using 1-sided type I error rate of 0.05 and 80% power. The sample size calculations are performed using the MCPMod approach assuming the six plausible dose response patterns as described in Section 7.3.1.1 and implemented using the statistical software R package 'DoseFinding' (R15-2001) version 0.9-12 released on 28 SEP 2014 (depends on R version ≥ 2.15.0). The R codes for the sample size calculations as well as the analyses using the MCPMod approach will be provided in the TSAP.

Table 7.7:1 Sample size calculation under different effect sizes for the composite MCCB score change from baseline with 80% power and one-sided alpha of 0.05

Standardized Effect size	0.3	**0.35**	0.4	0.45
Power = 80%				
N for Placebo	204	**150**	116	92
N for each active treatment arm	102	**75**	58	46
Total	612	**450**	348	276
Adjusting for 10% dropout				
N for Placebo	228	**168**	130	104
N for each active treatment arm	114	**84**	65	52
Total	684	**504**	390	312

A sample size of 75 evaluable patients in each of the BI 425809 arm and 150 evaluable patients in the placebo arm is needed to establish PoCC of a standardized effect size of 0.35 with an average power of 80% and one-sided alpha of 0.05. Assuming a 10% dropout rate which is considered reasonable based on CIAS trials to date, 84 patients in each of the BI 425809 arm and 168 patients in the placebo arm are required. Therefore a total sample size of 504 evaluable patients with 84 patients in each of the BI 426809 arm and 168 patients in the placebo arm is chosen for this phase II trial.

The sample size calculations in Table 7.7: 2 consider a range of effect size and power for a direct comparison between BI 425809 doses and the placebo. Two-sample t-test is used for these exploratory treatment comparisons without adjusting for multiplicity.

Table 7.7: 2 Sample size calculations under different effect sizes and power for the composite MCCB score change from baseline with one-sided alpha of 0.05

Effect size	0.3	0.35	0.4	0.45	0.5	0.55
Power = 85%						
N for each active treatment arm	151	111	85	68	55	46
N for Placebo	302	222	170	136	110	92
Total sample size adjusting for 10% dropout	1008	744	570	456	372	312
Power = 80%						
N for each active treatment arm	132	97	75	59	48	40
N for Placebo	264	194	150	118	96	80
Total sample size adjusting for 10% dropout	882	648	504	396	324	270
Power = 75%						
N for each treatment arm	117	86	66	53	43	36
N for Placebo	234	172	132	106	86	72
Total sample size adjusting for 10% dropout	780	576	444	354	288	240

The two-sample t-test method with unequal n's in nQuery Advisor® 6.1 statistical package by Statistical Solutions Ltd is used for the sample size calculations.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

The 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.
The rights of the investigator / trial site and of the sponsor with regard to publication of the results of this trial are described in the investigator contract / trial site's contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.
The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File)."

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The Investigator must give a full explanation to trial patients by using the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is

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

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Case Report Forms (CRF) / (e)CRF for individual patients will be provided by the Sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.
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. CRF/eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRF / eCRF, and written

informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

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

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For the BI 425809 this is the current version of the Investigator's Brochure (c02156531). The current versions of these reference documents are provided in the ISF. No AEs are classified as listed for matching placebo, trial design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, 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 last patient out (for details please refer to Section 6.2.3)
The IEC / competent authority in each participating EU member state will be notified about the end or early termination of the trial.

When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

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

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

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

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Batteries and questionnaires

Batteries and questionnaires which will be used in the clinical trial 1346.9 for assessing the end points and disease status were listed below:

1. MATRICS Consensus Cognitive Battery (MCCB)
2. Schizophrenia Cognition Rating Scale (SCoRS)
3. Positive and Negative Syndrome Scale (PANSS)
4. Columbia-Suicide Severity Rating Scale (C-SSRS) Screening/Baseline Version
5. Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version

For templates and instructions of the batteries and questionnaires, please refer to the ISF Section 15 “Trial Specific Supplies”.

10.1.2 Definition of positive Reports of Suicidal Ideation and Behavior

Results from each assessment of suicidal ideation and behavior per subject and visit will be categorized as positive or negative.
Positive reports of suicidal ideation and behavior are to be generated for
ANY of the following findings:
Ideation
- Active suicidal ideation with method and intent but no plan (type 4)
- Active suicidal ideation with method, intent and plan (type 5)

Behavior
- Completed suicide
- Suicide attempt
- Interrupted attempt
- Aborted attempt
- Preparatory actions toward imminent suicidal behaviors

Negative reports of suicidal ideation are generated when there are no indications of the above, i.e. suicidal ideation of type 1-3.
Positive reports *have* to be reported as Serious Adverse Events (SAEs), negative reports *can* be reported as (Serious) Adverse Events (AEs) as per investigator´s judgment.

10.8 OPHTHALMOLOGIC SUBSTUDY

10.8.1 Flowchart

MAIN	**Trial Periods**	**Screening Period**	**Randomized Treatment Period**					**End of Trial**	
	Visit	**1**	**2**	**3**	**4**	**5**	**6 EOT**	**Follow -up [1]**	**Follow up [2]**
	Study-Day	**7 to – 28**	**1**	**22**	**43**	**64**	**85**	**EOT+ 7**	**EOT+ 28**
SUB	**Sub-study Visit**	**Screening**				**On-treatment**		**Post 1[2]**	
	Time window for visits	-28 to -7 days				± 10		± 3	
	Sub-study Informed Consent	X							
	Best Corrected Visual Acuity	X				X[1]		X	
	Color Vision Test (F-M 100)	X				X[1]		X	
	Pupil Diameter Measurement	X				X[1]		X	
	Anterior / Posterior Biomicroscopy	X				X[1]		X	
	Intra-ocular Pressure	X				X[1]		X	
	Ocular Coherence Tomography	X				X[1]		X	
	Indirect Funduscopy	X				X[1]		X	

[1]Visual procedures to be completed at estimated peak exposure time point (120-300 minutes after dosing). Dosing on these days should be scheduled accordingly at the discretion of the investigator.

[2]If clinically relevant changes (compared to baseline) are documented at visit Post1 the same procedures need to be repeated at visit FU2±10 days. Further follow-up in case of ongoing AEs at the discretion of the investigator.

10.8.2 Objective

To investigate the ocular safety of BI 425809 in patients with Schizophrenia following oral administration of 2mg, 5mg, 10mg and 25mg compared to placebo in a 12 week treatment period.

10.8.3 Selection of Study Population

This sub-study will enrol patients from selected study sites participating in the 1346.9 study who will additionally meet the below criteria.

10.8.3.1 Inclusion Criteria

1. Patients who have given informed consent to participate in the 1346.9 and who (at the end of the screening visit procedures) can be foreseen to be randomized to active treatment in the discretion of the investigator.
2. Patients must have given written informed consent to the sub-study in accordance with GCP and local legislation prior to any sub-study procedures.

10.8.3.2 Exclusion Criteria

1. Presence of active ocular conditions with or without visual impairment due to any causes (e.g. wet-aged macular degeneration, pathologic myopia, 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.).

10.8.4 Sub-study Design

Ophthalmologic safety assessments will be done at the time-points described in the flowchart. At least 60 patients required to have approximately 8-10 evaluable patients for each of the 4 BI 425809 dose arms and approx. 16 - 20 evaluable patients for the placebo arm.

Patient recruitment status in this sub-study will be monitored closely to enable and to open the recruitment into this sub-study in additional countries, if this is required to meet the targeted recruitment.

10.8.5 Ophthalmological examinations

The following ophthalmological assessments will be performed in this study, at time-points given in the Flow Chart. All assessments should be evaluated by an ophthalmologist or certified ophthalmic technicians. The ophthalmologist will serve as a consultant to the investigator and report the results of the ophthalmological examinations supported by worksheets provided from study level. These worksheets will serve as source data and will be archived in the patients chart at the study site. All test results in each visit will be documented in the above mentioned source documents and entered in the eCRF. Any abnormal findings will be documented, and if applicable, severity grading 1-4 (1 = very mild, 2 = mild, 3 = moderate, 4 = severe) will be provided.
Any deterioration observed during the ophthalmologic assessments should be reported to the investigator and based on the clinical judgment, can be documented as an AE. The investigator may consult with the ophthalmologist on the grading of AEs at any time.
In case of clinical abnormal findings an additional ophthalmologic examination may be considered.

The description of the ophthalmological assessments below is meant to represent the current medical standard for these examinations. The ophthalmologist may deviate from these descriptions if deemed medically appropriate if it is (per medical judgment) ensured that the same diagnostic standard is met and the same medical conclusion can be drawn. Any deviation and the potential diagnostic consequences should be documented and communicated to the study site.

Best Corrected Visual Acuity (BCVA)
BCVA will be determined using Early Treatment Diabetic Retinal Scale (ETDRS) charts at a 4-meter testing distance under standard, certified lighting condition (Precision Vision CAT N02425). ETDRS Chart 1(CAT 2111) will be used for the right eye, Chart 2 (CAT 2112) for the left eye and Refraction Chart R (CAT 2110) for the refractive error. If the patient is unable to read at least the 20/100 line, the test will be repeated with the distance reduced to one meter. For those unable to read the ETDRS chart at any distance, the following steps will be count fingers, hands movements and light/no light perception. The same optotype will be used for each patient throughout the study. The refractive error using Refraction Chart R will be determined at the baseline visit and 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.

Farnsworth-Munsell 100 hue test (F-M 100)
Color vision testing using the Farnsworth-Munsell 100 (Munsell Color Services Lab, X-Rite, Inc.) hue test will be used to evaluate each patient's category of color vision or color vision deficiency in both eyes, separately. It consists of 93 colors mounted in plastic caps, housed in four separate cases (Serial No. 555103180814, 08/2014). Each case consists of two hinged panels which contain a quarter of the 85 numbered, removable color caps. Two caps are repeated and fixed as pilot colors at either end of one panel in each case, making a total of 93 caps. Each hue cap between the fixed anchors can be adjusted as the observer sees fit. The

final arrangement of the hue caps represents the aptitude of the visual system in discerning differences in color hue.
The standard software included in the FM 100 package will be used for scoring and analyzing the results. Total error score (TES) will be used as a measurement of color vision. Total error score and level of color vision deficiency classification (e.g. superior, average, low discrimination) will be recorded on the eCRF. Examination of color vision will be performed at during screening), Day 64±10 (peak exposure), and at End of Trial + 7.

Pupil Diameter Measurement
Both left and right pupil measurements will be taken separately using a pupil gauge under standardized lighting conditions. Measurements for each eye will be recorded in the eCRF.

Anterior and posterior biomicroscopy
The anterior and posterior chamber slit lamp examination will be done in conjunction with a biomicroscope (for example Haag Streit BC900). The examination of the anterior segment and posterior segments will include the eyelid, sclera, conjunctiva, cornea, iris, lens, and the anterior vitreous. The binocular slit-lamp examination (stereoscopic magnified view of the ocular structures) will be also performed for further documentation of the ocular findings. The anterior and posterior chamber slit lamp examination will be performed in both eyes. Examination results of normal or abnormal will be indicated, and if abnormal to provide the condition and severity grading from 1-4 scale. Photographs will be taken if a clinically significant abnormality is noted per ophthalmologist discretion. Results will be recorded in the eCRF.

Intra-Ocular Pressure Measurement (IOP)
Intra-ocular pressure of both eyes will be measured separately (using the Goldmann applanation tonometry (Haag Streit AT900) or a similar device).

Spectral domain optical coherence tomography (SD-OCT)
High definition optical coherence tomography (spectral domain OCT) 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. OCT images of both eyes will be captured and reported as normal or abnormal, and the central retinal thickness measurements will be recorded.
Further explanations and description of abnormalities will be provided for all abnormal results.
A central service vendor will be used to harmonize the OCT procedure and to centrally assess the results.

Indirect fundoscopy
Dilated indirect fundoscopy of the retina will be performed in previously dilated eyes (topical mydriatic eyedrops) with a proper lens and either a slit lamp microscope or a light attached to a headband. Indirect fundoscopy of the retina will be performed at Day -1 (Baseline), at Visit 5 (Day 64) and at End of Trial. Results of normal or abnormal exams will be recorded on the eCRF, with further explanation and severity gradings (Grade 1-4) for abnormal results.

Photographs will be taken if a clinically significant abnormality is noted per ophthalmologist discretion.

10.8.6 Endpoints

All of the analyses of the ophthalmologic measurement will be exploratory and no formal endpoints will be defined.

10.8.7 Planned Analyses Determination of Sample Size

10.8.7.1 Planned Analyses

No statistical testing will be performed. All safety analyses will be assessed in a descriptive way based on change from baseline for the following measurements at Week 9 (Visit 5) and Week 12 (Visit 6 – EoT visit):

- Number of letters correct based on the best corrected visual acuity test (BCVA)
- Total error score from the Farnsworth-Munsel 100 hue testing (F-M 100)
- Pupil diameter measurement
- Categorical changes (normal/abnormal) from the anterior and posterior biomicroscopy exam
- Intra-ocular pressure (IOP)
- Central retinal thickness as measured by High definition ocular coherence tomography (SD OCT)
- Categorical changes (normal/abnormal) from indirect fundoscopy of the retina.

10.8.7.2 Sample Size

It is planned to include a total of at least 60 subjects in this sub-study. The planned sample size is not based on a power calculation. The size of 10 subjects per dose group (with 20 patients in the placebo group) is in general considered as sufficient for the exploratory evaluation of multiple dose ophthalmologic assessment.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		21 Apr 2016
EudraCT number		2016-000285-28
BI Trial number		1346.9
BI Investigational Product(s)		BI 425809
Title of protocol		A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1.2
Description of change		A typo was corrected and information on Cyp2b6 induction was added.
Rationale for change		New information was added.
Section to be changed		2.1
Description of change		Information on a planned sub-study with ophthalmologic safety assessments was added.
Rationale for change		New information was added.
Section to be changed		3.3.3
Description of change		Herbal remedies were added to exclusion criterion # 13.
Rationale for change		Herbal medications that may potentially interfere with efficacy assessments were excluded.
Section to be changed		4.2.2.1
Description of change		“e.g” was added to the restriction for methadone

		and suboxon.
Rationale for change		Clarification was added.
Section to be changed		4.2.2.1
Description of change		Information regarding CYP2B6 sensitive drugs was added.
Rationale for change		New information was added.
Section to be changed		5.1.1
Description of change		WMS II was changed to WMS-III.
Rationale for change		Correction of typo.
Section to be changed		5.4.1 and Appendix 10.2
Description of change		Recording of food intake with study drug was added.
Rationale for change		Information will be required to study impact of food intake on exposure.
Section to be changed		5.1.2
Description of change		Correction to seven cognitive domains of MCCB.
Rationale for change		Correction of typo.
Section to be changed		5.3.6
Description of change		The following sentence was deleted: The reason for the decision on causal relationship for unlisted AEs needs to be provided in the (e)CRF.
Rationale for change		Clarification was received that this sentence is no longer required by local regulation of Japan.

11.2 GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		13 Dec 2017
EudraCT number		2016-000285-28
BI Trial number		1346.9
BI Investigational Product(s)		BI 425809
Title of protocol		A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Flowchart
Section to be changed		2.2
Description of change		“Proof of Concept” (PoC) was amended to “Proof of Clinical Concept” (PoCC)
Rationale for change		Correction
Section to be changed		2.3
Description of change		Addition of new information
Rationale for change		To align with IB update

Section to be changed		3.3.2
Description of change		Excl crit. #5 was updated: tubal occlusion/litigation no longer considered permanent sterilization but highly effective method of birth control
Rationale for change		To align with current guideline "Change to definition of Childbearing Potential" 001-MCS-40-106_RD-20
Section to be changed		3.3.3
Description of change		**Excl crit #9:** it was added that patients requiring change in **ongoing stable** benzodiazepine regimen will be excluded
Rationale for change		Clarification
Section to be changed		3.3.3
Description of change		**Excl crit #20:** wording to be changed to Known history of HIV infection and/or a positive result for ongoing Hepatitis B or C infection on the Visit 1 central lab report
Rationale for change		To check for ongoing infections at the time of screening
Section to be changed		2.3 and 3.3.3
Description of change		Excl crit #23: wording to be changed to Hemoglobin less than 120 g/L (12g/dL) in men or 115 g/L (11.5g/dL) in women
Rationale for change		new information was added
Section to be changed		3.3.3
Description of change		Excl crit #26: wording to be changed to positive urine drug screen at screening except for BZDs taken according to prescription and as an ongoing, stable regimen.
Rationale for change		For clarification to align with Excl. Crit#9 which allows ongoing stable BZD use
Section to be changed		3.3.3
Description of change		Exclusion criterion #28: wording was changed to "Patients for which cognitive impairment or symptom severity compromises the validity of the cognitive outcome measures, in the clinical judgement of the investigator"
Rationale for change		Clarification
Section to be changed		3.3.3
Description of change		Exclusion criterion #29: wording was changed to „Patient who did not make an effortful attempt to complete the cognition battery at screening in the clnical judgement of the investigator"
Rationale for change		Clarification
Section to be changed		4.1.3

Description of change		Wording was changed to: "According to the result of previous trials, BI 425809 was well tolerated in healthy subjects in single doses of up to 150 mg and multiple doses of up to 75 mg bid (150mg per day)."
Rationale for change		Clarification
Section to be changed		4.2.2.1
Description of change		Wording amended to Patients should not receive more than 4mg benztropine or no more than 50mg diphenhydramine (or equivalent doses of other anticholinergic or antihistaminic medication)
Rationale for change		For clarification
Section to be changed		4.2.2.1
Description of change		Wording amended to "Patient will not begin or increase frequency/duration of psychotherapy during the trial period, receive electroconvulsive therapy, nor begin any type of traditional/complementary therapies"
Rationale for change		For clarification
Section to be changed		4.2.2.2
Description of change		Cautionary statement regarding driving was amended "As a general precaution for CNS- active drugs, it is recommended that subjects should exercise caution when driving or operating machinery after drug administration."
Rationale for change		Clarification – more general recommendation without specific timeframe
Section to be changed		4.2.2.2
Description of change		Wording amended to: "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 **significantly** changed"
Rationale for change		Clarification
Section to be changed		
Description of change		
Rationale for change		

Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		Clarification

Rationale for change		Administrative reasons
Section to be changed		5.3.3
Description of change		The following wording was added: **"**Clinically significant abnormal laboratory results should be reported by the investigators in eCRF either on baseline condition (from V1 test) or on adverse event page (from subsequent visits test)."
Rationale for change		Clarification
Section to be changed		5.3.3
Description of change		Hepatitis B Surface antigen (qualitative) and Hepatitis C antibodies (qualitative) testing were added to the safety lab test plan
Rationale for change		To check for ongoing infections at the time of screening
Section to be changed		5.3.4
Description of change		Central vendor for ECG was added. Existing ECG at screening will no longer be accepted.

Rationale for change		Safety considerations and to align with 1346.23 trial
Section to be changed		5.3.6.1
Description of change		The following wording was added: Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between the discontinuation of the drug and must be reported as described in section 5.3.7 Adverse event collection and reporting, subsections "AE collection" and "AE reporting to sponsor and timelines".
Rationale for change		Alignment with new wording for current protocol template
Section to be changed		5.4.,7.3.5 and Appendix 10.2

Description of change		The following sentence was added "When the total sample size for the main study is reached, randomization in the imaging sub-study will stop and this may result in the number of patients randomized in the sub-study being less than 150 which is the planned sample size for the sub-study."
Rationale for change		Clarification

Section to be changed		6.2.2
Description of change		Wording was amended to: "The 1st dose of study medication from the newly assigned medication kit will be taken at the clinic within 15 minutes
Rationale for change		Clarification
Section to be changed		7.6

Description of change		Clarification regarding randomization and stratification into the main trial and the imaging sub-study
Rationale for change		Clarification

Section to be changed		Appendix 10.8
Description of change		Addition of ophthalmologic sub-study protocol as appendix 10.8
Rationale for change		as ophthalmologic substudy will be implemented in several countries.
Section to be changed		5.3.6.1
Description of change		Information about self injury, no suicidal intent and AE reporting for negative report (suicidal ideation type 1, 2 or 3) was added
Rationale for change		Clarification
Section to be changed		3.3.3 Exclusion criteria
Description of change		The following wording was added to exclusion criterion # 16: “that would jeopardize the patient´s safety while participating in the trial and their capability to participate”
Rationale for change		Clarification

11.3 GLOBAL AMENDMENT 3

Date of amendment		28 Mar 2019
EudraCT number **EU number**		2016-000285-28
BI Trial number		1346.9
BI Investigational Medicinal Product(s)		BI 425809
Title of protocol		A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		5.3.5.2 Assessment of suicidality
Description of change		Addition of investigator rated C-SSRS assessment to allow psychiatrists to repeat or validate the telephone assessment in case doubtful reports from the telephone assessment are obtained.
Rationale for change		The protocol asks for psychiatrists review of the report and requests that doubtful report should be repeated or reports be validated. However there is currently no systematic process to allow psychiatrists to repeat or validate the telephone assessment in case of doubt. Therefore we will provide sites with access to the investigator rated C-SSRS and provide corresponding training for this assessment, so psychiatrist can repeat doubtful reports.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader		03 Apr 2019 09:04 CEST
Approval-Team Member Medicine		03 Apr 2019 09:08 CEST
Author-Trial Clinical Pharmacokineticist		03 Apr 2019 09:27 CEST
Approval-Translational Medicine Expert		03 Apr 2019 09:35 CEST
Approval-Therapeutic Area		03 Apr 2019 09:55 CEST
Approval-Biostatistics		04 Apr 2019 01:43 CEST
Verification-Paper Signature Completion		05 Apr 2019 13:35 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**